Official Title: A Phase II, Multicenter, Open-Label, Single Arm Study to Evaluate the Pharmacodynamic Effects of Once Weekly Administration of Gantenerumab in Participants with Early (Prodromal to Mild) Alzheimer's Disease

NCT Number: NCT04592341

Document Date: Protocol Amendment Version 3: 16-May-2022

PROTOCOL

TITLE:	**A PHASE II, MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY TO EVALUATE THE PHARMACODYNAMIC EFFECTS OF ONCE WEEKLY ADMINISTRATION OF GANTENERUMAB IN PARTICIPANTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN29722
VERSION NUMBER:	3
EUDRACT NUMBER:	2020-001384-87
IND NUMBER:	102,266
NCT NUMBER:	NCT04592341
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic signature and date stamp on the final page of this document

PROTOCOL HISTORY

Protocol		*Associated Country-Specific Protocols*		
Version	***Date Final***	***Country***	***Version***	***Date Final***
3	*See electronic date stamp on the final page of this document.*	—	—	—
2	*17 November 2021*	—	—	—
1	*23 June 2020*	*United Kingdom*	*Addendum 1*	*2 November 2021*

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol WN49722 has been amended primarily to include an optional 2-year extension after 2 years in the study. The changes to the protocol, along with a rationale for each change, are summarized below:

- The study has been updated to include the optional 2-year extension. The schedule of assessments until Week 103 remains unchanged and the benefit–risk profile of gantenerumab remains unchanged. The following sections have been updated:
  - A rationale for adding the 2-year extension has been included. The extension of the study from Weeks 104 to 208 will allow the collection of additional long-term safety and tolerability information of the once-a-week regimen, as well as additional exploratory long-term pharmacokinetic/pharmacodynamic and biomarker information (Sections 1.3.1 and 3.3.4)
  - The study design has been updated to indicate that participants who opt for the 2-year extension will receive the final dose of study drug at Week 207. Final pharmacodynamic and efficacy assessments will be performed 1 week later at Week 208 (Sections 1.3.1, 3.1.1, 3.3.1, 4.3.2.1, 4.6.3, and 4.6.5).
  - Brain amyloid position emission tomography (PET) imaging assessment timepoints have been updated to include Weeks 156 and 208 (Sections 1.3.1 and 3.1.1).
  - The study schema has been updated to include the 2-year extension from Week 104 to Week 208 (Section 3.1.1, Figure 4).
  - The end of the study has been updated to be 224 weeks after the last participant is enrolled. The total duration of the study from screening of the first participant to the end of the study has been updated to be approximately 5 years (Section 3.2).
  - Language has been added to explain that the 2-year extension is optional and participants must consent to participate (Section 2; Section 4.5.12 has been added and subsequent sections have been renumbered).
  - Additional visits during the study extension have been added, with the last visit in the study at open-label extension (OLE) Week 208 and the follow-up visit at OLE Week 224 (Sections 3.1.1, 4.6.5, and 4.7.1; Appendix 1, Tables 5–10).
- Background information on clinical studies has been updated to reflect that the OLE phase of Studies WN25203 and WN28745 have been completed (Section 1.2.1). Data from the studies relating to amyloid-related imaging abnormalities and injection site reaction risks have been updated (Sections 5.1.1.1 and 5.1.1.2).
- The objectives have been updated primarily to include the Week 208 timepoint in the respective endpoints (Section 2). The following changes have been made:
  - The secondary and biomarker endpoints have been updated to include a change from baseline to Week 208

  - The change from baseline up to Week 208 in deposited amyloid as measured by brain amyloid PET centiloid levels has been added as an exploratory biomarker endpoint
  - The change from baseline to Week 208 has been included for the exploratory efficacy scales and home administration questionnaire
- During the course of the study, an autoinjector may become available in participating countries, if approved by local health authorities and Institutional Review Boards. Use of this device will be optional for participants who receive study treatment administration at home or at the site (Section 4.3.2). Reporting requirements for the autoinjector have also been updated (Section 5.4.4).
- The Medical Monitor has changed, and the Medical Monitor contact information has been deleted from Emergency Medical Contacts to avoid the inclusion of outdated telephone 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 (Section 5.4.1).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II, MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY TO EVALUATE THE PHARMACODYNAMIC EFFECTS OF ONCE WEEKLY ADMINISTRATION OF GANTENERUMAB IN PARTICIPANTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
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TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted] *M.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please 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:	**A PHASE II, MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY TO EVALUATE THE PHARMACODYNAMIC EFFECTS OF ONCE WEEKLY ADMINISTRATION OF GANTENERUMAB IN PARTICIPANTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
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NCT NUMBER:	NCT04592341
TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	II
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacodynamics, pharmacokinetics, and safety of gantenerumab in participants with early (prodromal to mild) Alzheimer's disease (AD). Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
• To evaluate the PD effect of a Q1W dosing regimen of gantenerumab on brain amyloid load as determined by PET imaging in participants with early (prodromal to mild) AD	• The change from baseline to Week 52 and to Week 104 in deposited amyloid as measured by brain amyloid PET CL levels [a]
Secondary Objective	**Corresponding Endpoint**
• To evaluate caregiver overall satisfaction and confidence with home administration	• Responses to home administration questionnaire (Caregiver) up to Week 52, Week 104 [a] *and Week 208* [b]
Safety Objective	**Corresponding Endpoints**
• To assess the safety of gantenerumab in participants with early (prodromal to mild) AD	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurologic systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline

PK/PD Objectives	Corresponding Endpoints
• To characterize the PK profile of gantenerumab using a new titration scheme and especially at the Q1W dosing frequency • To assess the PD effect of the dosing frequency (e.g., Q1W, Q2W) on brain amyloid	• Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints • The influence of dosing frequency information on the performance of a quantitative PK-PD model developed based on PK and PET from this and previous studies (e.g., WN29922 and WN39658) [a]
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the pharmacodynamic effect of gantenerumab at the Q1W dosing regimen on plasma and MRI *and PET* biomarkers	• Change from baseline in plasma biomarkers (including, but not limited to, phosphorylated tau and NFL) to Week 104 *and Week 208* [b] • Change from baseline to Week 104 *and Week 208* [b] in functional brain connectivity, as measured by resting-state functional MRI (where available) • Change from baseline to Week 104 *and Week 208* [b] in integrity of white matter, as measured by DTI-MRI (where available) • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants. • *The change from baseline up to Week 208 in deposited amyloid as measured by brain amyloid PET CL levels* [b]
Exploratory Objectives	**Corresponding Endpoints**
• To compare the effect of a Q1W to a Q2W dosing regimen on amyloid reduction using external controls • To evaluate the effects of gantenerumab at the Q1W dosing on cognitive and functional endpoints • To evaluate patient overall satisfaction with at home administration	• The change from baseline to Week 52 and to Week 104 in deposited amyloid as measured by brain amyloid PET compared with the change in the pivotal WN29922 and WN39658 studies • The change from baseline to Week 104 *and Week 208* [b] in the following: − The CDR-SOB − MMSE total score − ADAS-Cog11 and ADAS-Cog13 − Verbal Fluency Task − Coding − ADCS-ADL • Responses to home administration questionnaire (Patient) up to Week 104 *and Week 208* [b]

AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group-Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CL = Centiloid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NFL = neurofilament light chain; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; Q1W = once a week; Q2W = every 2 weeks; Q4W = every 4 weeks, *SAP = Statistical Analysis Plan*.

[a] The primary analysis is at Week 104, and details concerning interim analyses *which will consider Week 52 outcomes* are described in the *relevant* protocol *sections and SAP.*

[b] *Week 208 assessments are optional and only required if participants take part in the 2-year extension*

STUDY DESIGN

DESCRIPTION OF STUDY

Study WN29722 is a Phase II, multicenter, open-label, single arm, pharmacodynamic (PD) study in participants with early (prodromal to mild) AD to evaluate the effect of a once weekly (Q1W) dosing regimen on deposited amyloid as measured by change from baseline to Weeks 52 and 104 in brain amyloid positron emission tomography (PET). The dosing regimen being evaluated in current Phase III studies (WN29922 and WN39658) is gantenerumab 120 mg SC every 4 weeks (Q4W) for 12 weeks, followed by 255 mg SC Q4W for 12 weeks, and 510 mg SC Q4W for 12 weeks, prior to reaching the target dose of 510 mg SC Q2W. As an alternative to administering two 255-mg injections every 2 weeks (Q2W) at the target dose, the administration of gantenerumab as a single injection of 255 mg Q1W will be investigated in this study, to simplify the dosing regimen for patients and caregivers and to provide additional flexibility and convenience depending on individual patient's needs and preferences. In addition, Phase II Study WN29722 will evaluate the feasibility of home administration by study partners (non-professional caregivers), which is particularly relevant in conjunction with a Q1W dosing regimen.

Participants will be selected on the basis of a clinical diagnosis of probable AD (consistent with the National Institute on Aging/Alzheimer's Association [NIA-AA] Diagnostic Criteria and Guidelines for probable) or prodromal AD (consistent with the NIA-AA diagnostic criteria and guidelines for mild cognitive decline due to AD).

Eligible participants will be 50–90 years old, inclusive, and must have increased brain amyloid as indicated by positive amyloid PET scan by visual read. At the time of screening, participants must have a Mini-Mental State Examination (MMSE) score ≥ 22 points and a Clinical Dementia Rating global score (CDR-GS) of 0.5 or 1.0. To confirm objective memory impairment, participants must have a Clinical Dementia Rating (CDR) memory domain score ≥ 0.5.

In addition, all eligible participants should have a study partner (non-professional caregiver) who is willing and judged as capable of administering SC injections (exceptions can be made for participants who are able to attend weekly clinic visits or who are able to have weekly home nursing [HN]/site staff visits).

Neuroradiologic evaluation will use a standard magnetic resonance imaging (MRI) protocol (including T2*-weighted gradient−recalled echo [GRE] and fluid−attenuated inversion recovery [FLAIR]). Screening MRIs will be read by a central reader who will exclude participants with other structural causes of dementia, significant cerebral vascular pathology, more than five microbleeds, disseminated leptomeningeal hemosiderosis, or evidence of a prior cerebral macrohemorrhage.

Participants will be eligible for the study whether or not they are receiving standard-of-care symptomatic medications for AD (e.g., cholinesterase inhibitors or memantine, combination, or a medical food supplement). Intake of these medications must have been stable for ≥ 3 months prior to screening and until start of study treatment. All eligible participants have to meet eligibility criteria.

The study will consist of a screening period of up to 8 weeks for each participant who agrees to participate, signs the Informed Consent Form, and is eligible for the study. Eligible participants will then undergo the baseline visit (Day 1), when they will receive the first dose following completion of all relevant assessments. Participants will be enrolled in an open-label treatment period of 104 weeks *or 208 weeks for participants who take part in the optional 2-year extension*. The PET scans will be performed at screening (will be considered as baseline evaluation), Weeks 52, 104, *156, and 208* using florbetaben as the tracer at all sites (in exceptional circumstances, the use of flutemetamol may be acceptable at sites where florbetaben is not available, but only after prior written approval from the Sponsor). Participants will be treated according to the following dosing regimen: 120 mg Q4W (Day 1, Week 4, and Week 8), then 255 mg Q4W (Weeks 12, 16, and 20), and then 255 mg Q2W for 12 weeks (Weeks 24, 26, 28, 30, 32, and 34), followed by the target dose 255 mg Q1W (Weeks 36–*207*). Before reaching the maximum target dose (i.e., 255 mg Q1W), a minimum of three doses during the 120-mg Q4W and 255-mg Q4W dosing periods, and a minimum of six doses during 255-mg Q2W dosing period must be administered prior to uptitration. *Participants who do not take part in the optional 2-year extension will receive* the final dose of study drug *at* Week 103 *and final efficacy and PD* assessments will be performed 1 week later *at* Week 104. Participants who do not enter an extension study *after week 104* will have an additional follow-up visit 16 weeks after the Week 104 visit for safety assessments (Week 120 follow-up visit). *Participants who take part in the optional 2-year extension will receive the final dose of study drug at Week 207 and final efficacy and PD assessments will be performed 1 week later (Week 208).* Eligible participants may qualify for continued access or ongoing extension studies *after Week 208* as outlined in the protocol. *Participants who do not enter an extension study will have an additional follow-up visit 16 weeks after the Week 208 visit for safety assessments (Week 240 follow-up visit).*

Depending on the site and individual participant/caregiver suitability, participants will have the option to receive SC injections of gantenerumab at the site or at home by study staff, a home nurse, or a study partner (non-professional caregiver) after a defined period of appropriate training and supervision. *During the course of the study, an autoinjector may become available in participating countries, if approved by local health authorities and Institutional Review Boards (IRBs) (use of this device will be optional for participants who receive study treatment administration at home or at the site).* For more details on study treatment administration, see the protocol.

Participants will undergo brain MRI examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader (for more details regarding imaging-related criteria, see the protocol). Participants will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, and function. Blood samples for assessment of plasma biomarkers for AD and amyloid-related imaging abnormality (ARIA), pharmacokinetics, and exploratory genetic markers, and for the measurement of antibodies directed against gantenerumab will be obtained from all participants.

Participants who do not meet the criteria for participation in this study (screen failure) may qualify for re-screening at the investigator's discretion as described in the protocol. Participants must re-sign the consent form prior to re-screening. The investigator will record reasons for screen failure in the screening log.

NUMBER OF PARTICIPANTS

A total of 192 participants have been enrolled in participating countries. A total of 38 centers in 8 countries worldwide have participated in this study.

TARGET POPULATION

Inclusion Criteria

Participants must meet the following criteria for study entry:

- Ability to provide written consent signed by the participant (co-signed by the participant's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee [EC] or Institutional Review Board [IRB])
- Age 50–90 years old at screening, inclusive

- Probable AD dementia (consistent with NIA-AA core clinical criteria for probable AD dementia) or prodromal AD (consistent with the NIA-AA diagnostic criteria and guidelines for mild cognitive decline due to AD)
- Availability of a person (referred to as the study partner [non-professional caregiver] throughout this protocol) who:
  - Agrees to participate throughout the duration of study
  - Has sufficient cognitive and physical capacity including visual, auditory, and motor functioning, and is willing and capable of administering SC injections, as determined by the investigator (exceptions can be made for participants for which weekly clinic visits or weekly HN visits are possible)
  - 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, agrees to provide information at clinic visits (which requires study partner (non-professional caregiver) input for scale completion), and signs the necessary consent form.
  - Is fluent in the language used at the site and in 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 study duration.

    Every effort should be made to have same study partner (non-professional caregiver) participate throughout the duration of the study.
- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, clinical genotyping, and PET imaging)

  The participant should be capable of completing assessments either alone or with the help of the study partner (non-professional caregiver).
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by amyloid PET scan by qualitative read by the core/central PET laboratory
- Prodromal or mild symptomatology, as defined by a screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0, as well as a CDR memory domain score ≥ 0.5
- If the participant is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to screening and until start of study treatment
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial, unless these are related Roche sponsored non-interventional studies.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 16 weeks after the final dose of study drug

  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 acceptable 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.

Exclusion Criteria

Exclusions Related to Central Nervous System Disorders

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

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

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

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

  Nicotine use is allowed.

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

Imaging-Related Criteria

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

- According to the central MRI reader, MRI evidence of any of the following:
  - $>$2 lacunar infarcts

- Any territorial infarct >1 cm3
- Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the FLAIR sequence, which is ≥ 20 mm in any dimension

- More than five combined microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI (and not including any disseminated leptomeningeal hemosiderosis) based on the review performed by the central reader prior to start of study treatment
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

Cardiovascular Disorders

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

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

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

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

Hepatic and Renal Disorders

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

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

Infections and Immune Disorders

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

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

Metabolic and Endocrine Disorders

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

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

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

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

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

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

  A participant may be re-screened after 3 months to allow optimization of diabetic control.

Exclusions Related to Medications

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

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long-acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous administration of GV-971

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

- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no plans to initiate such medications prior to study start

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

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

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

- Anticoagulation medications within 3 months of screening with no plans to initiate any prior to start of study treatment

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

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

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

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

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

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

Other Exclusions

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

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

  This may be based on, for example, participant's sufficient education or work experience.
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Clinically significant abnormal screening blood or urine results that remain abnormal at retest
- Impaired coagulation (screening PT $> 1.2 \times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab excipients
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the participant at special risk, bias the assessment of the clinical or mental status of the participant to a significant degree, interfere with the participant's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility

  Participants who subsequently require residence in such facilities during the study may continue in the study and be followed for PD and safety data, provided that they have a study partner (non-professional caregiver) who meets the minimum requirement.
- Planned or recent (within 12 months prior to screening) exposure to ionizing radiation that in combination with the planned administrations of the radioligand would result in a cumulative exposure that exceeds recommended local guidelines

END OF STUDY

The end of the 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 for the last participant, whichever occurs later. The end of the study is expected to occur $224\ weeks$ after the last participant is enrolled.

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

LENGTH OF STUDY

The total length of the study, from screening of the first participant to the end of the study, is expected to be approximately $5\ years$.

INVESTIGATIONAL MEDICINAL PRODUCTS

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

TEST PRODUCT (INVESTIGATIONAL DRUG)

Gantenerumab

Gantenerumab will be administered by SC injection, at a dose of 120 mg Q4W (Day 1, Week 4, and Week 8), then 255 mg Q4W (Weeks 12, 16, and 20), and then 255 mg Q2W for 12 weeks (Weeks 24, 26, 28, 30, 32, and 34), followed by the target dose 255 mg Q1W (Weeks 36–*207*). Before reaching the maximum target dose (i.e., 255 mg Q1W), a minimum of three doses during the 120-mg Q4W and 255 mg Q4W dosing periods, and a minimum of six doses during the 255mg Q2W dosing period must be administered prior to uptitration.

Depending on the site and individual participant/caregiver suitability, participants will have the option to receive SC injections of gantenerumab at the site and (after a defined period of appropriate training and supervision of a caregiver) at home by study staff, home nurse, or study partner (non-professional caregiver). *During the course of the study, an autoinjector may become available in participating countries, if approved by local health authorities and IRBs (use of this device will be optional for participants who receive study treatment administration at home or at the site).* Participants will receive SC injections of gantenerumab by the investigator or an appointed qualified study staff for the first three doses of gantenerumab at the clinic. If participants have a study partner (non-professional caregiver) who is willing and judged capable of administering SC injections, this caregiver will receive training and observe dose administration at the first three dosing visits (i.e., Day 1, Week 4, and Week 8), and the injections will be done by the caregiver under staff supervision at the next four visits (i.e., Weeks 12, 16, 20, and 24). Following this supervised dosing at the clinic, subsequent dosing may be administered by the caregiver at home except for doses that coincide with a clinic visit, in which case the caregiver should administer the injection in clinic under investigator/study staff supervision. Study staff will document the outcome of the supervised administration.

The investigator will determine whether the participant is suitable for home administration by the study partner (non-professional caregiver), a home nurse, or appropriate study staff (according to local regulations).

At subsequent visits, the investigator will determine if the study partner (non-professional caregiver) continues to be suitable to perform home administration. If at any time the investigator or caregiver determines that home administration by the caregiver is unsuitable, then study drug must be administered at home or in the clinic by a home nurse or study staff.

Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or caregiver to elicit, in a non-leading way, information on medication errors and adverse events that may have occurred in the home setting. Therefore, there will be contact between the study staff and the participant/caregiver at least every 4 weeks. The study staff is encouraged to have more frequent calls with a particular participant/caregiver if considered appropriate by the investigator. In addition, participants/caregivers will be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening, or medication errors.

Training and supportive materials will be provided to the site and to the study partner (non-professional caregiver). Following the in-person instructional training and supervised administration at the site, adequate supply of gantenerumab will be provided.

For Q4W injections, a time window of ± 7 days is allowed for dosing. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. For both the Q2W injections and Q1W injections, the time window for dosing is ± 3 days. If the administration is not possible on the scheduled dosing day, the study medication should be administered as soon as possible within the time window from the scheduled dosing date. If the study drug cannot be administered within the time window, the dose should be skipped, and the participant should receive the next dose at the next scheduled time with the study medication dosing resumed in accordance with the original dosing schedule. Always return to the initial planned schedule or subsequent doses/visits.

Regardless of dose, each participant will undergo up to a total of *184 dosing visits* and home administrations as applicable in the study. Injections will be administered as one 0.8-mL (120-mg) dose or one 1.7-mL (255-mg) dose subcutaneously to the abdomen.

<u>Positron Emission Tomography Tracers</u>

All participants who are otherwise eligible at screening will be assessed for the presence of brain amyloid consistent with AD by PET imaging. The permitted amyloid PET ligands will be florbetaben (all sites) and flutemetamol (in exceptional circumstances, the use of flutemetamol may be acceptable at sites where florbetaben is not available, but only after prior written approval from the Sponsor). Florbetaben or flutemetamol will be provided in accordance with approved national and/or local standards.

According to E.U. guidance, 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 an 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.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary endpoint for this study is the change from baseline to Week 104 in brain amyloid load, as assessed by amyloid PET imaging using florbetaben as ligand and quantified on the CL conversion scale, in participants exposed to a Q1W administration regimen of SC gantenerumab. For the purposes of analysis, the screening amyloid PET scan may be considered the baseline evaluation.

Details about the primary estimand definition and corresponding statistical model specification, including handling of missing data will be described in the Statistical Analysis Plan (SAP). For example, a linear mixed-effects model with change from baseline as dependent variable, and baseline value and visit as covariate may be used.

Descriptive summary statistics of the change from baseline to Week 104 in brain amyloid CL load will also be produced. Descriptive summaries of the primary endpoint will present the mean, standard deviation, median, and minimum and maximum.

To evaluate the impact of different amyloid PET radioligands on the quantification of the PD effect of gantenerumab, a supplementary analysis will be performed similarly to the primary endpoint on the sample of participants scanned with florbetaben or flutemetamol in this study (if applicable).

DETERMINATION OF SAMPLE SIZE

Determination of sample size is relative to the sample of participants assessed by amyloid PET imaging using florbetaben. The sample size for this study is determined as the number of participants needed for the estimated change from baseline to Week 104 in amyloid PET load to fall into a 10 CL confidence interval around its true value. With a standard deviation of 25.67 CL, 192 participants are sufficient to fulfill this criterion.

The standard deviation of amyloid reduction was estimated using amyloid PET data from the ongoing studies WN25203 and WN28745 OLEs (based on a cutoff date of 14 October 2019), yielding a value of 25.67 CL.

Uncertainties of the parameters affecting the estimation (e.g., drop-out rate, study drug discontinuation rate, and standard deviation) were assumed to be equivalent to a decrease in sample size of up to around 35% and were corrected for accordingly. This drop-out rate is calculated based on the ongoing Study WN28745 OLE at Week 104. A sample size increase may be considered if factors external to the study would warrant a change to the sample size assumption.

