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

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STATISTICAL ANALYSIS PLAN

STUDY 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**

STUDY NUMBER: WN29722

STUDY NAME: GRADUATION

VERSION NUMBER: 1.0

ROCHE COMPOUND(S): Gantenerumab (RO4909832)

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DATE FINAL: See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on Roche SAP model document v2.0, revised 26 October 2020.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	see electronic date stamp on the last page of this document	Version 3.0, 16 May 2022

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AD	Alzheimer's Disease
ADA	anti-drug antibody
AE	adverse event
APOE ε4	apolipoprotein E allele ε4
ARIA-E	amyloid-related imaging abnormalities – edema/effusion
ARIA-H	amyloid-related imaging abnormalities – hemosiderin deposition
BGTS	Barkhof Grand Total Score
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating global score
CI	confidence interval
CL	centiloid
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
HAQ	Home Administration Questionnaire
HCP	health care professional
HN	home nursing
IA	interim analysis
ICE	intercurrent event
ICH	International Council on Harmonization
IMC	Internal Monitoring Committee
IND	investigational new drug
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
M-SE	MRI safety evaluable
NIA-AA	National Institute on Aging/Alzheimer's Association
OLE	open label extension
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic

Abbreviation or Term	Description
Q1W	once a week
Q2W	every two weeks
Q4W	every four weeks
ROI	region of interest
SAE	serious adverse events
SAP	Statistical Analysis Plan
SC	subcutaneous
SE	safety-evaluable
SUVR	standardized uptake value ratio

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) document is to describe the data handling rules, derivation rules, and statistical analysis methodologies, tables and/or graphical displays for the interim analysis (IA) and primary analysis of the data from Study WN29722 (hereafter referred to as "GRADUATION"). This document will focus on the statistical methodology underlying the interim and primary Clinical Study Reports (CSR).

The description of layouts for the CSR outputs, the details about the underlying analysis datasets and programs, and the linking of production outputs to sections in the CSR, are not within the scope of this document and will be covered in separate documents.

The language used in this SAP supersedes that in the protocol and protocol synopsis. This SAP document has been developed based on the study protocol (version 3) issued on 16 May 2022. The final analyses planned for the optional two-year extension of the study until Week 208 will be described in a subsequent version of this SAP or in a separate document.

1.1 OBJECTIVES, ENDPOINTS AND ESTIMANDS

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 first 104 weeks of the study are outlined in Table 1 below. Details of endpoints pertaining to the optional two-year extension of the study can be found in Protocol Section 2.

Table 1 Objectives and Corresponding Endpoints/Estimands for the Interim and Primary Analyses

	Interim Analyses	Primary Analyses
Primary Objective	**Corresponding Endpoint and Estimand**	**Corresponding Endpoint and Estimand**
• 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 in deposited amyloid as measured by brain amyloid PET CL levels **Estimand:** • **Target Population**: Early (prodromal to mild) AD population as identified by the inclusion and exclusion criteria, see Protocol Sections 4.1.1 and 4.1.2 • **Variable**: Change from baseline to Week 52 in amyloid PET Centiloid • **Treatment**: Prescribed study drug including up-titration to the target dose • **Population-level summary:** Variable mean within the treatment arm • **Intercurrent Event (ICE):** Substantial reduction in drug exposure due to the COVID-19 pandemic (defined as ≥ 4 missed dose-months). Treatment discontinuation due to any reason. These ICEs will be handled by hypothetical strategy.	• The change from baseline to Week 104 in deposited amyloid as measured by brain amyloid PET CL levels **Estimand:** • **Target Population**: Early (prodromal to mild) AD population as identified by the inclusion and exclusion criteria, see Protocol Sections 4.1.1 and 4.1.2 • **Variable**: Change from baseline to Week 104 in amyloid PET Centiloid • **Treatment**: Prescribed study drug including up-titration to the target dose • **Population-level summary**: Variable mean within the treatment arm • **Intercurrent Event (ICE):** Substantial reduction in drug exposure due to the COVID-19 pandemic (defined as ≥ 4 missed dose-months). Treatment discontinuation due to any reason. These ICEs will be handled by hypothetical strategy.
Secondary Objective	**Corresponding Endpoint**	**Corresponding Endpoint**
• To evaluate caregiver overall satisfaction and confidence with home administration	• Responses to home administration questionnaire (Caregiver) up to Week 52	• Responses to home administration questionnaire (Caregiver) up to Week 104

Table 1 Objectives and Corresponding Endpoints/Estimands (cont.)

	Interim Analyses	Primary Analyses
Safety Objective	**Corresponding Endpoints**	**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	• 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**	**Corresponding Endpoints**
• To characterize the PK profile of gantenerumab using a new titration scheme and especially at the Q1W dosing frequency	• Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints	• Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints
• To assess the PD effect of the dosing frequency (e.g., Q1W, Q2W) on brain amyloid	• 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., GRADUATE I and GRADUATE II)	• 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., GRADUATE I and GRADUATE II)

Table 1 Objectives and Corresponding Endpoints/Estimands (cont.)

	Interim Analyses	Primary Analyses
Exploratory Biomarker Objective	**Corresponding Endpoints**	**Corresponding Endpoints**
• To evaluate the pharmacodynamic effect of gantenerumab at the Q1W dosing regimen on plasma and MRI biomarkers	N/A	• Change from baseline in plasma biomarkers (including, but not limited to, phosphorylated tau and NFL) to Week 104 • Change from baseline to Week 104 in functional brain connectivity, as measured by resting-state functional MRI (where available) • Change from baseline to Week 104 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.

Table 1 Objectives and Corresponding Endpoints/Estimands (cont.)

	Interim Analyses	Primary Analyses
Exploratory Objectives	**Corresponding Endpoints**	**Corresponding Endpoints**
• To compare the effect of a Q1W to a Q2W dosing regimen on amyloid reduction using external controls[a]	• N/A	• The change from baseline to Week 52 and Week 104 in deposited amyloid as measured by brain amyloid PET compared with the change in the pivotal GRADUATE I and GRADUATE II studies[a]
• To evaluate the effects of gantenerumab at the Q1W dosing on cognitive and functional endpoints	• N/A	• The change from baseline to Week 104 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 52	
• To evaluate patient overall satisfaction with at home administration		• Responses to home administration questionnaire (Patient) up to Week 104

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.

[a] Pooled analyses with data from the pivotal Studies WN29922 (GRADUATE I) and WN39658 (GRADUATE II) will be described in a separate SAP and provided in a separate report.

1.2 STUDY DESIGN

GRADUATION is a Phase II, multicenter, open-label, single arm, pharmacodynamics (PD) study in participants with early (prodromal to mild) Alzheimer's Disease (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 positron emission tomography (PET). The dosing regimen being evaluated in current Phase III studies (WN29922 [hereafter referred to as "GRADUATE I"] and WN39658 [hereafter referred to as "GRADUATE II"]) is gantenerumab 120