INTERIM ANALYSIS

An interim analysis will be conducted on the latest data cut available at the time of the primary analysis for Studies WN29922 and WN39658. The maximum sample available at this timepoint with valid screening and Week 52 PET scans will be included in the analysis.

Change from baseline in amyloid PET load with the Q1W regimen will be assessed at Week 52. This may be compared with the predictions of the PK-PET model for this timepoint. At the time of the interim analysis, all available PK and safety data, responses to the Caregiver part of the home administration questionnaire, and exploratory endpoints may be reported descriptively as supporting evidence. The interim analysis will not impact the conduct of the study, i.e., early termination for futility or efficacy will not be considered.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	β–amyloid
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognition
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–hemosiderin deposition
AUC	area under the concentration–time curve
BGTS	Barkhof grand total score
BOLD	blood oxygenation level-dependent
Cav	average concentration
C_{max}	maximum concentration observed
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating global score
CFR	Code of Federal Regulations
CL	Centiloid
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSF	cerebral spinal fluid
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computed tomography
DTI	diffusion tensor imaging
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
FA	fractional anisotropy
FcγR	Fcγ receptor
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GRE	gradient-recalled echo
HbA_{1c}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
HN	home nursing
ICH	International Council for Harmonisation

Abbreviation	Definition
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
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging/Alzheimer's Association
OLE	open-label extension
PD	*p*harmacodynamic
PET	positron emission tomography
PK	*p*harmacokinetic
p-tau	phosphorylated tau
Q1W	once a week
Q2W	every 2 weeks
Q4W	every 4 weeks
RBR	Research Biosample Repository
rs-fMRI	resting-state functional magnetic resonance imaging
SAP	Statistical Analysis Plan
SUVR	standardized uptake value ratio
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

The World Health Organization estimates that approximately 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 (WHO 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 diagnosed at 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 and N-methyl-D-aspartate- receptor antagonists. These approved drugs are recognized to temporarily improve some clinical symptoms of AD in some patients but do not modify progression of the disease (Cummings et al. 2018).

Currently, one compelling therapeutic target (Graham et al. 2017) is β–amyloid (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 demonstrates activity for both major types of Aβ (Aβ1-40 and 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) and 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 anti-Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012; Klein et al. 2019), 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 (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 dosing regimens 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 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 participants enrolled in the OLEs of Studies WN25203 and WN28745. As of 1 May 2019, 363 participants had been exposed to G3 gantenerumab doses higher than 225 mg, and 309 participants 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 participants 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 (WN41874).

Based on safety results from OLE Studies WN25203 and WN28745, and on data from the PET sub studies that confirmed the pharmacodynamic (PD) effects of gantenerumab treatment (1200 mg SC Q4W) on Aβ plaque reduction (Klein et al. 2019), two pivotal multicenter, Phase III studies in participants 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; these studies are currently ongoing and are expected to be completed in 2023.

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

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

Study WN29722 is a Phase II, multicenter, open-label study in participants with early (prodromal to mild) AD to evaluate the PD effect of a once weekly (Q1W) dosing regimen on deposited amyloid, as measured by brain amyloid PET imaging at Week 52, Week 104 *(primary analysis), Week 156, and Week 208. To obtain additional long- term safety and tolerability follow-up information about the Q1W dosing regimen, as well as exploratory long-term pharmacokinetic (PK)/PD and biomarker information, participants will be followed through to the Week 208 timepoint on target dose*.

In the pivotal studies (WN29922 and WN39658), the target dose is administered as two injections of 255 mg SC Q2W (510 mg SC Q2W), delivered by a healthcare professional. In the future, a further option is administration of gantenerumab in a more flexible setting with study partners (non-professional caregivers) administering doses. In this case, when dosing is no longer connected to a need for a health care professional interaction, a Q1W home administration with a single injection of 255 mg SC may be a preferred regimen for some patients.

Study WN29722 will investigate a 255 mg Q1W administration schedule mandating only one single injection per dosing day and the option of health care professional or study party (non-professional caregiver) assisted home administration.

The dosing regimen in Study WN29722 (see Figure 4) is 120 mg Q4W (at Day 1, Week 4, and Week 8), then 255 mg Q4W (Weeks 12, 16, and 20), and then 255 mg Q2W (Weeks 24, 26, 28, 30, 32, and 34), followed by 255 mg Q1W (Weeks 36–*207*).

The regimen will differ in dosing frequency from the pivotal trials starting at Week 24; however, the total 4-weekly dose and the overall titration schedule of gantenerumab (by 4-weekly average) will remain the same as studied in the ongoing pivotal Phase III studies (WN29922 and WN39658). Both dosing regimens reach target dose of 1020 mg every 4 weeks (divided 510 mg SC Q2W in the pivotal studies or 255 mg SC Q1W in Study WN29722) at Week 36. The average exposure (area under the concentration–time curve [AUC]) is expected to be very similar based on population PK modelling from available data.

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.

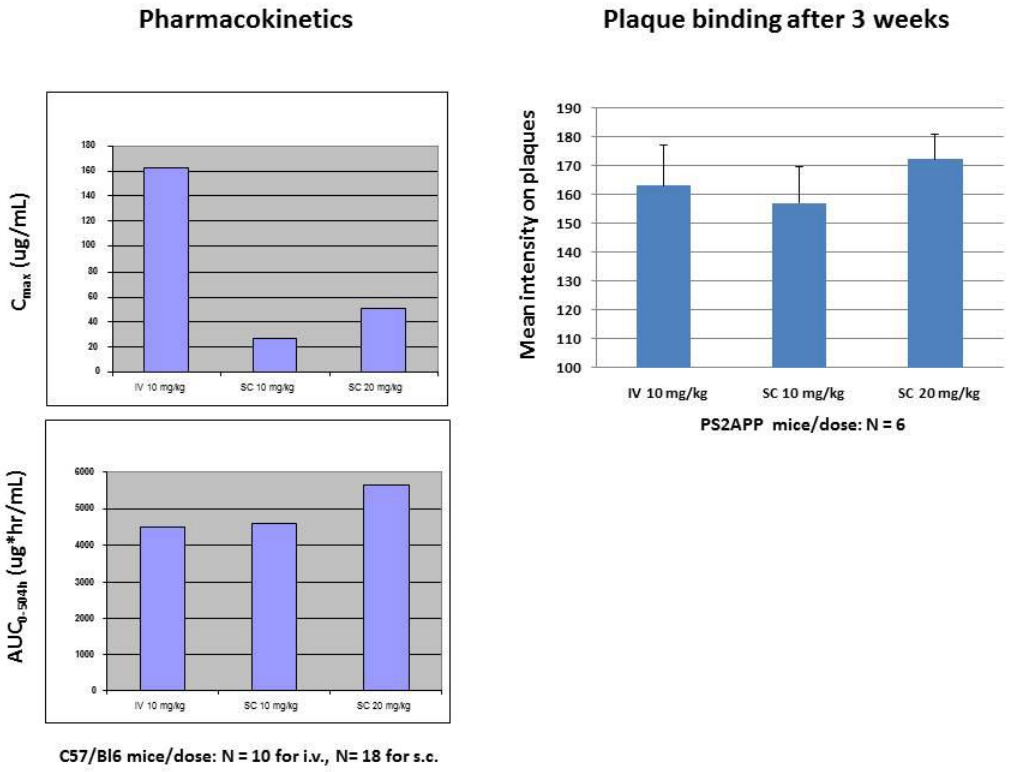
Accumulating clinical evidence supports that monoclonal anti-Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012; Sevigny et al. 2016; Klein et al. 2019), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in CSF (Ostrowitzki et 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.

The association between microglial-driven removal of aggregated brain amyloid and AUC has been shown in preclinical experiments and clinical studies. In addition, as

gantenerumab exhibits linear pharmacokinetics, the AUC from Time 0 to infinity after single dose reflects the steady state exposure after multiple doses.

Internal (Report No. 1040966, Figure 1) and external (Hang et al 2015a) information suggest that the effect of monoclonal antibodies like gantenerumab on plaque removal is driven by the total exposure and not maximum concentration observed (C_{max}). In a nonclinical study, the binding of gantenerumab on cerebral Aβ1−42 aggregates was investigated in transgenic PS2APP mice (Report No. 1040966). Plaque binding was assessed 3 weeks after administration of single doses of gantenerumab at 10 mg/kg IV, 10 mg/kg SC, or 20 mg/kg SC. This amyloid-β plaque binding data was compared with exposure data from a PK study in satellite groups treated under the same experimental conditions (Report No. 1037575). Results shown in Figure 1 indicate that while C_{max} is expectedly different across dose and administration route, minimal differences were seen in AUC at comparable doses of gantenerumab using IV or SC administration. Further, the degree of plaque binding (analogous to target engagement) was similar, regardless of administration route.

Figure 1 Gantenerumab Concentrations (Intravenous and Subcutaneous) and Plaque Binding (Mice)



AUC = area under the concentration–time curve; $AUC_{0\text{-}504h}$ = area under the concentration–time curve from 0 to 504 hours; C_{max} = maximum concentration observed; PK = pharmacokinetic.

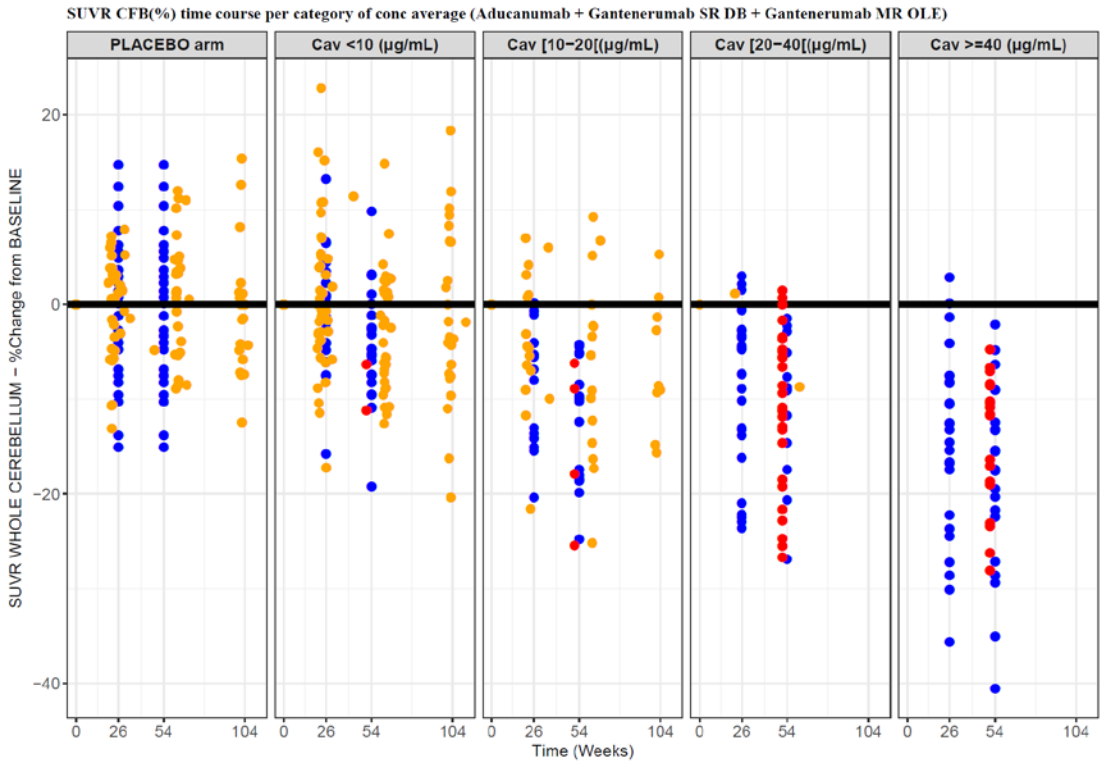
LEFT PANEL: Plasma PK parameters C_{max} (upper plot) and $AUC_{0\text{-}504h}$ (lower plot) in the satellite C57/Bl6 mice.

RIGHT PANEL: Gantenerumab binding to plaque measured 3 weeks after administration of single doses. Plaque binding across dose groups was related to AUC with no apparent correlation to C_{max} values.

In clinical trials, PET standardized uptake value ratio (SUVR) data using florbetapir reported for aducanumab (Hang et al. 2015a) and gantenerumab (WN25203) have been compared based on the average plasma concentration observed in each participant. The observed similarities in change from baseline PET SUVR values for aducanumab and gantenerumab when stratified by the average concentration (Cav) indicates that exposure is indeed the driver of plaque removal. As aducanumab was administered IV in the PRIME study, the C_{max} values were significantly higher (mean C_{max} of 250 μg/mL in the 10-mg/kg dose group) than the gantenerumab C_{max} concentrations tested in Study WN25203 (mean C_{max} of 17 μg/mL in the 225-mg dose group). The addition of actual plaque removal information from the WN28745 OLE study, in which doses of up

to 1200 mg have been tested, matched the results observed with aducanumab (see Figure 2).

Figure 2 Amyloid PET SUVR Percentage Change from Baseline by Time per Category of Plasma Concentration



Cav = average concentration; DB = double blind; CFB = change from baseline; MR = Marguerite RoAD (WN28745); OLE = open-label extension; PET = positron emission tomography; SR = SCarlet RoAD (WN25203); SUVR = standardized uptake value ratio.

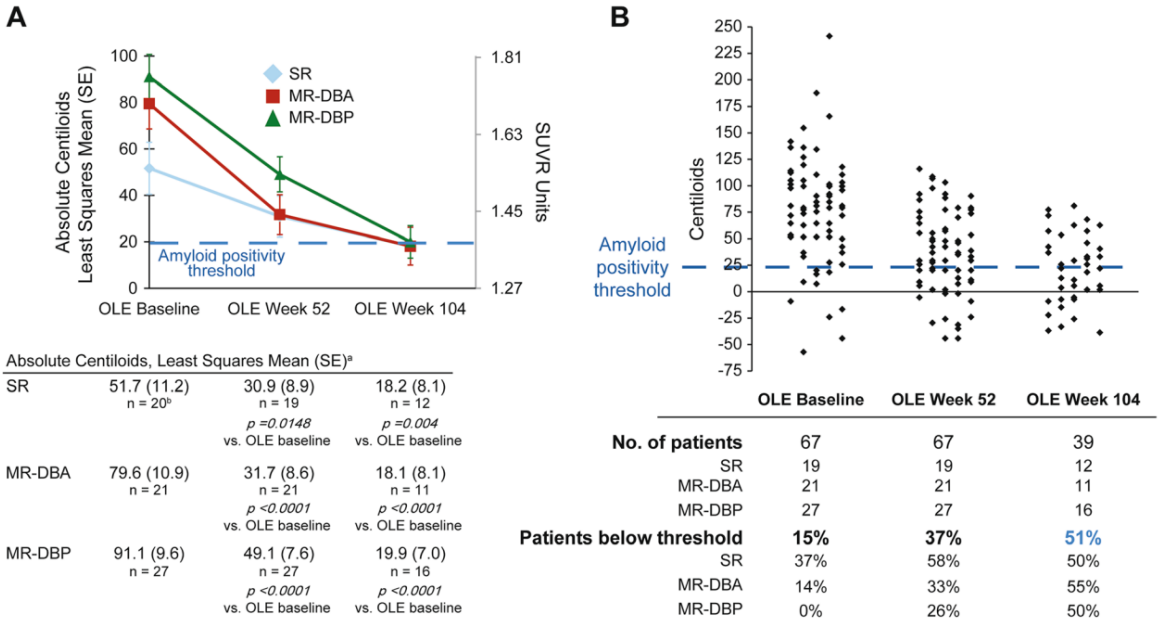
Note: Gantenerumab (Study WN25203 DB) data is shown in yellow, aducanumab (PRIME Phase 1b) data is shown in blue, and gantenerumab (Study WN28745 OLE) data is shown in red. Five different average concentration categories are displayed (from left to right): placebo, <10 µg/mL, 10−20 µg/mL, 20−40 µg/mL, and >40 µg/mL.

In line with the Sponsor`s hypothesis, that exposure (AUC) is the primary driver for amyloid removal, the authors of a recent aducanumab publication (Hang et al. 2015b) concluded that amyloid plaque removal was significantly correlated with aducanumab serum exposure Cav. Important to note is that amyloid reduction during treatment happens on a time scale of months, whereas fluctuations in plasma concentrations (peak-to-trough) have a time scale of days, supporting the hypothesis that the total exposure (or Cav) rather than the peak concentration is the main driver for amyloid removal.

Based on the established similarities between gantenerumab and aducanumab, a model characterizing the relationship between plasma drug concentration (PK) and PET response (i.e., the PD effect on amyloid load in the brain) was derived from both gantenerumab Study WN25203 data and aducanumab PRIME study data to determine the target dose of gantenerumab for the WN25203 OLE and WN28745 OLE studies. In the OLE studies, gantenerumab 1200 mg SC Q4W was predicted to achieve plasma levels comparable to aducanumab 10 mg/kg IV Q4W and to be associated with a comparable amyloid brain reduction, which, in the case of aducanumab, was associated with a statistically significant clinical effect after one year of treatment. To minimize the occurrence of ARIA–edema/effusion (ARIA-E) while achieving the target dose within a reasonable time frame, several titration schedules have been explored in the WN25203 OLE and WN28745 OLE studies.

Gantenerumab PK-PET models of amyloid reduction have been confirmed by PET data using florbetapir F 18 (Amyvid™) from the OLE studies (Klein et al. 2019b) and a marked and consistent reduction of amyloid load in participants receiving high-dose gantenerumab (1200 mg SC Q4W) was observed (Figure 3; Klein et al. 2019). An important anchor for interpreting PET results is the threshold for amyloid positivity, which is the quantitative threshold that best discriminates pathologically verified absence of plaques or sparse plaques from moderate to frequent plaques. A Centiloid value (CL) of 24 is generally recognized as the amyloid positivity threshold for florbetapir (Klein et al. 2019). Results from these ongoing studies show that following two years of treatment, 51% of subjects achieved below-threshold PET SUVR signals based on quantitative measures (see Figure 3, panel B).

Figure 3 Marked and Consistent Reduction of Amyloid Load in Participants Receiving High-Dose Gantenerumab



Absolute Centiloids, Least Squares Mean (SE)[a]			
SR	51.7 (11.2) n = 20[b]	30.9 (8.9) n = 19 *p =0.0148* vs. OLE baseline	18.2 (8.1) n = 12 *p =0.004* vs. OLE baseline
MR-DBA	79.6 (10.9) n = 21	31.7 (8.6) n = 21 *p <0.0001* vs. OLE baseline	18.1 (8.1) n = 11 *p <0.0001* vs. OLE baseline
MR-DBP	91.1 (9.6) n = 27	49.1 (7.6) n = 27 *p <0.0001* vs. OLE baseline	19.9 (7.0) n = 16 *p <0.0001* vs. OLE baseline

	OLE Baseline	OLE Week 52	OLE Week 104
No. of patients	67	67	39
SR	19	19	12
MR-DBA	21	21	11
MR-DBP	27	27	16
Patients below threshold	**15%**	**37%**	**51%**
SR	37%	58%	50%
MR-DBA	14%	33%	55%
MR-DBP	0%	26%	50%

MR-DBA = Marguerite RoAD (WN28745) pretreated subgroup; MR-DBP = Marguerite RoAD (WN28745) non-pretreated subgroup; OLE = open-label extension; SR = SCarlet RoAD (WN25203) subgroup; SUVR = standardized uptake value ratio.

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

In summary, data from nonclinical and clinical studies suggest that target engagement as shown by PET SUVR amyloid reduction depends on average exposure rather than C_{max}. Hence, a change in dosing frequency while maintaining average exposure is expected to have the same effect on amyloid removal. Evidence suggests that total dose, rather than dosing frequency, drives the treatment effect of gantenerumab to stimulate microglial−driven removal of aggregated brain amyloid. Therefore, it is expected that the target dose of 510 mg SC Q2W administered in the ongoing Phase III studies can also be administered as 255 mg SC Q1W without altering the treatment effect.

1.3.2 Benefit–Risk Rationale

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 in clinical studies.

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

Refer to Section 5.1.1 for information on anticipated risks for gantenerumab and risk mitigation measures, including guidelines for managing adverse events associated with gantenerumab.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of gantenerumab may be found in the Gantenerumab Investigator's Brochure.

Overall Benefit–Risk Summary

The benefit–risk assessment of gantenerumab treatment in Study WN29722 is based on the following:

- Gantenerumab has shown evidence of amyloid plaque reduction (i.e., observed evidence of brain amyloid reduction) and, thus, shows potential benefit in slowing the progression of AD.
- Nonclinical and clinical studies suggest that target engagement as shown by PET SUVR amyloid reduction is not C_{max}-driven but rather depends on average exposure. Therefore, it is expected that the target dose of 510 mg SC Q2W administered in the ongoing Phase III studies can also be administered as 255 mg SC Q1W without altering the treatment effect.
- Results from the double-blind portions, as well as from the OLEs of Studies WN25203 and WN28745, showed that ARIA findings are mostly asymptomatic, non-serious, of mild severity, and do not require permanent cessation of treatment. ARIAs are manageable with MRI monitoring and dose intervention algorithms, as detailed in Section 5.1.3.
- No new safety signals have been identified from the ongoing Phase III studies with gantenerumab with doses of up to 510 mg Q2W, which supports the safety of continued administration of gantenerumab uptitrated to the target dose in the current and planned studies, including Study WN29722. A higher ARIA risk is not expected in Study WN29722 compared with the Q2W regimen in the ongoing Phase III studies because the Q1W regimen will provide the same gantenerumab exposure with a lower C_{max}. The Sponsor's Internal Monitoring Committee (IMC) 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–hemosiderin deposition (ARIA-H), and ISRs and will make appropriate recommendations (see Section 3.1.2).
- Study WN29722 will provide the opportunity to enable an additional dosing regimen (i.e., a single injection of 255 mg SC Q1W), which will benefit individuals who prefer this approach.
- The overall risk of compromising the study effectiveness by introducing flexible care options, including home administration by study partners (non-professional caregivers), is deemed to be low. Mitigations are put in place to closely monitor and control the proper administration of the medication throughout the study. These include caregiver training, physician assessment, and investigators' checks. The

benefit is to provide a convenient option of home administration for the caregivers and the patients who would like to take advantage of this opportunity.

- Based on its mechanism of action, there is no reason to believe that gantenerumab administration would compromise the immunologic reaction of the body. 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 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 or more severe coronavirus disease 2019 (COVID-19) outcomes. Whereas people with AD, because of advanced age, may be in a higher-risk group for COVID-19, participation in Study WN29722 is not expected to increase that risk.
- Based on the available information, no interactions between gantenerumab *or the PET tracers used in this study* 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 the target dose of gantenerumab of 255 mg SC Q1W supports a clinical trial with this dosing regimen in the population with early (prodromal to mild) AD.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacodynamics, pharmacokinetics, and safety of gantenerumab in participants with early (prodromal to mild) AD. Specific objectives and corresponding endpoints for the study are outlined in Table 1 below.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the PD effect of a Q1W dosing regimen of gantenerumab on brain amyloid load as determined by PET imaging in participants with early (prodromal to mild) AD	• The change from baseline to Week 52 and to Week 104 in deposited amyloid as measured by brain amyloid PET CL levels [a]
Secondary Objective	**Corresponding Endpoint**
• To evaluate caregiver overall satisfaction and confidence with home administration	• Responses to home administration questionnaire (Caregiver) up to Week 52, Week 104 [a] *and Week 208* [b]
Safety Objective	**Corresponding Endpoints**
• To assess the safety of gantenerumab in participants with early (prodromal to mild) AD	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurologic systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
PK/PD Objectives	**Corresponding Endpoints**
• To characterize the PK profile of gantenerumab using a new titration scheme and especially at the Q1W dosing frequency • To assess the PD effect of the dosing frequency (e.g., Q1W, Q2W) on brain amyloid	• Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints • The influence of dosing frequency information on the performance of a quantitative PK-PD model developed based on PK and PET from this and previous studies (e.g., WN29922 and WN39658) [a]
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the pharmacodynamic effect of gantenerumab at the Q1W dosing regimen on plasma and MRI *and PET* biomarkers	• Change from baseline in plasma biomarkers (including, but not limited to, phosphorylated tau and NFL) to Week 104 *and Week 208* [b] (see Section 4.5.9) • Change from baseline to Week 104 *and Week 208* [b] in functional brain connectivity, as measured by resting-state functional MRI (where available) • Change from baseline to Week 104 *and Week 208* [b] in integrity of white matter, as measured by DTI-MRI (where available) • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants. • *The change from baseline up to Week 208 in deposited amyloid as measured by brain amyloid PET CL levels* [b]

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• To compare the effect of a Q1W to a Q2W dosing regimen on amyloid reduction using external controls • To evaluate the effects of gantenerumab at the Q1W dosing on cognitive and functional endpoints • To evaluate patient overall satisfaction with at home administration	• The change from baseline to Week 52 and to Week 104 in deposited amyloid as measured by brain amyloid PET compared with the change in the pivotal WN29922 and WN39658 studies • The change from baseline to Week 104 *and Week 208* [b] in the following: − The CDR-SOB − MMSE total score − ADAS-Cog11 and ADAS-Cog13 − Verbal Fluency Task − Coding − ADCS-ADL • Responses to home administration questionnaire (Patient) up to Week 104 *and Week 208* [b]

AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group- Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CL = Centiloid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NFL = neurofilament light chain; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; Q1W = once a week; Q2W = every 2 weeks; Q4W = every 4 weeks, *SAP = Statistical Analysis Plan*.

[a] The primary analysis is at Week 104 and details concerning interim analyses *which will consider Week 52 outcomes* are described in Section 3.3.5 and 6.9 *and the SAP*.

[b] *Week 208 assessments are optional and only required if participants take part in the 2-year extension*

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

Study WN29722 is a Phase II, multicenter, open-label, single arm, PD study in participants with early (prodromal to mild) AD to evaluate the effect of a Q1W dosing regimen on deposited amyloid as measured by change from baseline to Weeks 52 and 104 in brain amyloid PET. The dosing regimen being evaluated in current Phase III studies (WN29922 and WN39658) is gantenerumab 120 mg SC Q4W for 12 weeks, followed by 255 mg SC Q4W for 12 weeks, and 510 mg SC Q4W for 12 weeks, prior to reaching the target dose of 510 mg SC Q2W. As an alternative to administering two 255-mg injections Q2W at the target dose, the administration of gantenerumab as a single injection of 255 mg Q1W will be investigated in this study, to simplify the dosing regimen for patients and caregivers and to provide additional flexibility and convenience depending on individual patient's needs and preferences. In

addition, Phase II Study WN29722 will evaluate the feasibility of home administration by study partners (non-professional caregivers), which is particularly relevant in conjunction with a Q1W dosing regimen.

A total of 192 participants have been enrolled in participating countries. A total of 38 centers in 8 countries worldwide have participated in this study.

Participants will be selected on the basis of a clinical diagnosis of probable AD (consistent with the National Institute on Aging/Alzheimer's Association [NIA-AA] Diagnostic Criteria and Guidelines for probable AD; McKhann et al. 2011) or prodromal AD (consistent with the NIA-AA diagnostic criteria and guidelines for mild cognitive decline due to AD; Albert et al. 2011).

Eligible participants will be 50–90 years old, inclusive, and must have increased brain amyloid as indicated by positive amyloid PET scan by visual read. At the time of screening, participants must have a Mini-Mental State Examination (MMSE) score $\geq$22 points and a Clinical Dementia Rating global score (CDR-GS) of 0.5 or 1.0. To confirm objective memory impairment, participants must have a Clinical Dementia Rating (CDR) memory domain score $\geq$0.5.

In addition, all eligible participants should have a study partner (non-professional caregiver) who is willing and judged as capable of administering SC injections (exceptions can be made for participants who are able to attend weekly clinic visits or who are able to have weekly home nursing [HN]/site staff visits).

Neuroradiologic evaluation will use a standard MRI protocol (including T2*-weighted gradient−recalled echo [GRE] and fluid−attenuated inversion recovery [FLAIR]). Screening MRIs will be read by a central reader who will exclude participants with other structural causes of dementia, significant cerebral vascular pathology, more than five microbleeds, disseminated leptomeningeal hemosiderosis, or evidence of a prior cerebral macrohemorrhage.

Participants will be eligible for the study whether or not they are receiving standard-of-care symptomatic medications for AD (e.g., cholinesterase inhibitors or memantine, combination, or a medical food supplement). Intake of these medications must have been stable for $\geq$3 months prior to screening and until start of study treatment. All eligible participants have to meet eligibility criteria as detailed in Section 4.1.

The study will consist of a screening period of up to 8 weeks for each participant who agrees to participate, signs the Informed Consent Form, and is eligible for the study. Eligible participants will then undergo the baseline visit (Day 1), when they will receive the first dose following completion of all relevant assessments. Participants will be enrolled in an open-label treatment period of $up\ to\ 208\ weeks$. The PET scans will be

performed at screening (will be considered as baseline evaluation), Weeks 52,104*, 156, and 208*, using florbetaben as the tracer at all sites (in exceptional circumstances, the use of flutemetamol may be acceptable at sites where florbetaben is not available, but only after prior written approval from the Sponsor). Participants will be treated according to the following dosing regimen: 120 mg Q4W (Day 1, Week 4, and Week 8), then 255 mg Q4W (Weeks 12, 16, and 20), and then 255 mg Q2W for 12 weeks (Weeks 24, 26, 28, 30, 32, and 34), followed by the target dose 255 mg Q1W (Weeks 36–*207*). Before reaching the maximum target dose (i.e., 255 mg Q1W), a minimum of three doses during the 120-mg Q4W and 255-mg Q4W dosing periods, and a minimum of six doses during 255-mg Q2W dosing period must be administered prior to uptitration. *Participants who opt for the 2-year extension of Study WN29722 will receive the final dose of study drug at Week 207. Final PD and efficacy assessments will be performed 1 week later at Week 208. Eligible participants may qualify for continued access or ongoing extension studies as outlined in Section 4.3.5. Participants who do not enter an extension study will have an additional follow-up visit 16 weeks after the Week 208 visit for safety assessments (Week 224 follow-up visit).*

Participants who do not opt for the 2-year extension of Study WN29722, will receive the final dose of study drug at Week 103. Final PD and efficacy assessments will be performed 1 week later at Week 104. Eligible participants may qualify for continued access or ongoing extension studies as outlined in Section 4.3.5. Participants who do not enter an extension study will have an additional follow-up visit 16 weeks after the Week 104 visit for safety assessments (Week 120 follow-up visit).

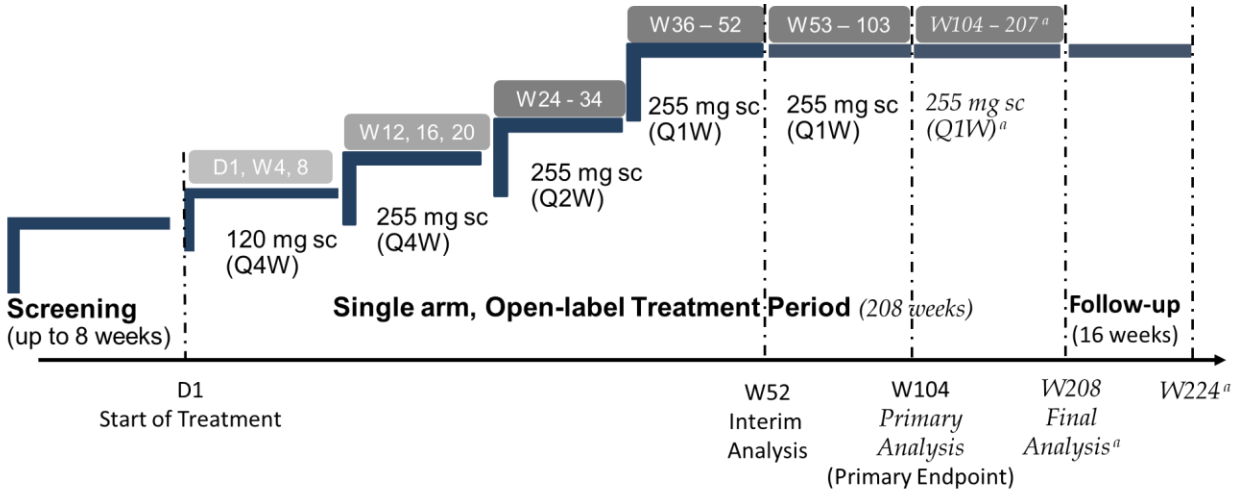
Depending on the site and individual participant/caregiver suitability, participants will have the option to receive SC injections of gantenerumab at the site or at home by study staff, a home nurse, or a study partner (non-professional caregiver) after a defined period of appropriate training and supervision. For more details on study treatment administration, see Section 4.3.2.1.

Participants will undergo brain MRI examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader (for more details regarding imaging-related criteria, see Section 4.1.2.2). Participants will also undergo standard tests to monitor safety (blood tests and ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, and function. Blood samples for assessment of plasma biomarkers for AD and ARIA, pharmacokinetics, and exploratory genetic markers, and for the measurement of antibodies directed against gantenerumab will be obtained from all participants.

Participants who do not meet the criteria for participation in this study (screen failure) may qualify for re-screening at the investigator's discretion as described in Section 4.6. Participants must re-sign the consent form prior to re-screening. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

Figure 4 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 4 Study Schema



D = day; Q1W = once a week; Q2W = every 2 weeks; Q4W = every 4 weeks; W = week.

[a] *Treatment period W104–207 is optional and only for participants who consent to the optional 2-year extension.*

3.1.2 Internal Monitoring Committee

The incidence, severity, and nature of adverse events, serious adverse events, ARIA-E and ARIA-H, and laboratory abnormalities will be assessed on a regular basis by the Sponsor's IMC, as documented in the IMC Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the 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 for the last participant, whichever occurs later. The end of the study is expected to occur *224 weeks* after the last participant is enrolled.

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

The total length of the study, from screening of the first participant to the end of the study, is expected to be approximately *5 years*.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Gantenerumab Dose and Titration Schedule

The dosing regimen in the pivotal WN29922 and WN39658 studies is as follows: 120 mg Q4W (Day 1, Week 4, and Week 8), then 255 mg Q4W (Weeks 12, 16, and 20), and then 510 mg Q4W (Weeks 24, 28, and 32), followed by 510 mg Q2W (Weeks 36–103). This schedule enables titration to target dose within 9 months, with

predicted overall ARIA-E rate of approximately 26% based on the current ARIA-E hazard model. The low starting doses and gradual increase in dosing (i.e., slow titration schedule) are expected to reduce the risk of ARIA-E for both apolipoprotein E (APOE) carriers and non-carriers. A higher ARIA risk is not expected in Study WN29722 compared with the Q2W regimen in the ongoing Phase III studies because the Q1W regimen will provide the same gantenerumab exposure with a lower C_{max}.

The dosing regimen in the current study (WN29722) will start with 120 mg Q4W (Day 1, Week 4, and Week 8), followed by 255 mg Q4W (Weeks 12, 16, and 20), and 255 mg Q2W (Weeks 24, 26, 28, 30, 32, and 34), followed by the target dose 255 mg Q1W (Weeks 36–*207*).

The regimen in the current study will differ in dosing frequency from the pivotal trials from Week 24 (with the start of 255 mg Q2W dosing). The total monthly dose and the overall length of the titration schedule of gantenerumab will remain the same as studied in the ongoing pivotal WN29922 and WN39658 studies.

Moreover, as presented in Section 1.2.1, data from nonclinical and clinical studies suggest that target engagement as shown by PET SUVR amyloid reduction is not C_{max}-driven but rather depends on average exposure. The target dose of 255 mg Q1W in this study is therefore expected to have the same effect on amyloid removal as the regimen in the pivotal studies.

To provide patients and caregivers with a more flexible alternative to clinic visits, the feasibility of health care professional or study partner (non-professional caregiver) assisted home dosing will be assessed as part of the study.

3.3.2 Rationale for Study Population

To compare the data obtained in this study with the Q2W dosing regimen in the ongoing pivotal Studies WN29922 and WN39658 in terms of change in PET amyloid load, the study population should be similar to the population in the pivotal studies.

For this reason, participants in this study are required to meet standard research criteria for mild AD (according to the NIA-AA research criteria and guidelines for AD; see Appendix 3) or prodromal AD (according to the NIA-AA research criteria and guidelines for mild cognitive impairment (MCI) due to AD; see Appendix 4). Note that the terms “prodromal AD” and “MCI due to AD” are considered to refer to the same population in this study and are defined according to NIA-AA research criteria and guidelines for MCI due to AD. Thus, participants with prodromal AD will present with documented objective evidence of deficit in one cognitive domain. Participants with mild AD must present with documented deficits in at least two cognitive domains and evidence of functional decline. Overall, the population will have a MMSE between 22 and 30 (inclusive) points and a CDR-GS of 0.5 or 1.0. The MMSE score provides evidence of no more than mild disease severity and the CDR-GS score indicates that the

participants have prodromal AD or cognitive and functional deficits consistent with mild AD.

Gantenerumab is an antibody that targets Aβ. Thus, the study population should have documented evidence of amyloid pathology. This participant selection approach is consistent with the NIA-AA research diagnostic criteria and guidelines for AD as well as with the Qualification Opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use on the use of CSF biomarkers for enrichment of trials in mild to moderate AD dementia (2012), and the U.S. Food and Drug Administration (FDA) draft guidance for early AD (2013). Although the FDA's guidance refers to the early stage of AD in which individuals present with clinical MCI, biomarkers of amyloid pathology are expected to add value to participant selection in mild AD studies, especially for anti-amyloid treatments (McKhann et al. 2011; Dubois et al. 2014, 2016). Biomarker enrichment is important for anti-amyloid therapy clinical trials because some results of early trials have demonstrated that approximately 20% of participants who are enrolled in trials based on a clinical diagnosis of AD alone may not have underlying amyloid pathology as assessed by amyloid PET (Doody et al. 2014; Salloway et al. 2014).

For enrollment in this study, biomarker evidence of Aβ deposition will be assessed by a centralized visual assessment of PET amyloid imaging, using florbetaben for participants at all sites (in exceptional circumstances, the use of flutemetamol may be acceptable at sites where florbetaben is not available, but only after prior written approval from the Sponsor).

3.3.3 Rationale for Open Label Design

The primary objective of this study is to evaluate the PD effect of a gantenerumab Q1W dosing regimen on brain amyloid load as determined by PET in participants with early (prodromal to mild) AD. Because the primary endpoint, change from baseline to Week 104 in deposited amyloid, is an objective biomarker endpoint, and because all cognitive and functional endpoints will be exploratory only, the study has an open-label design.

3.3.4 Rationale for Treatment Duration

A 2-year treatment duration has been selected as the most appropriate duration for assessment of the primary endpoint (change from baseline [Day 1] to Week 104 in deposited amyloid as shown on brain amyloid PET), as the majority of participants in the WN25203 OLE and WN28745 OLE studies achieved below-threshold PET SUVR signals based on quantitative measures (see Figure 3 and Section 1.3). To obtain additional timepoints for modeling and be in alignment with the schedule of imaging assessments in the pivotal Studies WN29922 and WN39658, PET scans will also be obtained at Week 52.

3.3.4.1 *Rationale for Optional Treatment Extension*

To obtain additional long-term safety and tolerability information about the Q1W dosing regimen, as well as additional exploratory long-term PK/PD and biomarker information, the study will be extended to 208 weeks in total.

3.3.5 Rationale for Interim Analysis

An interim analysis of PD parameters will be conducted on the latest data cut available at the time of the primary analysis for Studies WN29922 and WN39658. This analysis will include change from baseline in amyloid PET load at Week 52, and available PK, safety, and home administration data will be reported descriptively as supporting evidence. The PK/PD models, using the titration scheme of the pivotal WN29922 and WN39658 studies and of the current study (WN29722), predict average amyloid reductions of approximately 35 CL and 67 CL at Weeks 52 and 104, respectively. At Week 24, the time when the dosing regimens for this study begin to differ from the pivotal studies, the predicted average amyloid reduction will be in the range of 10 CL, i.e., significantly lower than the later timepoints. An interim analysis at 52 weeks will therefore provide meaningful information on the similarity or differences in amyloid reduction between different dosing regimens.

This analysis is conducted to provide data regarding the Q1W regimen that may be included as part of the initial filing if appropriate.

3.3.6 Rationale for Primary Outcome Measure: Brain Amyloid Load as Determined by Positron Emission Tomography

The use of amyloid PET to measure reduction in amyloid has been selected as a primary endpoint in this study. This approach is justified by the following:

- Substantial evidence supports the hypothesis that the primary mechanism of action for gantenerumab is clearance of Aβ plaques via high-affinity binding to aggregated Aβ, causing microglial activation and phagocytosis.
- Amyloid PET is a well-validated, quantitative method of measuring plaque burden in vivo in clinical studies of gantenerumab in AD and is therefore considered an accurate instrument for measuring potential differences in the PD effect of different dosing regimens.
- Clinical studies of gantenerumab and molecules with similar mechanisms of action have demonstrated significant time- and dose-dependent amyloid plaque reduction measured by amyloid PET, matching empirically derived, time- and AUC-dependent PK/PD models.
- Amyloid PET is a highly accurate measure of the PD effect of gantenerumab and is also a highly relevant biomarker based on recent group- and participant-level associations between amyloid PET reduction and clinical benefit observed with gantenerumab, aducanumab, and BAN2401.

To date, numerous in vitro, nonclinical, and clinical studies have demonstrated high-affinity binding of gantenerumab to aggregated forms of Aβ and the plaque-lowering capability of this antibody. While the exact mechanism of action is not fully understood, evidence supports the hypothesis that gantenerumab clears amyloid plaques via Fcγ receptor (FcγR)-mediated microglial recruitment and phagocytosis, followed by lysosomal degradation as demonstrated for differential human macrophages (Bohrmann et al. 2012; Ostrowitzki et al. 2017). A concentration-dependent reduction of amyloid plaque load has been seen via immunohistochemistry and quantitative image analysis ex vivo in post-mortem AD brain tissue slices. Nonclinical in vivo PS2APP mouse studies have demonstrated dose-dependent binding of gantenerumab to amyloid plaques, and triple-labeled pathology studies have shown co-localization of gantenerumab bound to amyloid plaque adjacent to microglia cells.

There is a large body of evidence showing that amyloid PET accurately quantifies in vivo amyloid plaque load in the brain (Klunk et al. 2004; Vandenberghe et. al. 2013). Quantitative SUVR has been shown to have high diagnostic accuracy in distinguishing pathologically confirmed amyloid burden levels of no plaques to sparse plaques from moderate to frequent plaques (Clark et al. 2011; Bullich et al. 2017). The SUVR quantification method also correlates well on a continuous scale with multiple histopathology measures including global highest neuritic plaque count and Aβ antibody immunohistochemistry (Clark et al. 2011; Choi et al., 2012; Joshi et al. 2012). Test/retest data of amyloid tracers show a low average coefficient of variation (worst case 1.94% using a whole cerebellum (Joshi et al. 2012; QIBA 2018).

To reduce potential variability resulting from the use of different amyloid PET ligands, florbetaben will be used as the amyloid PET ligand for screening and longitudinal assessments by all sites (in alignment with the ongoing Phase III gantenerumab Studies WN29922 and WN39658). In exceptional circumstances, the use of flutemetamol may be acceptable at sites where florbetaben is not available, but only after prior written approval from the Sponsor.

Recently, a CL methodology has been proposed to translate SUVR values to a more intuitive scale that is less dependent on amyloid tracer, imaging processing methodology, and SUVR reference region (Klunk et al. 2015). The CL scale is a linear regression transform of SUVR with anchors at 0 and 100, representing the mean amyloid burden of a young control and a typical AD participant group, respectively.

3.3.7 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being utilized to minimize participant burden and yet provide an adequate characterization of the population PK profile of gantenerumab, especially at the Q1W dosing regimen. The PK data will be combined with available data from other gantenerumab studies (e.g., WN25203 OLE, WN28745 OLE, WN25203, WN28745) and will be used to assess exposure-response relationships for relevant

imaging, plasma PD biomarkers, and efficacy and safety outcomes in participants with early (prodromal to mild) AD, as appropriate.

3.3.8 Rationale for Biomarker Assessments

3.3.8.1 Positron Emission Tomography

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

As detailed in Section 3.3.6, quantitative amyloid PET is an accurate biomarker of amyloid plaque burden for assessing target engagement and PD effect of gantenerumab treatment. Change in amyloid burden as measured by amyloid PET will provide relevant data to assess potential differences in PD effect due to different dosing regimens.

3.3.8.2 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 participants with AD (e.g., enlarged ventricles, decreased cortical thickness, decreased total brain volume, and hippocampal atrophy), and there is evidence for strong correlations between these imaging biomarkers and functional cognitive measures (Li and Wahlund 2011). Based on volumetric MRI measurements, the two most established markers of disease progression in longitudinal observational studies are hippocampal and whole brain atrophy (Fox et al. 2000, 2005; Jack et al. 2010), with ventricular expansion a related quantitative marker.

Therefore, to quantify the effects of gantenerumab on neurodegeneration, whole brain volume, ventricular enlargement, and regional brain volume, changes will be assessed at screening and following treatment. All MRI reads and volume measures will be conducted by the central reader.

In addition to the structural brain volume changes, changes in brain functioning of participants will be assessed using a blood oxygenation level-dependent (BOLD) resting-state functional MRI (rs-fMRI) procedure (at sites where this procedure is available) with a paradigm-free procedure (Greicius et al. 2004; Filippi and Agosta 2011). Increased concentrations of Aβ in the brains of participants with AD contribute to neuronal degeneration in the brain over time and have been associated with reduced functional connectivity of various brain networks using rs-fMRI (Sheline et al. 2010; Binnewijzend et al. 2012; Brier et al. 2012; Sheline and Raichle 2013). Resting-state functional connectivity has been found to be decreased in brain regions such as the

hippocampus, the default mode network (regions such as precuneus, anterior cingulate, and parietal and temporal cortices), and cortical regions in which the functional connectivity is continuously decreased as disease progresses. It has also been found to be decreased in cognitively normal elderly participants with brain amyloid deposition (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 participants with AD (Goveas et al. 2011; Solé-Padullés et al. 2013). Increased brain functional connectivity was found already after 3 months of treatment with donepezil, which correlated with changes in cognitive measures such as the Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog; Goveas et al. 2011; Solé-Padullés et al. 2013). Therefore, therapeutic interventions, which act to remove Aβ from the brains of participants with AD, may help to reverse the altered functional connectivity presumably caused by the accumulation of Aβ in the brain.

The integrity of white matter tracts will be assessed prior to and after treatment with gantenerumab using diffusion tensor imaging (DTI)-MRI techniques. The 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 AD groups 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 before and after treatment with gantenerumab.

3.3.8.3 Blood Biomarkers

AD is a heterogeneous disease. Therefore, all participants may not be equally likely to benefit from treatment with gantenerumab. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those participants who are most likely to respond to gantenerumab. PD biomarkers will be assessed to demonstrate evidence of biologic activity of gantenerumab in participants, to support selection of a recommended dose and dosing regimen, and to inform potential revisions to the PK sample collection schedule. Further details on biomarkers are described in Section 4.5.10.4.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing

adverse events or can lead to improved adverse event monitoring or investigation. For this study, 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 for this study.

3.3.9 Rationale for Home Administration Questionnaire

Administering an injection at home will be a new experience for many caregivers and it is important to gather feedback on their comfort level doing so. The home administration questionnaire will capture confidence, ease of use, convenience, and overall satisfaction with administering the medication from the study partner (non-professional caregiver) perspective (as a secondary outcome) and convenience and satisfaction from the patient perspective (as an exploratory outcome). Patients with more advanced disease may have difficulty responding to questionnaires and their responses may not be reliable. Nevertheless, the study will attempt to capture responses from all patients. It may be necessary to limit analysis of this endpoint to patients who are more cognitively able.

4. MATERIALS AND METHODS

4.1 PARTICIPANTS

This study has enrolled 192 participants with increased brain amyloid burden (defined according to PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA-AA criteria during the global enrollment phase. Additional criteria are defined in Sections 4.1.1 and 4.1.2.

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

4.1.1 Inclusion Criteria

Participants must meet the following criteria for study entry:

- Ability to provide written consent signed by the participant (co-signed by the participant's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee [EC] or Institutional Review Board [IRB])
- Age 50–90 years old at screening, inclusive
- Probable AD dementia (consistent with NIA-AA core clinical criteria for probable AD dementia; McKhann et al. 2011) or prodromal AD (consistent with the NIA-AA

diagnostic criteria and guidelines for mild cognitive decline due to AD; Albert et al. 2011)

- Availability of a person (referred to as the study partner [non-professional caregiver] throughout this protocol) who:
  - Agrees to participate throughout the duration of study
  - Has sufficient cognitive and physical capacity including visual, auditory, and motor functioning, and is willing and capable of administering SC injections, as determined by the investigator (exceptions can be made for participants for which weekly clinic visits or weekly HN visits are possible)
  - 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, agrees to provide information at clinic visits (which requires study partner (non-professional caregiver) input for scale completion), and signs the necessary consent form.
  - Is fluent in the language used at the site and in 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 study duration.

    Every effort should be made to have same study partner (non-professional caregiver) participate throughout the duration of the study.
- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, clinical genotyping, and PET imaging)

  The participant should be capable of completing assessments either alone or with the help of the study partner (non-professional caregiver).
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by amyloid PET scan by qualitative read by the core/central PET laboratory
- Prodromal or mild symptomatology, as defined by a screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0, as well as a CDR memory domain score ≥ 0.5
- If the participant is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to screening and until start of study treatment
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial, unless these are related Roche-sponsored non-interventional studies.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate

of < 1% per year during the treatment period and for at least 16 weeks after the final dose of study drug

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 acceptable 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.

4.1.2 Exclusion Criteria

4.1.2.1 Exclusions Related to Central Nervous System Disorders

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

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

  Participants with asymptomatic developmental venous anomalies may be eligible after discussion with the Medical Monitor.
- History or presence of posterior reversible encephalopathy syndrome

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

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

  Nicotine use is allowed.

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

4.1.2.2 Imaging-Related Criteria

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

- According to the central MRI reader, MRI evidence of any of the following:
  - $>$ 2 lacunar infarcts
  - Any territorial infarct $>$ 1 cm3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the FLAIR sequence, which is $\geq$ 20 mm in any dimension
- More than five combined microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI (and not including any disseminated

leptomeningeal hemosiderosis) based on the review performed by the central reader prior to start of study treatment

- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

4.1.2.3 Cardiovascular Disorders

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

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

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

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

4.1.2.4 Hepatic and Renal Disorders

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

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

4.1.2.5 Infections and Immune Disorders

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

- History of, or known to currently have HIV infection, or hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator, or

history of spirochete infection of the CNS (e.g., syphilis, Lyme disease, or borreliosis)

- Systemically, clinically significantly immunocompromised participants, owing to continuing effects of immune-suppressing medication

4.1.2.6 Metabolic and Endocrine Disorders

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

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

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

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

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

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

  A participant may be re-screened after 3 months to allow optimization of diabetic control.

4.1.2.7 Exclusions Related to Medications

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

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long-acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous administration of GV-971

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

- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no plans to initiate such medications prior to study start

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

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

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

- Anticoagulation medications within 3 months of screening with no plans to initiate any prior to start of study treatment

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

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

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

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

- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study

- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no plans to initiate any prior to study start

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

4.1.2.8 Other Exclusions

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

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

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

- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Clinically significant abnormal screening blood or urine results that remain abnormal at retest
- Impaired coagulation (screening PT $>$ 1.2 $\times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab excipients
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the participant at special risk, bias the assessment of the clinical or mental status of the participant to a significant degree, interfere with the participant's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility

  Participants who subsequently require residence in such facilities during the study may continue in the study and be followed for PD and safety data, provided that they have a study partner (non-professional caregiver) who meets the minimum requirement.

- Planned or recent (within 12 months prior to screening) exposure to ionizing radiation that in combination with the planned administrations of the radioligand would result in a cumulative exposure that exceeds recommended local guidelines

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

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

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 Study Treatment Formulation and Packaging

4.3.1.1 Gantenerumab

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

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

4.3.2 Study Treatment Dosage, Administration, and Compliance

Refer to the pharmacy manual and other applicable manuals for detailed instructions on drug preparation, storage, and administration.

Study treatment may be administered by a study partner (non-professional caregiver) at the participant's home or another suitable location depending on the individual participant/study partner (non-professional caregiver) suitability. A vial adapter will be available in countries where it has been approved to withdraw the medication from the vial into a disposable syringe (this device will be optional for health care professionals and required for non-professional caregivers). *During the course of the study, an autoinjector may become available in participating countries, if approved by local health authorities and IRBs. Use of this device will be optional for participants who receive study treatment administration at home or at the site.* Study treatment may also 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 HN 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 overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.13. If applicable, study partners (non-professional caregivers) will confirm completed administration in the home (non-clinic) setting using a caregiver diary (including date, time, correct injection location, and amount). Further details will be described in the Caregiver Manual.

Guidelines for dosage modification and treatment interruption or discontinuation for participants who experience adverse events are provided in Section 5.1.3.1.

4.3.2.1 Gantenerumab

Gantenerumab will be administered by SC injection, at a dose of 120 mg Q4W (Day 1, Week 4, and Week 8), then 255 mg Q4W (Weeks 12, 16, and 20), and then 255 mg Q2W for 12 weeks (Weeks 24, 26, 28, 30, 32, and 34), followed by the target dose 255 mg Q1W (Weeks 36–*207*). Before reaching the maximum target dose (i.e., 255 mg Q1W), a minimum of three doses during the 120-mg Q4W and 255-mg Q4W dosing periods, and a minimum of six doses during the 255-mg Q2W dosing period must be administered prior to uptitration.

The dosing schedule is shown Appendix 1.

Depending on the site and individual participant/caregiver suitability, participants will have the option to receive SC injections of gantenerumab at the site and (after a defined period of appropriate training and supervision of a caregiver) at home by study staff, home nurse, or study partner (non-professional caregiver).

Participants will receive SC injections of gantenerumab by the investigator or an appointed qualified study staff for the first three doses of gantenerumab at the clinic. If participants have a study partner (non-professional caregiver) who is willing and judged capable of administering SC injections, this caregiver will receive training and observe dose administration at the first three dosing visits (i.e., Day 1, Week 4, and Week 8), and the injections will be done by the caregiver under staff supervision at the next four visits (i.e., Weeks 12, 16, 20, and 24). Following this supervised dosing at the clinic, subsequent dosing may be administered by the caregiver at home except for doses that coincide with a clinic visit, in which case the caregiver should administer the injection in clinic under investigator/study staff supervision. Study staff will document the outcome of the supervised administration.

The investigator will determine whether the participant is suitable for home administration by the study partner (non-professional caregiver), a home nurse, or appropriate study staff (according to local regulations).

At subsequent visits as specified in the Appendix 1, the investigator will determine if the study partner (non-professional caregiver) continues to be suitable to perform home administration. If at any time the investigator or caregiver determines that home administration by the caregiver is unsuitable, then study drug must be administered at home or in the clinic by a home nurse or study staff.

Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or caregiver to elicit, in a non-leading way, information on medication errors and adverse events that may have occurred in the home setting. Therefore, there will be contact between the study staff and the participant/caregiver at least Q4W. The study staff is encouraged to have more frequent calls with a particular participant/caregiver if considered appropriate by the investigator. In addition, participants/caregivers will be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening, or medication errors.

Training and supportive materials will be provided to the site and to the study partner (non-professional caregiver). Following the in-person instructional training and supervised administration at the site, adequate supply of gantenerumab will be provided.

For Q4W injections, a time window of ±7 days is allowed for dosing. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. For both the Q2W injections and Q1W injections, the time window for dosing is ±3 days. If the administration is not possible on the scheduled dosing day, the study medication should be administered as soon as possible within the time window from the scheduled dosing date. If the study drug cannot be administered within the time window, the dose should be skipped, and the participant should receive the next dose at the next scheduled time with the study medication dosing resumed in accordance with the original dosing schedule. Always return to the initial planned schedule or subsequent dose/visits.

Regardless of dose, each participant will undergo up to a total of 80 dosing visits and home administrations as applicable in the study. Injections will be administered as one 0.8-mL (120-mg) dose or one 1.7-mL (255-mg) dose subcutaneously to the abdomen.

4.3.3 Positron Emission Tomography Tracers

All participants who are otherwise eligible at screening will be assessed for the presence of brain amyloid consistent with AD by PET imaging. The permitted amyloid PET ligands will be florbetaben (all sites) and flutemetamol (in exceptional circumstances, the use of flutemetamol may be acceptable at sites where florbetaben is not available, but only after prior written approval from the Sponsor). Florbetaben or flutemetamol will be provided in accordance with approved national and/or local standards.

According to E.U. guidance, 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 an 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 Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor where required by local regulations. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or home nurse]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, IMP distribution to each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received and ensuring that participants are provided with doses specified by the protocol. Used and unused IMP distributed to each participant will be returned by participant's study partner (non-professional caregiver) to the study site and appropriately accounted for.

The study site should follow all instructions included with each shipment of IMP. 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. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received at the site and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs shipped to the site must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff. Participants will be provided with storage instructions for home dosing.

For home dosing, study drug must be transported from the site to the participant's home by the participant, caregiver, or a Sponsor-approved courier service, per local requirements. If transported by the participant or caregiver, the study drug must be placed in a cooler with an ice pack to maintain the appropriate storage temperature. The cooler and ice pack for study drug transport will be provided by the Sponsor or designee.

Only participants enrolled in the study may receive the IMP, and only authorized staff may supply the IMP, and only authorized staff and study partners (non-professional caregivers) may administer the IMP.

The IMP 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 accountability log.

Refer to the pharmacy manual and/or the home administration manual and Gantenerumab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to Gantenerumab

The Sponsor will offer continued access to Sponsor study drug (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 Sponsor study drug (gantenerumab) after completing the study if all of the following conditions are met:
- The participant has a life-threatening or severe medical condition and requires continued Sponsor study drug treatment for his or her well-being.
- There are no appropriate alternative treatments available to the participant.
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

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

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

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

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

Eligible participants may qualify for continued access or ongoing extension studies as outlined above.

4.4 CONCOMITANT THERAPY

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

4.4.1 Permitted Therapy

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

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

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

- Anticonvulsant medications for an approved pain indication
- Selective serotonin reuptake inhibitors for the treatment of depressive symptoms
- Over-the-counter and/or herbal medications, food additive, or any other agent or supplement intended to improve cognition or reduce cognitive decline
- Medications used to treat a mood or anxiety disorder given as maintenance treatment (with the exception of benzodiazepine)
- Intermittent use of short-acting (non-extended release) opioid medications for pain except within 2 days or 5 half-lives (whichever is the longer) of any cognitive assessment (up to a maximum of 3 consecutive days per month)

- Intermittent use of benzodiazepines, including alprazolam, lorazepam, oxazepam, triazolam, or temazepam, or a one-time dose of diazepam or a short-acting hypnotic medication (e.g., zolpidem) if use is intermittent for sleep or anxiety, except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- A dose of benzodiazepine for pre-surgical and pre-imaging sedation at appropriate visits if allowed by the EC or IRB
- Intermittent use of centrally acting antihistamine medications except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- Under certain circumstances, initiation of anti-hemostasis medications during the study conduct

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

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

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

4.4.2 Prohibited Therapy

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

4.5 STUDY ASSESSMENTS

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

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained from all participants and their study partners (non-professional caregivers) before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled participants and their study partners (non-professional caregivers) and for those 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 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

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

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

4.5.3 Physical Examinations

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

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

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

4.5.4 Vital Signs

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

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

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

4.5.5 Positron Emission Tomography Scan

Two radioligands may be used in this study: florbetaben for participants at all sites (in exceptional circumstances, the use of flutemetamol may be acceptable at sites where florbetaben is not available, but only after prior written approval from the Sponsor).

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

A positive PET scan using any amyloid tracer, acquired outside this study protocol is not permissible to confirm participant inclusion due to the longitudinal PET imaging requirements for all subjects enrolled in this study.

After obtaining the signed Informed Consent Form at the clinical study site, the following assessments and procedures will be performed for all participants during each amyloid PET scanning session:

- The responsible physician or his or her designee at the PET imaging center will confirm a participant's suitability for undergoing the PET imaging after a brief medical assessment, which may include weight. The PET scan should not be performed if the participant has an ongoing ARIA-E.
- For women of childbearing potential (including those who have had a tubal ligation), a urine pregnancy test will be conducted within 24 hours before the PET scan. The result must be negative for the participant to receive the amyloid tracer.
- The participant must void his or her bladder prior to scanning.
- Placement of an IV catheter into a forearm or antecubital vein for the injection of the investigational PET tracer must occur.
- A target dose of 300 [± 10%] MBq for florbetaben or 185 [± 10%] MBq for flutemetamol will be administered intravenously as a single slow bolus. The cannula

will be immediately flushed with up to 5–15 mL of saline solution. It is recognized that due to scheduling, transit, or manufacturing issues, from time to time, it is possible that an imaging center may be delivered a dose of amyloid radioligand that is less than the target dose. In these cases, participants may still be injected. However, if the dose is < 70% of the target dose, no injection should be performed and the participant should be rescheduled for imaging.

- A head fixation system (which may vary between the participating imaging centers) will be used. Each participant will be placed horizontally with his or her head positioned in the PET camera's field of view.
- A computed tomography (CT) or radioisotope transmission scan, for attenuation correction, should be performed prior to or immediately following the PET emission scan, using a low-dose CT or isotope transmission scan and encompass the entire head to include the brain from most superior cortical regions through the inferior portion of the cerebellum.
- At selected sites using florbetaben that can support dynamic imaging and imaging starting at the time of tracer injection, an optional early-frame PET scan of up to 60 minutes in length will be acquired as soon as the infusion is completed to allow assessment of cerebral perfusion. The initial scan will be followed by another 20-minute scan (as described below) with a short break in between.
- After an uptake period targeting 90 (± 1) minutes, and at most 90 (± 5) minutes after administration of amyloid radioligand, the 20-minute brain PET imaging will begin.
- The participant will be discharged after a physician or designee has been assured of the participant's well-being.

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

4.5.6 Home Administration Assessments

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

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

Whenever possible, cognitive and functional assessments should be performed at the visit timepoints indicated in the schedule of activities (see Appendix 1). However, in exceptional circumstances for post-Day 1 visits, if the study partner (non-professional 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 cognitive and functional assessments used for eligibility and as exploratory outcome measures in this trial involve subjective judgment, the adequacy of participant and study partner (non-professional 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 some eligibility assessments as well as for some other scales, audio recordings may be used for quality assurance purposes. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

4.5.6.1 Clinical Dementia Rating Scale

The 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 Sum of Boxes score is a detailed quantitative general index that provides more information than the CDR-GS in patients with mild dementia (Berg 1988; Morris et al. 2001; O'Bryant et al. 2010) and is scored from 0 to 18 with higher scores indicating greater impairment. The CDR characterizes six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview with the participant and a reliable informant or collateral source (e.g., a study partner [non-professional caregiver]).

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

4.5.6.2 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 patient-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 patient-based assessment.

4.5.6.4 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a patient-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 patient-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 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 patients 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 to 78, with higher scores indicating better functioning.

4.5.6.7 Home Administration Questionnaire

The home administration questionnaire will be completed at site visits as specified in Appendix 1, and comprises 4 items to be completed by study partner (non-professional caregiver) and 2 items to be completed by participants. The Caregiver portion of the questionnaire includes confidence with administration, convenience, ease of use, and overall satisfaction. Each item is rated on a 4-point verbal Likert scale and respondents will be asked to consider their most recent at home administration in answering these questions. Participants will complete satisfaction and convenience items with the same response options. Responses to this questionnaire may be captured electronically and transferred to the database directly from the core laboratory.

4.5.6.8 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, Coding, ADCS-ADL, CDR, MMSE, and C-SSRS.

4.5.7 Columbia-Suicide Severity Rating Scale

The C-SSRS (https://cssrs.columbia.edu/) is an assessment tool used to assess the lifetime suicidality of a patient (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality. The C-SSRS baseline will be collected at baseline and the C-SSRS since the last visit will be collected at subsequent visits as indicated in the schedule of activities (see Appendix 1).

The assessment will be completed by a certified C-SSRS rater after he or she interviews the participant and the participant's study partner (non-professional caregiver) during the study visit.

4.5.8 Brain Magnetic Resonance Imaging

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

Where available, exploratory MRI techniques including rs-fMRI and DTI will also be acquired. In addition, the screening MRI will be used to help determine whether the exclusion criteria are met (e.g., number of microbleeds, presence of mass lesions).

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

MRI scans will include the following sequences:

- 3D T1-weighted GRE scans
- T2*-weighted GRE scans
- T2-weighted FLAIR scans
- BOLD rs-fMRI, if available (to assess resting-state functional connectivity at investigative sites having the required software and sequences)
- DTI-MRI, if available (to assess fiber tract integrity)

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

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

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessment of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7−10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. The MRI results must be made available to investigators prior to next dosing or prior to the Week 104 visit (refer to Section 5.1.3 for additional details on MRI safety management).

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

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

4.5.9 Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

As part of site qualification, one to two volunteers (preferably two) at each site should be recruited and scanned using the same machine and the same sequences to be used for site qualification before any participant is scanned in this study. The choice of healthy volunteers is at the discretion of the investigator and/or the imaging center, and the volunteer must provide written consent to take part in the scanning calibration. Volunteers must not have any contraindications for MRI scanning (evaluation per local procedures at the imaging site), and they will not be enrolled in the study or undergo any other assessments as part of the trial. If volunteer scans are acquired, they will be reviewed for suitable image quality and used for qualitative comparison with additional scans with the same volunteer acquired after certain events as follows: at the time of a major upgrade to the site's scanner, any other event deemed significant enough to affect image quality, or per central reader guidance. This procedure will help ensure consistency in scanning quality over the duration of the study. Two volunteers are ideal in case one volunteer is no longer readily available for test scanning.

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

4.5.10 Laboratory, Biomarker, and Other Biological Samples

4.5.10.1 Standard Laboratory Samples

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

- Serum chemistry: 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)

  HbA_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, methylmalonic acid, T4, free T4, and TSH levels will also be assessed according to the schedule of activities.

- Hematology: hemoglobin, hematocrit, RBC count (with morphology), WBC count, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils
- Screening serology: HIV, hepatitis B, and hepatitis C
- Coagulation: PT and aPTT
- Urine for drugs of abuse:

  At screening only, urine samples will be analyzed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone. Results will be used to verify participant eligibility pertaining to drugs of abuse. Inconclusive results may be repeated once during the screening period. Investigators should use their best clinical judgment in cases where results may be erroneous (e.g., permitted use of opiates or ingestion of food/food supplements).

- Urinalysis: at screening only

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

- Urine for pregnancy test

  Urine pregnancy testing will be performed at screening, within 24 hours before a PET scan, after the last study drug dose and if a woman is suspected to have become pregnant (only for women of childbearing potential including those who have had a tubal ligation), and at the site for any other female participants if required by local regulations. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

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

4.5.10.2 Pharmacokinetic Samples

Blood samples will be collected for measurement of plasma concentrations of gantenerumab as specified in the schedule of activities (see Appendix 1).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of gantenerumab. Samples collected for analyses of gantenerumab (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Remaining volumes from these samples may also be used for any further RO4909832-related exploratory analyses or assay development/validation experiments.

An additional PK sample for the assessment of plasma concentrations of gantenerumab will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E, or occurrence of ARIA-H meeting discontinuation criteria.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

The PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

4.5.10.3 Samples for Immunogenicity Analysis

Antibodies to gantenerumab will be evaluated in plasma samples collected from all participants according to the schedule of activities (see Appendix 1). Additionally, plasma samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Plasma samples will be screened for antibodies binding to gantenerumab and the titer of confirmed positive samples will be reported.

The detection of antibodies to gantenerumab will be performed through use of a validated assay method under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for gantenerumab plasma concentration to enable interpretation of the antibody data. Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to gantenerumab.

Remaining volumes from these samples may also be used for further characterization of potential immune responses and for any RO4909832-related exploratory analyses or assay development/validation experiments.

4.5.10.4 Biomarker Samples

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Blood samples for genotyping apolipoprotein E gene allele ε4 (APOE ε4) status, clusterin (apolipoprotein J) genotypes, and FcγR genotype

  APOE ε4 status will be determined and will be unblinded to the Sponsor, but blinded to the investigator and participant. Investigators and participants will have access to this information if they elect to at the end of the study. If already known, the APOE ε4 status will still need to be confirmed. In addition, as much as possible, participant APOE ε4 status should remain blinded to the site and central MRI readers.

- Blood samples for RNA extraction

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

  An additional sample 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, or resolved ARIA-E).

- Plasma samples for exploratory research on biomarkers and biomarker assay

  The sample may be used to evaluate biomarkers including, but not limited to, Aβ, tau, neurofilament light chain, and neurogranin.

  An additional sample 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, or resolved ARIA-E).

Screening blood (for RNA extraction) and plasma samples, including those collected from individuals who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

Biomarker samples will be collected according to the schedule outlined in Appendix 1. Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.13), blood and plasma biomarker

samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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.

4.5.11 Electrocardiograms

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

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The 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, and brain MRI scans). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

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

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

4.5.12 *Optional Procedures*

Consenting participants will enter an optional 2-year extension after Week 104 until Week 208. Participants that consent to the optional extension will be required to

complete the procedures and assessments described in Tables 1-3 and 5-10 in Appendix 1.

The Informed Consent Form will contain a separate section that addresses the optional 2-year extension. A separate, specific signature will be required to document a participant's agreement to undergo the optional extension. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Informed Consent Form. The investigator should document whether or not the study partner has given consent to participate and (if applicable) the date(s) of consent, by completing Study Partner Informed Consent Form.

4.5.13 Optional Samples for Research Biosample Repository

4.5.13.1 Overview of the Research Biosample Repository

The Research Biosample Repository (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 patients 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

4.5.13.2 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 4.5.13.2) will not be applicable at that site.

4.5.13.3 Sample Collection

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

- Leftover blood from the clinical genotyping sample and clinical RNA sample, plasma biomarker sample, 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 researcher's understanding of disease pathobiology. The WGS and the 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 patients 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.

The 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).

4.5.13.4 Confidentiality

The RBR samples and associated data will be labeled with a unique participant 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.

4.5.13.5 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.

4.5.13.6 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. 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.

4.5.13.7 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 TIMING OF STUDY ASSESSMENTS

4.6.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site. After providing written informed consent, participants who are willing to participate in the study will undergo all screening assessments within 8 weeks prior to the baseline visit, as detailed in the schedule of activities (see Appendix 1). Participants must fulfill all the entry criteria for participation in the study and the results must be available prior to the baseline visit.

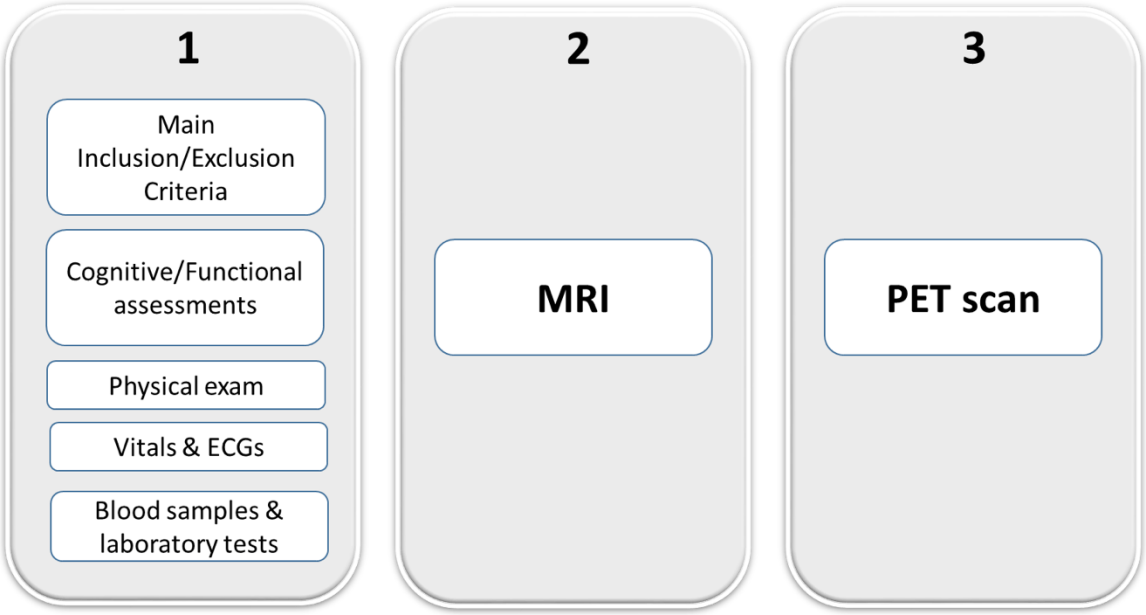
It is recommended that the MMSE assessment will be completed at first. In case the participant would not qualify based on the MMSE inclusion criteria, re-screening of the participant is not allowed.

In case of an abnormal laboratory or ECG result at screening that may normalize upon retest, investigators have the option to repeat the tests (prior to baseline and within the 8-week screening window) once to confirm the test results before enrolling a participant at baseline.

In rare cases in which a MRI scan needs to be repeated or any other unexpected delay due to logistical or technical reasons, the screening period may be extended by some days. Extending the screening period beyond 8 weeks must be approved by the Medical Monitor and should be for exceptional circumstances only; careful scheduling should remain a priority.

The recommended order of screening assessments is shown in Figure 5.

Figure 5 Order of Screening Assessments



ECG = electrocardiogram; MRI = magnetic resonance imaging; PET = positron emission tomography.

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

Participant Assessments	Study Partner (Non-Professional Caregiver) Assessments
1. MMSE 2. CDR (participant interview)	CDR (study partner [non-professional caregiver] input)

CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination.

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

If a participant does not qualify on the basis of applicable tests other than the MMSE, the participant may be re-screened again after at least 3 months have elapsed if recruitment for the study is still ongoing.

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

Participants may be re-screened if the protocol is amended such that they would satisfy the amended criteria and if recruitment for the study is still ongoing. In this case, all screening assessments must be repeated with the exception of PET scan within eligible ranges. Given that APOE status will not change over time, there is no need to repeat clinical genotyping in case of re-screening.

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

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

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

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

4.6.2 Assessments at Baseline

To be enrolled into the study and to receive the study drug, participants must have no significant change in medical, psychiatric, or neurologic conditions or change in medication since screening. The recommended order of assessments and rating scales is as follows:

- Clinical assessments (e.g., CDR, MMSE, and ADAS-Cog), including all those that require study partner (non-professional caregiver) input, should be completed before any invasive safety assessments.
- Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, anti-drug antibody (ADA), and 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	Study Partner (Non-Professional 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. C-SSRS	1. CDR (study partner [non-professional caregiver] input) 2. ADCS-ADL

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;
MMSE = Mini-Mental State Examination.

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

4.6.3 Assessments during the Treatment Period

In the treatment period, participants will receive up to 80 SC administrations of study drug over the course of 103 weeks. The final efficacy and *PD* assessments are scheduled at Week 104, 1 week after the final dose *for those participants who do not take part in the 2-year extension.*

Participants who take part in the 2-year extension will receive up to 184 SC administrations of study drug over the course of 207 weeks. The final efficacy and PD assessments are scheduled at Week 208, 1 week after the final dose.

The same recommended order of clinical assessments and rating scales as above for the baseline visit should be followed (omitting those that are not conducted per the schedule of activities; see Appendix 1). The home administration questionnaire should be performed after the cognition and function assessments.

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

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

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Appendix 1), gantenerumab will be administered subcutaneously at room temperature. For the first four doses, participants should be observed for a

minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses (i.e., Doses 5 and beyond). Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, the drug administrator must remain with the participant for a minimum of 1 hour after each injection.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site. Participants and their study partners (non-professional caregivers) will be alerted to watch for signs of anaphylactic and anaphylactoid reactions, and given emergency contact information to use as soon as possible if any such signs are noted.

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

4.6.4 Procedures for New Magnetic Resonance Imaging Findings

In addition to any local reading according to local procedures and requirements, all MRI scans will be reviewed by an expert central reader within approximately 1 week of receipt and a report provided to the site. For the purposes of overall study relevant decisions and recommendations, including participant eligibility as well as for analysis, results from the expert central reader will be used. Any time the central reader identifies a new MRI finding the study center medical staff and the Sponsor will be rapidly notified (see Section 4.5.8).

Refer to Section 5.1.3 for instructions in the event of new MRI findings (ARIA-E and ARIA-H).

4.6.5 Assessments at Study Completion or Early Termination Visit and at Follow-Up

Participants who *opt for the 2-year extension and* complete the treatment period (defined as completion of *207 weeks* of study drug treatment) have to complete the final PD and efficacy assessments 1 week after the final dose *(Week 208)*. Subsequently, participants are asked to come back for the follow-up *safety* assessments 16 weeks after *Week 208 (Week 224)*, unless they are transitioning to a *further gantenerumab* OLE study.

Participants who do not opt for the 2-year extension of Study WN29722 will receive the final dose of study drug at Week 103, and Week 104 final PD and efficacy assessments will be performed 1 week later. Participants who do not enter an extension study will have an additional follow-up visit 16 weeks after the Week 104 visit for safety assessments (Week 120 follow-up visit).

All participants who withdraw from treatment or discontinue from the study early (during the treatment period) will be asked to return 1 week 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 PD data (i.e., the primary endpoints as well as assessments of cognition and function) at visits that have the assessments (e.g., Weeks 24, 52, and 76) per the schedule of activities until the end of the treatment period (including Weeks 104 and 120 *for participants who do not opt into the 2-year extension and Weeks 208 and 224 for participants who opt for the 2-year extension*). If participants who withdraw from treatment are not willing to return for collection of safety (except MRI) and PD data, then they will be asked to come back for the follow-up assessments 16 weeks after the early termination visit.

Autopsy reports, including cause of death, for all participants who die during the study should be requested.

Refer to the schedule of activities to be performed at the study completion (*either* Week 104*, 208* or early termination visit) in Appendix 1.

4.6.6 Unscheduled Assessments

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

4.7 TREATMENT, PARTICIPANT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

Participants must 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
- Upon evidence of more than 15 ARIA-H, cumulatively
- Any disseminated leptomeningeal hemosiderosis

All participants who withdraw from treatment will be asked to return 1 week after 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 PD data (i.e., the primary endpoints as well as assessments of cognition and function) at visits that have the assessments (e.g., Weeks 24, 52, and 76)

per the schedule of activities until the end of the treatment period (including *Weeks 208* and *224*).

- If study drug is discontinued permanently for participants dosed at home, any remaining study drug doses should be returned to the study site (if applicable).

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

4.7.2 Participant Discontinuation from the Study

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
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the participant
- Participant non-compliance with the study and/or study procedures, defined as missing more than three consecutive dose administrations (with Q4W dosing regimen), more than six consecutive dose administrations (with Q2W dosing regimen), or more than twelve consecutive dose administrations (with Q1W dosing regimen) because of non-safety-related reasons or more than half of the dosing visits in a calendar year.

All participants who discontinue from the study early will be asked to return 1 week after final dose of study drug to complete the early termination visit.

- If participants dosed at home discontinue the study early, any remaining study drug doses should be returned to the study site (if applicable).

Every effort should be made 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. However, participants will not be followed for any reason after consent has been withdrawn. 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.

4.7.3 Study Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants
- Participant enrollment is unsatisfactory
- Sponsor determines it is the best interest of the participants

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

4.7.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all participants have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Gantenerumab is not yet approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with gantenerumab in completed and ongoing studies. The identified risks for gantenerumab are outlined below. Please refer to the Gantenerumab Investigator's Brochure for a complete summary of safety information.

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

5.1.1 Risks Associated with Gantenerumab

5.1.1.1 Amyloid-Related Imaging Abnormalities

The 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 APOE ε4 status (Piazza and Winblad 2016).

The mechanism underlying the development of ARIA-E and ARIA-H during anti-amyloid treatment is not yet fully understood. Because anti-Aβ 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 (Haeberlein 2019).

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.

In the double-blind phase of Study WN25203 (prodromal AD), ARIA events were time, dose, and APOE ε4 allele status dependent. The incidence of ARIA-E was 0.8% in the placebo, 6.6% in the 105-mg gantenerumab, and 13.5% in the 225-mg gantenerumab groups. For ARIA-H, the incidence was 13.2% in the placebo, and 22.9% and 16.2% in the 105-mg and 225-mg gantenerumab treatment groups, respectively. The rates of new ARIA-E were highest between 3 and 6 months of treatment (3.8% and 7.5% in the 105-mg and 225-mg gantenerumab groups, respectively) and decreased substantially after the first year of treatment (incidence of up to 2.3% in the 225-mg gantenerumab group in approximately 2 years). The median MRI Barkhof grand total score (BGTS; Barkhof et al. 2013) of these findings was 3. Most ARIA events were asymptomatic and did not lead to clinically significant consequences. A total of 5 participants (1.8%) from the 105-mg gantenerumab arm and 6 participants (2.3%) from the 225-mg gantenerumab arm experienced symptoms related to ARIA findings; the most commonly reported symptom was headache (5 participants). Other symptoms reported with ARIA-E included visual disturbances (left eye diplopia and upper left quadrantanopia), focal seizure (dysarthria/aphasia that lasted for 10 minutes), anxiety, hyperreflexia, confusional state, disturbance in attention, cognitive disorder, malaise, and dizziness.

Symptomatic ARIAs were of mild severity and were non-serious except for one serious adverse event of focal seizure.

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

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

The WN25203 and WN28745 OLE studies *have been completed. In the OLE phase of Study WN25203,* all 154 participants dosed with gantenerumab in the WN25203 OLE study had a post-baseline MRI scan. Of 154 participants, 47 participants (30.5%) had new ARIA-E (median maximum BGTS of 7.0), and *20 participants (13.0%)* had new ARIA-H without ARIA-E. The majority of ARIA-E findings were asymptomatic, with *19* of 47 participants with new ARIA-E MRI findings reporting associated CNS adverse events. The CNS adverse events were mostly mild to moderate in intensity, non-serious, and did not require permanent cessation of study treatment *(with the exception of the SAE of cerebral hematoma)*. Most symptomatic ARIA-E cases resolved with protocol-defined ARIA management rules. In *4* of the *19 participants* with ARIA-E MRI findings who reported associated CNS adverse events, the events were reported as serious. *Three participants reported events of seizure (n=2) and cerebral haematoma which was severe in intensity and one participant reported confusion that was moderate in intensity.*

In the OLE phase of Study WN28745, as of 11 January 2021 (snapshot date) 219 of 225 participants dosed with gantenerumab had a post-baseline MRI scan. Seventy-one of 219 participants (32.4%) had new ARIA-E (median maximum BGTS of 9.0), and *26* of 219 participants *(11.9%)* had ARIA-H without ARIA-E. The majority of ARIA-E events were asymptomatic, with *22* of 71 participants with ARIA-E MRI findings reporting associated CNS adverse events. The CNS adverse events were mostly mild to moderate in intensity, non-serious, did not require permanent cessation of study treatment, and resolved with protocol-defined ARIA management rules. In 4 of the *22 participants* with symptomatic ARIA-E, the events were reported as serious (ischemic stroke, generalized tonic-clonic seizure, epilepsy, and hemiplegia).

Study WN29722 will require an MRI scan documenting the absence of ARIA-E, more than five ARIA-H, or 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's IMC.

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

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

5.1.1.2 Injection Reactions and Hypersensitivity

Gantenerumab may cause a local ISR 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.

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

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

In the OLE phase of Study WN25203, ISRs have been reported in 56 of 154 participants (36.4%) dosed with gantenerumab in the WN25203 OLE study. All ISRs were non-serious and mild *except one which was of moderate intensity*, and the majority resolved without treatment. Overall, 3 of 56 participants (5.4%) who had an ISR received treatment, which included topical steroids and antihistamines.

In the OLE phase of Study WN28745, as of 11 January 2021, ISRs have been reported in *90* of 225 participants *(40.0%)* treated with gantenerumab. All ISRs were non-serious, with the majority being mild and resolving without treatment. Overall, *10* of *90 participants (11.1%)* who had an ISR received treatment, which included topical steroids and antihistamines. One participant *(0.4%)* experienced a severe event (injection-site pain after receiving a 600 mg dose via a pump, resulting in dose modification [i.e., uptitration was delayed]); this ISR resolved within 24 hours.

Regular reviews of ISR data from the OLE Studies WN25203 and WN28745, and the pivotal Studies WN29922 and WN39658 have not identified any new or unexpected safety findings.

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

As with administration of any exogenous protein, a potential exists for the development of hypersensitivity reactions, including anaphylaxis. A hypersensitivity reaction may present during any injection, although typically would not present during the first injection. For subsequent injections, more severe injection reaction symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction.

A potential exists for the occurrence of systemic injection reactions, which are related to cytokine release and/or other chemical mediators. These may be clinically indistinguishable from hypersensitivity reactions, including anaphylaxis. In comparison to hypersensitivity reactions, systemic injection reactions could occur on first exposure to gantenerumab in participants with no history of prior opportunities for sensitization.

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Appendix 1), gantenerumab will be administered subcutaneously at room temperature. For the first 4 doses, participants should be observed for a minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses (i.e., Doses 5 and beyond). Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, the drug administrator must remain with the participant for a minimum of 1 hour after each injection.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site. Participants and their study partners (non-professional caregivers) will be alerted to watch for signs of anaphylactic and anaphylactoid reactions, and given emergency contact information to use as soon as possible if any such signs are noted.

The investigator may order any pertinent laboratory tests, including an unscheduled ADA test, in the event any hypersensitivity reaction occurs.

If anaphylaxis or a serious hypersensitivity reaction occurs, study drug must be discontinued permanently, and any remaining study drug doses should be returned to the study site (if applicable). Blood samples for the presence of ADA and PK-PD will be obtained.

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.

For the management of suspected immunogenicity-associated hypersensitivity/anaphylaxis, see section above.

5.1.2 Risks Associated with Amyloid PET Tracer

5.1.2.1 Risks Associated with Radiation

The risks associated with radiation in Study WN29722 are considered minimal, owing to the low dose of tracer that is administered and based on nonclinical and clinical experience available to date. The principal risks associated with PET imaging are those associated with IV line placement, the discomfort associated with acquisition of the images while keeping the head stable in the scanner, and radiation exposure because of the radiotracer dose and transmission or CT scanning. To date, the most frequently reported adverse events with amyloid radioligands are ISRs, increased blood pressure, headache, dizziness, and nausea (see Sections 5.1.2.2 and 5.1.2.3 for specific details about each tracer).

Radiation Exposure

The dose of whole body effect radiation resulting from the recommended injected radioactivity is similar for florbetaben and flutemetamol and is well below the maximum annual effective dose limitations recommended in the United States, the European Union, and other countries where amyloid PET imaging will be used. The recommended 300-MBq dose of florbetaben results in a 5.8-mSv absorbed dose, and the 185-MBq dose of flutemetamol results in 5.9 mSv. Additional radiation dose results from CT or transmission scan used for attenuation correction of the PET emission data. The CT scan in PET/CT scanners will be configured as a low-dose CT and will add approximately 0.1 mSv to the dose from amyloid tracers. In dedicated PET scanners without CT scans, the transmission scan adds only a negligible amount of radiation dose.

Radiation exposure for florbetaben and flutemetamol doses can be found in their respective Investigator's Brochures and in the Technical Operations Manual.

Refer to local and national guidelines for recommended annual radiation exposure. For comparison, the annual dose associated with the natural background is 2.4 mSv. The recommended maximum annual whole-body dose from research scans in the United States is 50 mSv. In the European Union, 10 mSv per year is the recommended maximum dose for research scans, corresponding to a risk category "Category IIb" with a "minor to intermediate" level of risk (Verbruggen et al. 2008). Amyloid scans should only be performed if the investigator has determined that a participant's total past and planned annual radiation exposure does not exceed local guidelines.

5.1.2.2 Florbetaben

The most commonly reported adverse reactions after injection of florbetaben are injection-site pain (3.9%), injection-site irritation (1.2%), and injection or application-site erythema (1.7%). Florbetaben contains up to 1.5 μmol of sodium (i.e., 33 mg) per dose.

This should be taken into account for participants on a sodium-controlled diet. Florbetaben contains up to 118 mg of ethanol (alcohol), which is equivalent to 30 mL of beer or 12.5 mL of wine per dose. This can be harmful for those suffering from alcoholism and is also to be taken into account in pregnant or breastfeeding women and high-risk groups such as participants with liver disease or epilepsy.

In countries where florbetaben PET radioligand is approved for marketing, for more information see the approved local product information. In countries where the florbetaben PET radioligand is not approved for marketing, the Investigator's Brochure will be provided.

5.1.2.3 Flutemetamol

The most commonly reported adverse reactions after injection of flutemetamol are flushing (2%), increased blood pressure (1%), headache (1%), dizziness (1%), nausea (1%), and hypertension (1%). Flutemetamol contains up to 9.0 mg of sodium and 70 μL of ethanol.

In countries where flutemetamol PET radioligand is approved for marketing, for more information see the approved local product information. In countries where the flutemetamol PET radioligand is not approved for marketing, the Investigator's Brochure will be provided.

Other adverse reactions could be related in part to the PET-scan apparatus and procedures; careful attention should be taken to make the participant aware of the planned procedures and to maximize participant comfort in the scanner. Venous catheter insertion can be associated with bruising, infection, or clot formation. Using proper placement techniques will minimize such risks. Experience in previous human clinical trials has revealed no clinically meaningful changes in vital signs, electrocardiogram, or laboratory changes following treatment with florbetaben and flutemetamol.

5.1.3 Management of Participants Who Experience Adverse Events

5.1.3.1 Dose Modifications and Treatment Interruption

Participants will undergo brain MRI examinations prior to every dose increase (pre-uptitration MRI scans) and according to the schedule of activities once the target dose is achieved. The pre-uptitration MRI scans will determine eligibility for the next uptitration dose. Before reaching the maximum target dose (i.e., 255 mg Q1W), a minimum of three doses during 120-mg Q4W and 255-mg Q4W dosing periods, and a minimum of six doses during the 255-mg Q2W dosing period must be administered prior to uptitration.

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

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

- In case of asymptomatic ARIA-E and BGTS ≥ 1 and < 4: Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI scan 4 weeks later (for participants on Q1W dosing frequency, this can be after the third or fourth dose).

  As long as BGTS is < 4 and ≥ 1, continue study drug at the same dose level and repeat MRI scan 4 weeks later until the event resolves (for participants on Q1W dosing frequency, this can be after the third or fourth dose). Once ARIA-E resolves, resume dosing including uptitration. For participants in the uptitration phase, obtain a MRI scan per the titration schedule. For participants on the target dose, perform another MRI scan 3 months after study drug reintroduction.

- Additional measures for nonclinical administration by study partner (non-professional caregiver): Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to elicit, in a non-leading way, information on medication errors and adverse events that may have occurred in the home setting. Therefore, there will be frequent contact between the study staff and the participant/study partner (non-professional caregiver). In addition, participants/study partners (non-professional caregivers) will be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening. These requirements will aid symptomatic ARIA-E detection and dose intervention, as described below, in the case of an asymptomatic ARIA-E that becomes symptomatic at a later date.

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

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

  When symptoms and ARIA-E resolve, reintroduce study drug at the next scheduled dosing visit, at the same dose given at the time the event was detected.

  Perform an MRI scan after the first dose while participants are on a Q4W dosing frequency, or after the second dose while participants are on a Q2W dosing frequency, or after the third or fourth dose while participants are on a Q1W dosing frequency.

  If no new ARIA-E is detected, resume uptitration and obtain an MRI per the titration schedule. For participants on the Q1W dosing frequency, perform another MRI scan 3 months after study drug reintroduction.

- The investigator may choose to perform additional MRI monitoring for ARIA at any time.
- Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings.
- Any recurrence of ARIA-E: Treat using the same procedures as for the first event (based on symptoms and BGTS).
- Participants who develop ARIA-H $>$ 15 cumulatively will be discontinued from study drug (the cumulative number should not include any disseminated leptomeningeal hemosiderosis, i.e., more than 3 focal leptomeningeal hemosiderosis cumulatively. A focal leptomeningeal hemosiderosis is counted as one ARIA-H).
- In cases where both ARIA-E and ARIA-H occur, the most conservative approach should be followed.
- In exceptional cases, as determined by the Sponsor and investigator:

  Q4W monitoring may no longer be necessary in case of an ARIA-E that is asymptomatic with BGTS $<$ 4 and considered stable over consecutive MRI images; or symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue.

  The study drug can be either reintroduced or uptitrated, as applicable, in case of an asymptomatic ARIA-E that has stabilized at BGTS $<$ 4; or a symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue.
- An additional plasma and blood sample for the assessment of exploratory biomarkers will be obtained as soon as practical (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.
- A PK sample will be obtained as soon as practical (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).
- Any other new significant findings will be reviewed by the Medical Monitor and appropriate dose action will be proposed.

The Sponsor's IMC will review the incidence and other characteristics of ARIA and may recommend adjustment of dosing regimen and/or ARIA management for the overall study population or for a specific APOE ε4 genotype.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital

signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition; 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 [NCI CTCAE]; 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

Data on associated symptoms and safety MRI scans will be collected for the following selected adverse events:

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

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

Adverse events that occur during the participant's participation in imaging procedures at the imaging center or that are reported at the time of the participant's visit to the imaging center will be communicated to the referring clinical site. Conversely, any clinically significant adverse events reported to the clinical site that may affect the participation of any one participant or all participants enrolled in this study will be communicated to the imaging center within 24 hours of learning of the event.

Clinical observations by the responsible physician or designee at the imaging center, as well as vital sign measurements performed at the imaging center, will be recorded in the source data only and will not be part of the clinical study database unless any of these clinical observations/vital signs are clinically significant and constitute adverse events as assessed by the responsible physician or designee at the imaging site.

All adverse events that occur or are reported during the participant's visit at the imaging center will be retrospectively entered into the clinical database by the clinical site without the need to complete an Adverse Event Worksheet.

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each participant contact. All adverse events, whether reported by the participant, the study partner (non-professional 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 but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

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

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

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

After initiation of study drug, all adverse events will be reported until the participant's last follow-up visit, as defined in the Schedule of Assessments.

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 2 provides guidance for assessing adverse event severity.

Table 2 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 ARIA Findings

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

- Symptomatic ARIA-E (i.e., onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings), and/or
- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), and/or
- Findings that are otherwise clinically significant in the investigator's judgment

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

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

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

5.3.5.2 Injection Reactions

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

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

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

5.3.5.3 Diagnosis versus Signs and Symptoms

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

5.3.5.4 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious", providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.6 Abnormal Laboratory Values

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

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

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

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

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

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

5.3.5.7 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.8 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.6) 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 this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

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

5.3.5.11 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is 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
- Hospitalization due to expected progression of underlying disease
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The participant has not experienced an adverse event

5.3.5.13 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

  In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.}

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 (or matching placebo), 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 (or matching placebo), 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 data by the Sponsor, and safety analyses will not be performed using clinical outcome assessment (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 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including *country-specific* toll-free numbers for the Emergency Medical Call Center *have been* distributed to investigators *and are filed in the investigator site file.*

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

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

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

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the participant's last visit (including long-term follow-up visits). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit

the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations 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 embryo-fetal 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 embryo-fetal 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

In this study, the vial adapter ReadyPack™ (FDA registration number K963583) manufactured by the company West Pharma will be provided to the study partner (non-professional caregiver) to aid study drug administration to the participant. The vial adapter is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the vial adapter batch number, as reported on the blister, 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.

In this study, gantenerumab, in an autoinjector, may be provided to the study partner (non-professional caregiver), home nurse or site staff to administer study drug to the participant. The investigator must report all complaints to the Sponsor whether they pertain to the study drug or to the autoinjector part of the product. The investigator should document as much information as possible on the IMP Deviation Form, including the batch number, as reported on the label, 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 use of the gantenerumab autoinjector 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 per the Schedule of Assessments), 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/Special Situations 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

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is relative to the sample of participants assessed by amyloid PET imaging using florbetaben. The sample size for this study is determined as the number of participants needed for the estimated change from baseline to Week 104 in amyloid PET load to fall into a 10 CL confidence interval around its true value. With a standard deviation of 25.67 CL (see below), 192 participants are sufficient to fulfill this criterion.

The standard deviation of amyloid reduction was estimated using amyloid PET data from the ongoing Studies WN25203 and WN28745 OLEs (based on a cutoff date of 14 October 2019), yielding a value of 25.67 CL.

Uncertainties of the parameters affecting the estimation (e.g., drop-out rate, study drug discontinuation rate, and standard deviation) were assumed to be equivalent to a decrease in sample size of up to around 35% and were corrected for accordingly. This drop-out rate is calculated based on the ongoing Study WN28745 OLE at Week 104. A sample size increase may be considered if factors external to the study would warrant a change to the sample size assumption.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of participants who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (e.g., age, sex, race, disease stage, APOE $\varepsilon 4$ status, use and non-use of background therapy for AD) will be summarized descriptively.

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 PRIMARY AND SECONDARY ENDPOINT ANALYSES

6.4.1 Primary Endpoint

The primary endpoint for this study is the change from baseline to Week 104 in brain amyloid load, as assessed by amyloid PET imaging using florbetaben as ligand and quantified on the CL conversion scale, in participants exposed to a Q1W administration regimen of SC gantenerumab. For the purposes of analysis, the screening amyloid PET scan may be considered the baseline evaluation.

Details about the primary estimand definition and corresponding statistical model specification, including handling of missing data will be described in the Statistical Analysis Plan (SAP). For example, a linear mixed-effects model with change from baseline as dependent variable, and baseline value and visit as covariate may be used.

Descriptive summary statistics of the change from baseline to Week 104 in brain amyloid CL load will also be produced. Descriptive summaries of the primary endpoint will present the mean, standard deviation, median, and minimum and maximum.

To evaluate the impact of different amyloid PET radioligands on the quantification of the PD effect of gantenerumab, a supplementary analysis will be performed similarly to the primary endpoint on the sample of participants scanned with florbetaben or flutemetamol in this study (if applicable).

6.4.2 Secondary Endpoint

The secondary objective for this study is the caregiver's confidence in his or her ability to perform the injection and his or her perception of the ease of injection, as well as the caregiver's satisfaction with and convenience of home administration. The corresponding endpoint consists of the responses to the caregiver part of the home administration questionnaire; these responses at various timepoints during study conduct will be summarized using descriptive statistics.

6.5 SAFETY ANALYSES

All participants who have received at least one dose of the study drug, whether prematurely withdrawn from the study or not, and who completed the associated assessments and sample collection will be included in the safety analysis.

Safety will be assessed through descriptive summaries of the following endpoints:

- Incidence, nature, and severity of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, severity, and timing of ISRs
- Incidence, nature, and severity of serious adverse events
- Incidence, nature, and severity of adverse events
- Incidence of adverse events of special interest
- Incidence of treatment discontinuations due to adverse events
- Mean changes in clinical laboratory tests from baseline over time; incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events
- Mean change in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Physical and neurologic examination abnormalities
- Mean change in vital signs (blood pressure, pulse rate) from baseline over time and incidence of abnormal vital sign measurements
- Changes in C-SSRS scores from baseline over time
- Number and proportion of participants with ADAs during the study relative to the number and proportion of participants with ADAs at baseline

The incidence, severity, and nature of adverse events, serious adverse events, ARIA-E and ARIA-H, and laboratory abnormalities will be assessed on a regular basis by the Sponsor's IMC, as documented in the IMC Charter.

6.6 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Details of the PK analyses will be described in a separate analysis plan, and the results will be reported in a separate document from the Clinical Study Report.

Observed 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 will be incorporated to establish the population PK model. The selection of parameters and the derivation of individual measures of exposure, such as AUC, C_{max}, and trough serum concentration, will depend on the final PK model used for this analysis.

Where applicable, the relationships between drug PK exposure and the efficacy and safety endpoints of gantenerumab will be explored. The previously developed PK-PET models will be initially used to compare the expected PET reduction under Q1W regimen

with the observed PET reduction to provide supporting evidence for the independence of frequency of administration and plaque clearance. If needed, the PK-PET model will be updated by adding the data collected in this study. The influence of the gantenerumab dosing regimens (Q1W, Q2W, and Q4W) on the relationships between exposure and amyloid reduction will then be specifically assessed.

6.7 BIOMARKER ANALYSES

The exploratory biomarker analysis will quantify the change from baseline, using MRI at baseline and follow-up at Weeks 52 and 104, in the following imaging biomarkers:

- Whole brain volume
- Regional brain volumes
- Ventricular volume

In addition, exploratory biomarker analysis will be performed to assess functional brain connectivity and fiber tract integrity at baseline and Week 104. Additional statistical modeling and subgroup analysis may be considered and will eventually be specified in the SAP.

Exploratory fluid biomarkers will be assessed for tau and amyloid pathology as well as neurodegeneration, including, but not limited to, the following:

- p-tau
- Aβ1-42
- Neurofilament light chain

The plasma concentration of these biomarkers will be assessed and analyzed using descriptive statistics, subgroup analysis, or statistical models if appropriate. The change from baseline in these biomarkers will also be estimated. Exploratory biomarkers may be reported separately.

6.8 EXPLORATORY ANALYSES

The change from baseline in the continuous, exploratory endpoints listed in Table 1 (including cognition and function endpoints, and endpoints measuring other AD symptoms and effects) will be analyzed using descriptive statistics or statistical models if appropriate. Further details will be given in the SAP.

Additionally, the feasibility of using amyloid PET data from the ongoing Studies WN29922 and WN39658 as an external control group will be explored for a comparison of measured amyloid reduction between dosing regimens. Additional details will be given in the SAP.

6.9 INTERIM ANALYSIS

6.9.1 Planned Interim Analysis

An interim analysis will be conducted on the latest data cut available at the time of the primary analysis for Studies WN29922 and WN39658. The maximum sample available at this timepoint with valid screening and Week 52 PET scans will be included in the analysis.

Change from baseline in amyloid PET load with the Q1W regimen will be assessed at Week 52. This may be compared with the predictions of the PK-PET model for this timepoint. At the time of the interim analysis, all available PK and safety data, responses to the Caregiver part of the home administration questionnaire, and exploratory endpoints may be reported descriptively as supporting evidence. The interim analysis will not impact the conduct of the study, i.e., early termination for futility or efficacy will not be considered.

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.

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 CLINICAL 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 Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

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 (seeSection 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 participant identification number. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

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

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

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, which may include data on genomic variants, 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 prior to study initiation. 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

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 40 sites globally will participate to enroll 192 participants. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate participant safety throughout the study.

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 health care 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 Screening up to Week 34 *for All Participants*

Assessment/Procedure	Screen	BL [a]	Dose-Escalation Period												UV
	Wk −8 to Wk −1	Day 1	Day 4	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 [b]	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	
Visit type [c]		I	I	I	I	I	I	I	I	-	T	-	T	-	I
Informed consent(s) [d]	x														
Review of inclusion/exclusion criteria	x	x													
Medical history, personal status, and demographics	x														
Clinical genotyping sample [e]	x														
Urinalysis [f]	x														
Urine sample for drugs of abuse [g]	x														
Coagulation (PT and aPTT)	x														
Viral serology (HIV, hepatitis B, and hepatitis C)	x														
12-lead ECG [h]	x	x				x			x						x
Plasma PK sample [i]		x	x						x						x [j]
Plasma ADA sample		x							x						x
Serum chemistry [k] and hematology [l]	x	x							x						x
Plasma biomarker sample	x								x						x [j]

Table 1 Screening up to Week 34 *for All Participants* (cont.)

Assessment/Procedure	Screen	BL [a]	Dose-Escalation Period												UV
	Wk –8 to Wk –1	Day 1	Day 4	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 [b]	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	
Clinical RNA samples	x														x [j]
Complete physical and neurologic exams [m]	x	x													
Limited physical exams [n]									x						x
Weight and height [o]	x	x							x						x
MRI [e, p]	x [q]					x			x						x [r]
PET scan [e]	x														
Clinical Dementia Rating	P&CG	P&CG							P&CG						P&CG
MMSE	P	P							P						P
ADAS-Cog 13		P							P						P
Verbal Fluency Task		P							P						P
Coding		P							P						P
ADCS-ADL		CG							CG						CG
C-SSRS BL/SLV		P							P						P
Home administration questionnaire															P&CG
Vital signs [s]	x	x	x	x	x	x	x	x	x						x
Concomitant medications	x	x	x	x	x	x	x	x	x		x		x		x
Adverse events [t]	x	x	x	x	x	x	x	x	x		x		x		x
Urine pregnancy test [u]	x														x

Table 1 Screening up to Week 34 *for All Participants* (cont.)

Assessment/Procedure	Screen	BL [a]	Dose-Escalation Period												UV
	Wk −8 to Wk −1	Day 1	Day 4	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 [b]	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	
Study drug administration (dose level [mg]) [v]		C (120)		C (120)	C (120)	S (255)	S (255)	S (255)	S (255)	H (255)	H (255)	H (255)	H (255)	H (255)	-
Caregiver diary [w]										x	x	x	x	x	

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; BL = baseline; APOE = apolipoprotein E; ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality-edema/effusion; ARIA-H = amyloid-related imaging abnormality-hemosiderin deposition; C = clinic administration by study staff; CG = caregiver completion; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; ET = early termination; H = visit appropriate for home/nonclinical administration, where applicable; I = in-clinic visit; MMA = methylmalonic acid; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; P = participant completion; P&CG = participant and caregiver completion; PET = positron emission tomography; PK = pharmacokinetic; Q1W = once a week; Q2W = every 2 *weeks*; Q4W = every 4 weeks; S = supervised at-clinic administration, where applicable; Screen = screening; SLV = since last visit; T = telephone visit; UV = unscheduled visit; Wk = week.

Notes: For Q4W injections, the dosing window is ±7 days, and the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. For Q2W and Q1W injections, the dosing window is ±3 days. The time window is +3 days for non-dosing Day 4.

Participants should use the actual Day 1 visit to calculate the timing of all subsequent visits, regardless of whether out-of-window visits may have occurred.

For participants who terminate early, assessments listed in the ET visit should be completed.

[a] Visit may be split over 2 days. All cognitive and functional assessments should be completed within 1 week prior to the first dose. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing, prior to dosing.

[b] 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, prior to dosing. Whenever possible, cognitive and functional *and PET* assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, for visits after start of study treatment, if the study partner (non-professional 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.

Table 1 Screening up to Week 34 *for All Participants* (cont.)

[c] Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to collect adverse event information and any other updates regarding the participant's health. The study staff is encouraged to have more frequent calls with a particular participant/study partner (non-professional caregiver) if considered appropriate by the investigator.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] PET and MRI scans at screening should be performed once all other screening results are available and none exclude the participant from the trial. In case of re-screening a participant, all screening assessments must be repeated other than the amyloid PET testing if performed within the previous 6 months for this study and within eligible ranges. Given that APOE status will not change over time, there is no need to repeat clinical genotyping in case of re-screening.

[f] Performed at the site by dipstick for blood, protein, glucose, and pH.

[g] Urine samples will be analyzed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone.

[h] 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, and brain MRI scans). 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.

[i] Accurate recording of the time of study drug administration and PK sample is necessary.

[j] An additional plasma and 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. 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).

[k] 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). During the screening period, Week 52, and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, MMA, T4, free T4, and TSH levels will also be assessed and should ideally be collected at least 4 hours after meals.

[l] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

Table 1 Screening up to Week 34 *for All Participants* (cont.)

[m] 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.

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

[o] Height measured at screening only.

[p] During the uptitration period, MRIs must be performed after the third dose of current dose level whilst on the Q4W schedule, or after the sixth dose of current dose level whilst on the Q2W schedule. MRIs should be performed at least 7 days prior to dose uptitration to the next dose level and the results must be available for review by the investigator or their qualified designee before the dosing can proceed. It is not recommended that the MRI is performed on the same day as the investigational medicinal product administration. During the Q4W schedule, it is recommended to do the MRI at least 10 days after the third dose of the current dose level.

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

[r] Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan as described in Sections 4.5.8 and 5.1.3.1.

[s] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[t] Adverse event information should be collected either at clinic visits or via a telephone call during at-home administration.

[u] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test at screening, within 24 hours before a PET scan, after the last study drug dose, and if a woman is suspected to have become pregnant. 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.

[v] Study drug administration should be performed only after all assessments for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed for a minimum of 2 hours after dosing for the first four doses. From the fifth dose, the observation time may be reduced to a minimum of 1 hour. At any supervised administration by study partner (non-professional caregiver), additional training may be given as per the investigator's judgment.

[w] If applicable, study partners (non-professional caregivers) will confirm completed administration in the home (nonclinical) setting using a caregiver diary (including date, time, correct injection location, and amount). They will also be asked to bring the diary to each visit to the clinic.

Table 2 Weeks 36–59 *for All Participants*

Assessment/Procedure	Target Dose												UV
	Wk 36	Wk 37–39	Wk 40	Wk 41–43	Wk 44	Wk 45–47	Wk 48	Wk 49–51	Wk 52 [a]	Wk 53–55	Wk 56	Wk 57–59	
Visit type [b]	I	-	T	-	T	-	T	-	I	-	T	-	I
12-lead ECG [c]									x				x
Plasma PK sample [d]	x								x				x [e]
Plasma ADA sample	x								x				x
Serum chemistry [f] and hematology [g]									x				x
Plasma biomarker samples	x								x				x [e]
Clinical RNA samples													x [e]
Limited physical exams [h]									x				x
Weight									x				x
MRI [i]	x						x [j]						x [k]
PET scan									x				
Clinical Dementia Rating									P&CG				P&CG
MMSE									P				P
ADAS-Cog 13									P				P
Verbal Fluency Task									P				P
Coding									P				P
ADCS-ADL									CG				CG
C-SSRS BL/SLV									P				P

Table 2 Weeks 36–59 *for All Participants* (cont.)

Assessment/Procedure	Target Dose												UV
	Wk 36	Wk 37–39	Wk 40	Wk 41–43	Wk 44	Wk 45–47	Wk 48	Wk 49–51	Wk 52 [a]	Wk 53–55	Wk 56	Wk 57–59	
Home administration questionnaire	P&CG								P&CG				P&CG
Vital signs [l]	x								x				x
Concomitant medications	x		x		x		x		x		x		x
Adverse events [m]	x		x		x		x		x		x		x
Urine pregnancy test [n]									x				x
Study drug administration (dose level [mg]) [o]	S (255)	H (255)	H (255)	H (255)	H (255)	H (255)	H (255)	H (255)	S (255)	H (255)	H (255)	H (255)	-
Caregiver diary [p]		x	x	x	x	x	x	x		x	x	x	

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 = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality-edema/effusion; ARIA-H = amyloid-related imaging abnormality-hemosiderin deposition; BL = baseline; CG = caregiver completion; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; ET = early termination; H = visit appropriate for home/nonclinical administration, where applicable; I = in-clinic visit; MMA = methylmalonic acid; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; P = participant completion; P&CG = participant and caregiver completion; PET = positron emission tomography; PK = pharmacokinetic; Q1W = once a week; S = supervised at-clinic administration, where applicable; SLV = since last visit; T = telephone visit; UV = unscheduled visit; Wk = week.

Notes: For Q1W injections, the dosing window is ± 3 days.

Participants should return to initial planned schedule per Day 1 for subsequent visits.

For participants who terminate early, assessments listed in the ET visit should be completed.

[a] Visit may be split over 2 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, prior to dosing. Whenever possible, cognitive and functional assessments *and PET* should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the study partner (non-professional 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.

Table 2 Weeks 36–59 *for All Participants* (cont.)

[b] Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to collect adverse event information and any other updates regarding the participant's health. The study staff is encouraged to have more frequent calls with a particular participant/study partner (non-professional caregiver) if considered appropriate by the investigator.

[c] Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The 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, and brain MRI scans). 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.

[d] Accurate recording of the time of study drug administration and PK sample is necessary.

[e] An additional plasma and 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. 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).

[f] 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). During the screening period, Week 52, and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, MMA, T4, free T4, and TSH levels will also be assessed and should ideally be collected at least 4 hours after meals.

[g] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

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

[i] During the target dose period, MRIs should be performed at least 7 days but not more than 13 days before the dosing visit that requires a safety MRI result. Results must be available for review by the investigator or their qualified designee before the dosing at the visit that requires a safety MRI can proceed.

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

[k] Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan as described in Sections 4.5.8 and 5.1.3.1.

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

Table 2 Weeks 36–59 *for All Participants* (cont.)

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] Adverse event information should be collected either at clinic visits or via a telephone call during at-home administration.

[n] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy at screening, within 24 hours before a PET scan, after the last study drug dose, and if a woman is suspected to have become pregnant. 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 for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed for a minimum of 2 hours after dosing for the first four doses. From the fifth dose, the observation time may be reduced to a minimum of 1 hour. At any supervised administration by study partner (non-professional caregiver), additional training may be given as per the investigator's judgment.

[p] If applicable, study partners (non-professional caregivers) will confirm completed administration in the home (nonclinical) setting using a caregiver diary (including date, time, correct injection location, and amount). They will also be asked to bring the diary to each visit to the clinic.

Table 3 Weeks 60–83 *for All Participants*

Assessment/Procedure	Target Dose												UV
	Wk 60	Wk 61–63	Wk 64	Wk 65–67	Wk 68	Wk 69–71	Wk 72	Wk 73–75	Wk 76 [a]	Wk 77–79	Wk 80	Wk 81–83	
Visit type [b]	T	-	I	-	T	-	T	-	I	-	T	-	
12-lead ECG [c]									x				x
Plasma PK sample [d]									x				x [e]
Plasma ADA sample									x				x
Serum chemistry [f] and hematology [g]									x				x
Plasma biomarker samples									x				x [e]
Clinical RNA samples													x [e]
Limited physical exams [h]									x				x
Weight									x				x
MRI [i]	x								x				x [j]
PET scan													
Clinical Dementia Rating									P&CG				P&CG
MMSE									P				P
ADAS-Cog 13									P				P
Verbal Fluency Task									P				P
Coding									P				P
ADCS-ADL									CG				CG
C-SSRS BL/SLV									P				P

Table 3 Weeks 60–83 *for All Participants (cont.)*

Assessment/Procedure	Target Dose												
	Wk 60	Wk 61–63	Wk 64	Wk 65–67	Wk 68	Wk 69–71	Wk 72	Wk 73–75	Wk 76 [a]	Wk 77–79	Wk 80	Wk 81–83	UV
Home administration questionnaire									P&CG				P&CG
Vital signs [k]			x						x				x
Concomitant medications	x		x		x		x		x		x		x
Adverse events [l]	x		x		x		x		x		x		x
Urine pregnancy test [m]													x
Study drug administration (dose level [mg]) [n]	H (255)	H (255)	S (255)	H (255)	H (255)	H (255)	H (255)	H (255)	S (255)	H (255)	H (255)	H (255)	
Caregiver diary [o]	x	x		x	x	x	x	x		x	x	x	

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 = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality-edema/effusion; ARIA-H = amyloid-related imaging abnormality-hemosiderin deposition; BL = baseline; CG = caregiver completion; C-SSRS = Columbia–Suicide Severity Rating Scale; ET = early termination; H = visit appropriate for home/nonclinical administration, where applicable; I = in-clinic visit; MMA = methylmalonic acid; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; P = participant completion; P&CG = participant and caregiver completion; PET = positron emission tomography; PK = pharmacokinetic; Q1W = once a week; S = supervised at-clinic administration, where applicable; SLV = since last visit; T = telephone visit; UV = unscheduled visit; Wk = week.

Notes: For Q1W injections, the dosing window is ±3 days.

Participants should return to initial planned schedule per Day 1 for subsequent visits.

For participants who terminate early, assessments listed in the ET visit should be completed.

[a] Visit may be split over 2 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, prior to dosing. Whenever possible, cognitive and functional assessments *and PET* should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the study partner (non-professional 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.

Table 3 Weeks 60–83 *for All Participants (cont.)*

[b] Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to collect adverse event information and any other updates regarding the participant's health. The study staff is encouraged to have more frequent calls with a particular participant/study partner (non-professional caregiver) if considered appropriate by the investigator.

[c] Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The 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, and brain MRI scans). 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.

[d] Accurate recording of the time of study drug administration and PK sample is necessary.

[e] An additional plasma and 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. 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).

[f] 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). During the screening period, Week 52, and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, MMA, T4, free T4, and TSH levels will also be assessed and should ideally be collected at least 4 hours after meals.

[g] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

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

[i] During the target dose period, MRIs should be performed at least 7 days but not more than 13 days before the dosing visit that requires a safety MRI result. Results must be available for review by the investigator or their qualified designee before dosing at the visit that requires a safety MRI can proceed.

[j] Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan as described in Sections 4.5.8 and 5.1.3.1.

[k] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

Table 3 Weeks 60–83 *for All Participants (cont.)*

[l] Adverse event information should be collected either at clinic visits or via a telephone call during at-home administration.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test at screening, within 24 hours before a PET scan, after the last study drug dose, and if a woman is suspected to have become pregnant. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed for a minimum of 2 hours after dosing for the first four doses. From the fifth dose, the observation time may be reduced to a minimum of 1 hour. At any supervised administration by study partner (non-professional caregiver), additional training may be given as per the investigator's judgment.

[o] If applicable, non-professional caregivers (study partners) will confirm completed administration in the home (nonclinical) setting using a caregiver diary (including date, time, correct injection location, and amount). They will also be asked to bring the diary to each visit to the clinic.

Table 4 Weeks 84–104, Early Termination Visit, and Follow-Up *for Participants Who Do Not Take Part in 2-Year Extension*

Assessment/ Procedure	Target Dose											ET [a]	FU	UV
	Wk 84	Wk 85–87	Wk 88	Wk 89–91	Wk 92	Wk 93–95	Wk 96	Wk 97–99	Wk 100 [a]	Wk 101–103	Wk 104 [a]		Wk 120	
Visit type [b]	T	-	I	-	T	-	T	-	T	-	I	I	I	
12-lead ECG [c]											x	x	x	x
Plasma PK sample [d]											x	x	x	x [e]
Plasma ADA sample											x	x	x	x
Serum chemistry [f] and hematology [g]											x	x	x	x
Plasma biomarker sample											x	x		x [e]
Clinical RNA sample											x	x		x [e]
Complete physical and neurologic exams [h]											x	x		
Limited physical exams [i]											x	x		x
Weight											x	x	x	x
MRI [j]											x [k]	x [k]		x [l]
PET scan											x	x [m]		
Clinical Dementia Rating											P&CG	P&CG		P&CG
MMSE											P	P		P
ADAS-Cog 13											P	P		P
Verbal Fluency Task											P	P		P
Coding											P	P		P

Table 4 Weeks 84–104, Early Termination Visit, and Follow-Up *for Participants Who Do Not Take Part in 2-Year Extension (cont.)*

Assessment/ Procedure	Target Dose											ET [a]	FU	UV
	Wk 84	Wk 85–87	Wk 88	Wk 89–91	Wk 92	Wk 93–95	Wk 96	Wk 97–99	Wk 100 [a]	Wk 101–103	Wk 104 [a]		Wk 120	
ADCS-ADL											CG	CG		CG
C-SSRS BL/SLV											P	P		P
Home administration questionnaire											P&CG	P&CG		P&CG
Vital signs [n]			x								x	x	x	x
Concomitant medications	x		x		x		x		x		x	x	x	x
Adverse events [o]	x		x		x		x		x		x	x	x	x
Urine pregnancy test [p]											x	x		x
Study drug administration (dose level [mg]) [q]	H (255)	H (255)	S (255)	H (255)	H (255)	H (255)	H (255)	H (255)	H (255)	H (255)			-	
Caregiver diary [r]	x	x		x	x	x	x	x	x	x				

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 = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality-edema/effusion; ARIA-H = amyloid-related imaging abnormality-hemosiderin deposition; BL = baseline; CG = caregiver completion; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; ET = early termination; FU = follow-up; H = visit appropriate for home/nonclinical administration, where applicable; I = in-clinic visit; MMA = methylmalonic acid; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; P = participant completion; P&CG = participant and caregiver completion; PET = positron emission tomography; PK = pharmacokinetic; S = supervised at-clinic administration, where applicable; Q1W = once a week; SLV = since last visit; T = telephone visit; UV = unscheduled visit.

Notes: For Q1W injections, the dosing window is ±3 days.

Participants should return to initial planned schedule per Day 1 for subsequent visits.

For participants who terminate early, assessments listed in the ET visit should be completed.

Table 4 Weeks 84–104, Early Termination Visit, and Follow-Up *for Participants Who Do Not Take Part in 2-Year Extension (cont.)*

[a] Visit may be split over 2 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, prior to dosing. Whenever possible, cognitive and functional assessments *and PET* should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the study partner (non-professional caregiver), the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to collect adverse events information and any other updates regarding the participant's health. The study staff is encouraged to have more frequent calls with a particular participant/study partner (non-professional caregiver) if considered appropriate by the investigator.

[c] Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The 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, and brain MRI scans). 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.

[d] Accurate recording of the time of study drug administration and PK sample is necessary.

[e] An additional plasma and 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. 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).

[f] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period, Week 52, and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, MMA, T4, free T4, and TSH levels will also be assessed and should ideally be collected at least 4 hours after meals.

[g] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

[h] 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.

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

Table 4 Weeks 84–104, Early Termination Visit, and Follow-Up *for Participants Who Do Not Take Part in 2-Year Extension (cont.)*

[j] During the target dose period, MRIs should be performed at least 7 days but not more than 13 days before the dosing visit that requires a safety MRI result. Results must be available for review by the investigator or their qualified designee before dosing at the visit that requires a safety MRI can proceed.

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

[l] Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan as described in Sections 4.5.8 and 5.1.3.1.

[m] In the event a participant terminates early, an amyloid PET scan should only be collected if at least 6 months have elapsed since the previous amyloid PET scan and if compatible with local/national regulation for annual radiation exposure limit.

[n] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[o] Adverse event information should be collected either at clinic visits or via a telephone call during at-home administration.

[p] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy at screening, within 24 hours before a PET scan, after the last study drug dose and if a woman is suspected to have become pregnant. 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 for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed a minimum of 2 hours after dosing for the first four doses. From the fifth dose, the observation time may be reduced to a minimum of 1 hour. At any supervised administration by study partner (non-professional caregiver), additional training may be given as per the investigator's judgment.

[r] If applicable, non-professional caregivers (study partners) will confirm completed administration in the home (nonclinical) setting using a caregiver diary (including date, time, correct injection location, and amount). They will also be asked to bring the diary to each visit to the clinic.

Table 5 Weeks 84–107 for Participants Who Take Part in 2-Year Extension

	Target Dose												
Assessment/ Procedure	*Wk 84*	*Wk 85–87*	*Wk 88*	*Wk 89–91*	*Wk 92*	*Wk 93–95*	*Wk 96*	*Wk 97–99*	*Wk 100*	*Wk 101–103*	*Wk 104* [a]	*Wk 105–107*	*UV*
Visit type [b]	*T*	-	*I*	-	*T*	-	*T*	-	*T*	-	*I*	-	
12-lead ECG [c]											*x*		*x*
Plasma PK sample [d]											*x*		*x* [e]
Plasma ADA sample											*x*		*x*
Serum chemistry [f] *and hematology* [g]											*x*		*x*
Plasma biomarker sample											*x*		*x* [e]
Clinical RNA sample											*x*		*x* [e]
Complete physical and neurologic exams [h]											*x*		
Limited physical exams [i]													*x*
Weight											*x*		*x*
MRI [j]											*x* [k]		*x* [l]
PET scan											*x*		
Clinical Dementia Rating											*P&CG*		*P&CG*
MMSE											*P*		*P*
ADAS-Cog 13											*P*		*P*
Verbal Fluency Task											*P*		*P*

Table 5 Weeks 84–107 for Participants Who Take Part in 2-Year Extension (cont.)

	Target Dose												
Assessment/Procedure	*Wk 84*	*Wk 85–87*	*Wk 88*	*Wk 89–91*	*Wk 92*	*Wk 93–95*	*Wk 96*	*Wk 97–99*	*Wk 100*	*Wk 101–103*	*Wk 104* [a]	*Wk 105–107*	*UV*
Coding											*P*		*P*
ADCS-ADL											*CG*		*CG*
C-SSRS BL/SLV											*P*		*P*
Home administration questionnaire											*P&CG*		*P&CG*
Vital signs [m]			*x*								*x*		*x*
Concomitant medications	*x*		*x*		*x*		*x*		*x*		*x*		*x*
Adverse events [n]	*x*		*x*		*x*		*x*		*x*		*x*		*x*
Urine pregnancy test [o]											*x*		*x*
Study drug administration (dose level [mg]) [p]	*H (255)*	*H (255)*	*S (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*S (255)*	*H (255)*	
Caregiver diary [q]	*x*	*x*		*x*	*x*	*X*	*x*	*x*	*x*	*x*		*x*	

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 =amyloid-related imaging abnormality; ARIA-E =amyloid-related imaging abnormality-edema/effusion; ARIA-H =amyloid-related imaging abnormality-hemosiderin deposition; BL =baseline; CG =caregiver completion; C-SSRS =Columbia–Suicide Severity Rating Scale; DTI =diffusion tensor imaging; ET =early termination; FU =follow-up; H =visit appropriate for home/nonclinical administration, where applicable; I =in-clinic visit; MMA =methylmalonic acid; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; P =participant completion; P&CG =participant and caregiver completion; PET =positron emission tomography; PK =pharmacokinetic; S =supervised at-clinic administration, where applicable; Q1W =once a week; SLV =since last visit; T =telephone visit; UV =unscheduled visit.

Notes: For Q1W injections, the dosing window is ±3 days.

Participants should return to initial planned schedule per Day 1 for subsequent visits.

Table 5 Weeks 84–107 for Participants Who Take Part in 2-Year Extension (cont.)

For participants who terminate early, assessments listed in the ET visit should be completed.

[a] *Visit may be split over 2 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, prior to dosing. Whenever possible, cognitive and functional assessments and PET should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the study partner (non-professional caregiver), the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.*

[b] *Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to collect adverse events information and any other updates regarding the participant's health. The study staff is encouraged to have more frequent calls with a particular participant/study partner (non-professional caregiver) if considered appropriate by the investigator.*

[c] *Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The 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, and brain MRI scans). 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.*

[d] *Accurate recording of the time of study drug administration and PK sample is necessary.*

[e] *An additional plasma and 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. 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).*

[f] *Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period, Week 52, and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, MMA, T4, free T4, and TSH levels will also be assessed and should ideally be collected at least 4 hours after meals.*

[g] *Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.*

[h] *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.*

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

Table 5 Weeks 84–107 for Participants Who Take Part in 2-Year Extension (cont.)

[j] *During the target dose period, MRIs should be performed at least 7 days but not more than 13 days before the dosing visit that requires a safety MRI result. Results must be available for review by the investigator or their qualified designee before dosing at the visit that requires a safety MRI can proceed.*

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

[l] *Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan as described in Sections 4.5.8 and 5.1.3.1.*

[m] *Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.*

[n] *Adverse event information should be collected either at clinic visits or via a telephone call during at-home administration.*

[o] *Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy at screening, within 24 hours before a PET scan, after the last study drug dose and if a woman is suspected to have become pregnant. 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.*

[p] *Study drug administration should be performed only after all assessments for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed a minimum of 2 hours after dosing for the first four doses. From the fifth dose, the observation time may be reduced to a minimum of 1 hour. At any supervised administration by study partner (non-professional caregiver), additional training may be given as per the investigator's judgment.*

[q] *If applicable, non-professional caregivers (study partners) will confirm completed administration in the home (nonclinical) setting using a caregiver diary (including date, time, correct injection location, and amount). They will also be asked to bring the diary to each visit to the clinic.*

Table 6 Weeks 108–131 for Participants Who Take Part in 2-Year Extension

	Target Dose													
Assessment/Procedure	*Wk 108*	*Wk 109–111*	*Wk 112*	*Wk 113–115*	*Wk 116*	*Wk 117–119*	*Wk 120*	*Wk 121–123*	*Wk 124*	*Wk 125–127*	*Wk 128*	*Wk 129*	*Wk 130* [a]	*UV*
Visit type [b]	*T*	-	*T*	-	*I*	-	*T*	-	*T*	-	*T*	-	*I*	
12-lead ECG [c]													*x*	*x*
Plasma PK sample [d]														*x* [e]
Plasma ADA sample														*x*
Serum chemistry [f] *and hematology* [g]													*x*	*x*
Plasma biomarker samples														*x* [e]
Clinical RNA samples														*x* [e]
Limited physical exams [h]													*x*	*x*
Weight													*x*	*x*
MRI [i]													*x*	*x* [j]
PET scan														
Clinical Dementia Rating													*P&C G*	*P&C G*
MMSE													*P*	*P*
ADAS-Cog 13													*P*	*P*
Verbal Fluency Task													*P*	*P*
Coding													*P*	*P*

Table 6 Weeks 108–131 for Participants Who Take Part in 2-Year Extension (cont.)

	Target Dose												
Assessment/Procedure	*Wk 108*	*Wk 109 –111*	*Wk 112*	*Wk 113–115*	*Wk 116*	*Wk 117–119*	*Wk 120*	*Wk 121–123*	*Wk 124*	*Wk 125–127*	*Wk 128*	*Wk 129*	*Wk 130* [a]	*UV*
ADCS-ADL													*CG*	*CG*
C-SSRS BL/SLV													*P*	*P*
Home administration questionnaire													*P&CG*	*P&CG*
Vital signs [k]					*x*								*x*	*x*
Concomitant medications	*x*		*x*		*x*		*x*		*x*		*x*		*x*	*x*
Adverse events [l]	*x*		*x*		*x*		*x*		*x*		*x*		*x*	*x*
Urine pregnancy test [m]														*x*
Study drug administration (dose level [mg]) [n]	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*S (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*S (255)*	
Caregiver diary [o]	*x*	*x*	*x*	*x*		*x*	*x*	*x*	*x*	*x*	*x*	*x*		

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 =amyloid-related imaging abnormality; ARIA-E =amyloid-related imaging abnormality-edema/effusion; ARIA-H =amyloid-related imaging abnormality-hemosiderin deposition; BL =baseline; CG =caregiver completion; C-SSRS =Columbia–Suicide Severity Rating Scale; DTI =diffusion tensor imaging; ET =early termination; FU =follow-up; H =visit appropriate for home/nonclinical administration, where applicable; I =in-clinic visit; MMA =methylmalonic acid; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; P =participant completion; P&CG =participant and caregiver completion; PET =positron emission tomography; PK =pharmacokinetic; S =supervised at-clinic administration, where applicable; Q1W =once a week; SLV =since last visit; T =telephone visit; UV =unscheduled visit.

Notes: For Q1W injections, the dosing window is ±3 days.

Participants should return to initial planned schedule per Day 1 for subsequent visits.

For participants who terminate early, assessments listed in the ET visit should be completed.

Table 6 Weeks 108–131 for Participants Who Take Part in 2-Year Extension (cont.)

[a] *Visit may be split over 2 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, prior to dosing. Whenever possible, cognitive and functional assessments and PET should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the study partner (non-professional caregiver), the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.*

[b] *Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to collect adverse events information and any other updates regarding the participant's health. The study staff is encouraged to have more frequent calls with a particular participant/study partner (non-professional caregiver) if considered appropriate by the investigator.*

[c] *Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The 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, and brain MRI scans). 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.*

[d] *Accurate recording of the time of study drug administration and PK sample is necessary.*

[e] *An additional plasma and 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. 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).*

[f] *Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period, Week 52, and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, MMA, T4, free T4, and TSH levels will also be assessed and should ideally be collected at least 4 hours after meals.*

[g] *Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.*

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

[i] *During the target dose period, MRIs should be performed at least 7 days but not more than 13 days before the dosing visit that requires a safety MRI result. Results must be available for review by the investigator or their qualified designee before dosing at the visit that requires a safety MRI can proceed.*

Table 6 Weeks 108–131 for Participants Who Take Part in 2-Year Extension (cont.)

[j] *Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan as described in Sections 4.5.8 and 5.1.3.1.*

[k] *Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.*

[l] *Adverse event information should be collected either at clinic visits or via a telephone call during at-home administration.*

[m] *Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy at screening, within 24 hours before a PET scan, after the last study drug dose and if a woman is suspected to have become pregnant. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.*

[n] *Study drug administration should be performed only after all assessments for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed a minimum of 2 hours after dosing for the first four doses. From the fifth dose, the observation time may be reduced to a minimum of 1 hour. At any supervised administration by study partner (non-professional caregiver), additional training may be given as per the investigator's judgment.*

[o] *If applicable, non-professional caregivers (study partners) will confirm completed administration in the home (nonclinical) setting using a caregiver diary (including date, time, correct injection location, and amount). They will also be asked to bring the diary to each visit to the clinic.*

Table 7 Weeks 132–155 for Participants Who Take Part in 2-Year Extension

	Target Dose													
Assessment/Procedure	*Wk 131–133*	*Wk 134*	*Wk 135–137*	*Wk 138*	*Wk 139–141*	*Wk 142*	*Wk 143–145*	*Wk 146*	*Wk 147–149*	*Wk 150*	*Wk 151-153*	*Wk 154*	*Wk 155*	*UV*
Visit type [a]	-	*T*	-	*T*	-	*I*	-	*T*	-	*T*	-	*T*	-	
12-lead ECG [b]														*x*
Plasma PK sample [c]														*x* [d]
Plasma ADA sample														*x*
Serum chemistry [e] *and hematology* [f]														*x*
Plasma biomarker samples														*x* [d]
Clinical RNA samples														*x* [d]
Limited physical exams [g]														*x*
Weight														*x*
MRI [h]														*x* [i]
PET scan														
Clinical Dementia Rating														*P&CG*
MMSE														*P*
ADAS-Cog 13														*P*
Verbal Fluency Task														*P*
Coding														*P*

Table 7 Weeks 132–155 for Participants Who Take Part in 2-Year Extension (cont.)

Assessment/Procedure	*Target Dose*													*UV*
	Wk 131–133	*Wk 134*	*Wk 135–137*	*Wk 138*	*Wk 139–141*	*Wk 142*	*Wk 143–145*	*Wk 146*	*Wk 147–149*	*Wk 150*	*Wk 151–153*	*Wk 154*	*Wk 155*	
ADCS-ADL														*CG*
C-SSRS BL/SLV														*P*
Home administration questionnaire														*P&CG*
Vital signs [j]						*x*								*x*
Concomitant medications		*x*		*x*		*x*		*x*		*x*		*x*		*x*
Adverse events [k]		*x*		*x*		*x*		*x*		*x*		*x*		*x*
Urine pregnancy test [l]														*x*
Study drug administration (dose level [mg]) [m]	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*S (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	
Caregiver diary [n]	*x*	*x*	*x*	*x*	*x*		*x*	*x*	*x*	*x*	*x*	*x*	*x*	

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 =amyloid-related imaging abnormality; ARIA-E =amyloid-related imaging abnormality-edema/effusion; ARIA-H =amyloid-related imaging abnormality-hemosiderin deposition; BL =baseline; CG =caregiver completion; C-SSRS =Columbia–Suicide Severity Rating Scale; DTI =diffusion tensor imaging; ET =early termination; FU =follow-up; H =visit appropriate for home/nonclinical administration, where applicable; I =in-clinic visit; MMA =methylmalonic acid; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; P =participant completion; P&CG =participant and caregiver completion; PET =positron emission tomography; PK =pharmacokinetic; S =supervised at-clinic administration, where applicable; Q1W =once a week; SLV =since last visit; T =telephone visit; UV =unscheduled visit.

Notes: For Q1W injections, the dosing window is ±3 days.

Participants should return to initial planned schedule per Day 1 for subsequent visits.

For participants who terminate early, assessments listed in the ET visit should be completed.

Table 7 Weeks 132–155 for Participants Who Take Part in 2-Year Extension (cont.)

[a] *Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to collect adverse events information and any other updates regarding the participant's health. The study staff is encouraged to have more frequent calls with a particular participant/study partner (non-professional caregiver) if considered appropriate by the investigator.*

[b] *Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The 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, and brain MRI scans). 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.*

[c] *Accurate recording of the time of study drug administration and PK sample is necessary.*

[d] *An additional plasma and 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. 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, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period, Week 52, and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, MMA, T4, free T4, and TSH levels will also be assessed and should ideally be collected at least 4 hours after meals.*

[f] *Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.*

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

[h] *During the target dose period, MRIs should be performed at least 7 days but not more than 13 days before the dosing visit that requires a safety MRI result. Results must be available for review by the investigator or their qualified designee before dosing at the visit that requires a safety MRI can proceed.*

[i] *Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan as described in Sections 4.5.8 and 5.1.3.1.*

[j] *Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.*

[k] *Adverse event information should be collected either at clinic visits or via a telephone call during at-home administration.*

Table 7 Weeks 132–155 for Participants Who Take Part in 2-Year Extension (cont.)

[l] *Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy at screening, within 24 hours before a PET scan, after the last study drug dose and if a woman is suspected to have become pregnant. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.*

[m] *Study drug administration should be performed only after all assessments for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed a minimum of 2 hours after dosing for the first four doses. From the fifth dose, the observation time may be reduced to a minimum of 1 hour. At any supervised administration by study partner (non-professional caregiver), additional training may be given as per the investigator's judgment.*

[n] *If applicable, non-professional caregivers (study partners) will confirm completed administration in the home (nonclinical) setting using a caregiver diary (including date, time, correct injection location, and amount). They will also be asked to bring the diary to each visit to the clinic.*

Table 8 Weeks 156–179 for Participants Who Take Part in 2-Year Extension

Assessment/Procedure	*Target Dose*												*UV*
	Wk 156 [a]	*Wk 157–159*	*Wk 160*	*Wk 161–163*	*Wk 164*	*Wk 165–167*	*Wk 168*	*Wk169 –171*	*Wk 172*	*Wk 173–175*	*Wk 176*	*Wk 177–179*	
Visit type [b]	*I*	-	*T*	-	*T*	-	*I*	-	*T*	-	*T*	-	
12-lead ECG [c]	*x*												*x*
Plasma PK sample [d]	*x*												*x* [e]
Plasma ADA sample	*x*												*x*
Serum chemistry [f] *and hematology* [g]	*x*												*x*
Plasma biomarker samples	*x*												*x* [e]
Clinical RNA samples													*x* [e]
Limited physical exams [h]	*x*												*x*
Weight	*x*												*x*
MRI [i]	*x* [j]												*x* [k]
PET scan	*x*												
Clinical Dementia Rating	*P&CG*												*P&CG*
MMSE	*P*												*P*
ADAS-Cog 13	*P*												*P*
Verbal Fluency Task	*P*												*P*
Coding	*P*												*P*

Table 8 Weeks 156–179 for Participants Who Take Part in 2-Year Extension (cont.)

	Target Dose												
Assessment/Procedure	*Wk 156* [a]	*Wk157–159*	*Wk 160*	*Wk 161–163*	*Wk 164*	*Wk 165–167*	*Wk 168*	*Wk169–171*	*Wk 172*	*Wk 173–175*	*Wk 176*	*Wk 177–179*	*UV*
ADCS-ADL	*CG*												*CG*
C-SSRS BL/SLV	*P*												*P*
Home administration questionnaire	*P&CG*												*P&CG*
Vital signs [l]	*x*						*x*						*x*
Concomitant medications	*x*		*x*		*x*		*x*		*x*		*x*		*x*
Adverse events [m]	*x*		*x*		*x*		*x*		*x*		*x*		*x*
Urine pregnancy test [n]	*x*												*x*
Study drug administration (dose level [mg]) [o]	*S (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*S (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	
Caregiver diary [p]		*x*	*x*	*x*	*x*	*x*		*x*	*x*	*x*	*x*	*x*	

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 =amyloid-related imaging abnormality; ARIA-E =amyloid-related imaging abnormality-edema/effusion; ARIA-H =amyloid-related imaging abnormality-hemosiderin deposition; BL =baseline; CG =caregiver completion; C-SSRS =Columbia–Suicide Severity Rating Scale; DTI =diffusion tensor imaging; ET =early termination; FU =follow-up; H =visit appropriate for home/nonclinical administration, where applicable; I =in-clinic visit; MMA =methylmalonic acid; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; P =participant completion; P&CG =participant and caregiver completion; PET =positron emission tomography; PK =pharmacokinetic; S =supervised at-clinic administration, where applicable; Q1W =once a week; SLV =since last visit; T =telephone visit; UV =unscheduled visit.

Notes: For Q1W injections, the dosing window is ±3 days.

Participants should return to initial planned schedule per Day 1 for subsequent visits.

For participants who terminate early, assessments listed in the ET visit should be completed.

Table 8 Weeks 156–179 for Participants Who Take Part in 2-Year Extension (cont.)

[a] *Visit may be split over 2 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, prior to dosing. Whenever possible, cognitive and functional assessments and PET should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the study partner (non-professional caregiver), the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.*

[b] *Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to collect adverse events information and any other updates regarding the participant's health. The study staff is encouraged to have more frequent calls with a particular participant/study partner (non-professional caregiver) if considered appropriate by the investigator.*

[c] *Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The 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, and brain MRI scans). 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.*

[d] *Accurate recording of the time of study drug administration and PK sample is necessary.*

[e] *An additional plasma and 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. 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).*

[f] *Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period, Week 52, and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, MMA, T4, free T4, and TSH levels will also be assessed and should ideally be collected at least 4 hours after meals.*

[g] *Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.*

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

[i] *During the target dose period, MRIs should be performed at least 7 days but not more than 13 days before the dosing visit that requires a safety MRI result. Results must be available for review by the investigator or their qualified designee before dosing at the visit that requires a safety MRI can proceed.*

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

Table 8 Weeks 156–179 for Participants Who Take Part in 2-Year Extension (cont.)

[k] *Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan as described in Sections 4.5.8 and 5.1.3.1.*

[l] *Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.*

[m] *Adverse event information should be collected either at clinic visits or via a telephone call during at-home administration.*

[n] *Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy at screening, within 24 hours before a PET scan, after the last study drug dose and if a woman is suspected to have become pregnant. 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 for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed a minimum of 2 hours after dosing for the first four doses. From the fifth dose, the observation time may be reduced to a minimum of 1 hour. At any supervised administration by study partner (non-professional caregiver), additional training may be given as per the investigator's judgment.*

[p] *If applicable, non-professional caregivers (study partners) will confirm completed administration in the home (nonclinical) setting using a caregiver diary (including date, time, correct injection location, and amount). They will also be asked to bring the diary to each visit to the clinic.*

Table 9 Weeks 180–203 for Participants Who Take Part in 2-Year Extension

Assessment/Procedure	*Target Dose*													*UV*
	Wk 180	*Wk 181*	*Wk 182* [a]	*Wk 183–185*	*Wk 186*	*Wk 187–189*	*Wk 190*	*Wk 191–193*	*Wk 194*	*Wk 195–197*	*Wk 198*	*Wk 199–201*	*Wk 202*	
Visit type [b]	*T*	-	*I*	-	*T*	-	*T*	-	*I*	-	*T*	-	*T*	
12-lead ECG [c]			*x*											*x*
Plasma PK sample [d]														*x* [e]
Plasma ADA sample														*x*
Serum chemistry [f] *and hematology* [g]			*x*											*x*
Plasma biomarker samples														*x* [e]
Clinical RNA samples														*x* [e]
Limited physical exams [h]			*x*											*x*
Weight			*x*											*x*
MRI [i]			*x*											*x* [j]
PET scan														
Clinical Dementia Rating			*P&C G*											*P&C G*
MMSE			*P*											*P*
ADAS-Cog 13			*P*											*P*
Verbal Fluency Task			*P*											*P*
Coding			*P*											*P*

Table 9 Weeks 180–203 for Participants Who Take Part in 2-Year Extension (cont.)

	Target Dose												
Assessment/Procedure	*Wk 180*	*Wk 181*	*Wk 182*[a]	*Wk 183–185*	*Wk 186*	*Wk 187–189*	*Wk 190*	*Wk 191–193*	*Wk 194*	*Wk 195–197*	*Wk 198*	*Wk 199–201*	*Wk 202*	*UV*
ADCS-ADL			*CG*											*CG*
C-SSRS BL/SLV			*P*											*P*
Home administration questionnaire			*P&CG*											*P&CG*
Vital signs [k]			*x*						*x*					*x*
Concomitant medications	*x*		*x*		*x*		*x*		*x*		*x*		*x*	*x*
Adverse events [l]	*x*		*x*		*x*		*x*		*x*		*x*		*x*	*x*
Urine pregnancy test [m]														*x*
Study drug administration (dose level [mg]) [n]	*H (255)*	*H (255)*	*S (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	*S (255)*	*H (255)*	*H (255)*	*H (255)*	*H (255)*	
Caregiver diary [o]	*x*	*x*		*x*	*x*	*x*	*x*	*x*		*x*	*x*	*x*	*x*	

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 =amyloid-related imaging abnormality; ARIA-E =amyloid-related imaging abnormality-edema/effusion; ARIA-H =amyloid-related imaging abnormality-hemosiderin deposition; BL =baseline; CG =caregiver completion; C-SSRS =Columbia–Suicide Severity Rating Scale; DTI =diffusion tensor imaging; ET =early termination; FU =follow-up; H =visit appropriate for home/nonclinical administration, where applicable; I =in-clinic visit; MMA =methylmalonic acid; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; P =participant completion; P&CG =participant and caregiver completion; PET =positron emission tomography; PK =pharmacokinetic; S =supervised at-clinic administration, where applicable; Q1W =once a week; SLV =since last visit; T =telephone visit; UV =unscheduled visit.

Notes: For Q1W injections, the dosing window is ±3 days.

Participants should return to initial planned schedule per Day 1 for subsequent visits.

For participants who terminate early, assessments listed in the ET visit should be completed.

Table 9 Weeks 180–203 for Participants Who Take Part in 2-Year Extension (cont.)

[a] *Visit may be split over 2 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, prior to dosing. Whenever possible, cognitive and functional assessments and PET should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the study partner (non-professional caregiver), the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.*

[b] *Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to collect adverse events information and any other updates regarding the participant's health. The study staff is encouraged to have more frequent calls with a particular participant/study partner (non-professional caregiver) if considered appropriate by the investigator.*

[c] *Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The 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, and brain MRI scans). 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.*

[d] *Accurate recording of the time of study drug administration and PK sample is necessary.*

[e] *An additional plasma and 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. 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).*

[f] *Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period, Week 52, and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, MMA, T4, free T4, and TSH levels will also be assessed and should ideally be collected at least 4 hours after meals.*

[g] *Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.*

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

[i] *During the target dose period, MRIs should be performed at least 7 days but not more than 13 days before the dosing visit that requires a safety MRI result. Results must be available for review by the investigator or their qualified designee before dosing at the visit that requires a safety MRI can proceed.*

Table 9 Weeks 180–203 for Participants Who Take Part in 2-Year Extension (cont.)

[j] *Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan as described in Sections 4.5.8 and 5.1.3.1.*

[k] *Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.*

[l] *Adverse event information should be collected either at clinic visits or via a telephone call during at-home administration.*

[m] *Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy at screening, within 24 hours before a PET scan, after the last study drug dose and if a woman is suspected to have become pregnant. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.*

[n] *Study drug administration should be performed only after all assessments for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed a minimum of 2 hours after dosing for the first four doses. From the fifth dose, the observation time may be reduced to a minimum of 1 hour. At any supervised administration by study partner (non-professional caregiver), additional training may be given as per the investigator's judgment.*

[o] *If applicable, non-professional caregivers (study partners) will confirm completed administration in the home (nonclinical) setting using a caregiver diary (including date, time, correct injection location, and amount). They will also be asked to bring the diary to each visit to the clinic.*

Table 10 Weeks 204–207, Early Termination Visit, and Follow-up for Participants Who Take Part in 2-Year Extension

	Target Dose				ET [a]	FU	UV
Assessment/ Procedure	Wk 203–205	Wk 206	Wk 207	Wk 208 [a]		Wk 224	
Visit type [b]	-	T	-	I	I	I	
12-lead ECG [c]				x	x	x	x
Plasma PK sample [d]				x	x	x	x [e]
Plasma ADA sample				x	x	x	x
Serum chemistry [f] and hematology [g]				x	x	x	x
Plasma biomarker sample				x	x		x [e]
Clinical RNA sample				x	x		x [e]
Complete physical and neurologic exams [h]				x	x		
Limited physical exams [i]							x
Weight				x	x	x	x
MRI [j]				x [k]	x [k]		x [l]
PET scan				x	x [m]		
Clinical Dementia Rating				P&CG	P&CG		P&CG
MMSE				P	P		P
ADAS-Cog 13				P	P		P

Table 10 Weeks 204–207, Early Termination Visit, and Follow-up for Participants Who Take Part in 2-Year Extension (cont.)

	Target Dose				ET [a]	FU	UV
Assessment/ Procedure	Wk 203–205	Wk 206	Wk 207	Wk 208 [a]		Wk 224	
Verbal Fluency Task				P	P		P
Coding				P	P		P
ADCS-ADL				CG	CG		CG
C-SSRS BL/SLV				P	P		P
Home administration questionnaire				P&CG	P&CG		P&CG
Vital signs [n]				x	x	x	x
Concomitant medications		x		x	x	x	x
Adverse events [o]		x		x	x	x	x
Urine pregnancy test [p]				x	x		x
Study drug administration (dose level [mg]) [q]	H (255)	H (255)	H (255)			-	
Caregiver diary [r]	x	x	x				

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 =amyloid-related imaging abnormality; ARIA-E =amyloid-related imaging abnormality-edema/effusion; ARIA-H =amyloid-related imaging abnormality-hemosiderin deposition; BL =baseline; CG =caregiver completion; C-SSRS =Columbia–Suicide Severity Rating Scale; DTI =diffusion tensor imaging; ET =early termination; FU =follow-up; H =visit appropriate for home/nonclinical administration, where applicable; I =in-clinic visit; MMA =methylmalonic acid; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; P =participant completion; P&CG =participant and caregiver completion; PET =positron emission tomography; PK =pharmacokinetic; S =supervised at-clinic administration, where applicable; Q1W =once a week; SLV =since last visit; T =telephone visit; UV =unscheduled visit.

Table 10 Weeks 204–207, Early Termination Visit, and Follow-up for Participants Who Take Part in 2-Year Extension (cont.)

Notes: For Q1W injections, the dosing window is ±3 days.

Participants should return to initial planned schedule per Day 1 for subsequent visits.

For participants who terminate early, assessments listed in the ET visit should be completed.

[a] *Visit may be split over 2 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, prior to dosing. Whenever possible, cognitive and functional assessments and PET should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the study partner (non-professional caregiver), the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.*

[b] *Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and/or study partner (non-professional caregiver) to collect adverse events information and any other updates regarding the participant's health. The study staff is encouraged to have more frequent calls with a particular participant/study partner (non-professional caregiver) if considered appropriate by the investigator.*

[c] *Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The 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, and brain MRI scans). 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.*

[d] *Accurate recording of the time of study drug administration and PK sample is necessary.*

[e] *An additional plasma and 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. 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).*

[f] *Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period, Week 52, and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, MMA, T4, free T4, and TSH levels will also be assessed and should ideally be collected at least 4 hours after meals.*

[g] *Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.*

Table 10 Weeks 204–207, Early Termination Visit, and Follow-up for Participants Who Take Part in 2-Year Extension (cont.)

[h] *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.*

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

[j] *During the target dose period, MRIs should be performed at least 7 days but not more than 13 days before the dosing visit that requires a safety MRI result. Results must be available for review by the investigator or their qualified designee before dosing at the visit that requires a safety MRI can proceed.*

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

[l] *Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan as described in Sections 4.5.8 and 5.1.3.1.*

[m] *In the event a participant terminates early, an amyloid PET scan should only be collected if at least 6 months have elapsed since the previous amyloid PET scan and if compatible with local/national regulation for annual radiation exposure limit.*

[n] *Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.*

[o] *Adverse event information should be collected either at clinic visits or via a telephone call during at-home administration.*

[p] *Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy at screening, within 24 hours before a PET scan, after the last study drug dose and if a woman is suspected to have become pregnant. 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 for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed a minimum of 2 hours after dosing for the first four doses. From the fifth dose, the observation time may be reduced to a minimum of 1 hour. At any supervised administration by study partner (non-professional caregiver), additional training may be given as per the investigator's judgment.*

[r] *If applicable, non-professional caregivers (study partners) will confirm completed administration in the home (nonclinical) setting using a caregiver diary (including date, time, correct injection location, and amount). They will also be asked to bring the diary to each visit to the clinic.*

Appendix 2
Management Rules for Amyloid-Related Imaging Abnormalities

Event	Characteristics	Action to Be Taken
ARIA-E	Asymptomatic ARIA-E and BGTS < 4	• Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI scan 4 weeks later (for participants on Q1W dosing frequency, this can be after the third or fourth dose). • As long as BGTS is < 4 and ≥ 1, continue study drug at the same dose level and repeat MRI 4 weeks later (for participants on Q1W dosing frequency, this can be after the third or fourth dose). • Once ARIA-E resolves, resume dosing including uptitration. For participants in the uptitration phase, obtain a MRI scan per the titration schedule. For participants on the target dose, perform another MRI scan 3 months after study drug reintroduction.
	Symptomatic ARIA-E (of any size) or asymptomatic ARIA-E and BGTS ≥ 4	• Temporarily interrupt study drug and perform MRI scans at 4-week intervals until symptoms and ARIA-E resolve. • When symptoms and ARIA-E resolve, reintroduce study drug at dose given at the time the event was detected. • Perform a MRI scan after the first dose while participants are on a Q4W dosing frequency, or after the second dose while participants are on a Q2W dosing frequency or after the third or fourth dose for participants on a Q1W dosing frequency. • If no new ARIA-E is detected, resume uptitration and obtain an MRI per the titration schedule. For participants on the Q1W dosing frequency, perform another MRI scan 3 months after study drug reintroduction.
	Any recurrence of ARIA-E	• Treat the same as the first event (based on symptoms and BGTS).
ARIA-H	ARIA-H > 15 cumulatively (should not include any disseminated LH)	• Permanently discontinue study drug.

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–hemosiderin deposition; BGTS = Barkhof grand total score; LH = leptomeningeal hemosiderosis; MRI = magnetic resonance imaging; Q1W = once a week; Q2W = every 2 weeks; Q4W = every 4 weeks.

The investigator may choose to perform additional magnetic resonance imaging (MRI) monitoring for amyloid-related imaging abnormality (ARIA) at any time.

Symptomatic amyloid-related imaging abnormality-edema/effusion (ARIA-E) is defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings.

Any recurrence of ARIA-E: Treat using the same procedures as for the first event (based on symptoms and Barkhof grand total score [BGTS]).

Participants who develop amyloid-related imaging abnormality–hemosiderin deposition (ARIA-H) $>$ 15 cumulatively will be discontinued from study drug (the cumulative number should not include any disseminated leptomeningeal hemosiderosis, i.e., more than 3 focal leptomeningeal hemosiderosis cumulatively. A focal leptomeningeal hemosiderosis is counted as one ARIA-H).

In cases where both ARIA-E and ARIA-H occur, the most conservative approach should be followed.

In exceptional cases, as determined by the Sponsor and investigator:

Q4W monitoring may no longer be necessary in case of an ARIA-E that is asymptomatic with BGTS $<$ 4 and considered stable over consecutive MRI images; or symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue.

The study drug can be either reintroduced or uptitrated, as applicable, in case of an asymptomatic ARIA-E that has stabilized at BGTS $<$ 4; or a symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue.

A pharmacokinetic 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).

An additional plasma and 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, or resolved ARIA-E).

Any other new significant findings will be reviewed by the Medical Monitor and appropriate dose action will be proposed.

Appendix 3
National Institute on Aging-Alzheimer's Association Criteria for Mild Alzheimer's Disease

NIA-AA Category	Description
Probable dementia: core clinical criteria Meets criteria for dementia described earlier in the text, and, in addition, has the following characteristics:	A. Insidious onset: Symptoms have a gradual onset over months to years, not sudden over hours or days. B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: 1. Amnestic presentation • It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text. 2. Non-amnestic presentations • Language presentation: The most prominent deficits are in word finding, but deficits in other cognitive domains should be present. • Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. • Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurologic disease, or a non-neurologic medical comorbidity or use of medication that could have a substantial effect on cognition.

NIA-AA Category	Description
Probable AD dementia with increased level of certainty	**Probable AD dementia with documented decline** In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology. Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations. **Probable AD dementia in a carrier of a causative AD genetic mutation** In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2) increases the certainty that the condition is caused by AD pathology. The working group noted that carriage of the ε4 allele of the APOE gene was not sufficiently specific to be considered in this category.
Probable AD dementia with evidence of the AD pathophysiological process	AD dementia is part of a continuum of clinical and biological phenomena. AD dementia is fundamentally a clinical diagnosis. To make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; APOE = apolipoprotein E; CSF = cerebral spinal fluid; NIA-AA = National Institute on Aging-Alzheimer's Association; PET = positron emission tomography.

REFERENCE

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9.

Appendix 4
National Institute on Aging-Alzheimer's Association Criteria for Prodromal Alzheimer's Disease (Mild Cognitive Impairment due to Alzheimer's Disease

NIA-AA Category	Clinical and Cognitive Criteria
Clinical criteria	• Cognitive concern reflecting a change in cognition reported by participant or informant or clinician (i.e., historical or observed evidence of decline over time) • Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains) • Preservation of independence in functional abilities • Not demented
Etiology of MCI consistent with AD pathophysiological process	• Rule out vascular, traumatic, medical causes of cognitive decline, when possible. • Provide evidence of longitudinal decline in cognition, when feasible. • Report history consistent with AD genetic factors, when relevant.
Prodromal AD dementia with evidence of the AD pathophysiological process	Prodromal AD is part of a continuum of clinical and biological phenomena. Prodromal AD is fundamentally a clinical diagnosis. To make a diagnosis of prodromal AD with biomarker support, the core clinical diagnosis of prodromal AD must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; CSF = cerebral spinal fluid; MCI = mild cognitive impairment; NIA-AA = National Institute on Aging-Alzheimer's Association; PET = positron emission tomography.

REFERENCES

Albert MS, DeKosky ST, Dickson B, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–9.

Signature Page for: System identifier:RIM-CLIN-439968
Protocol - WN29722 - GANTENERUMAB - v3 - Global/Core - Published

Approval Task	[redacted] Company Signatory 16-May-2022 09:55:36 GMT+0000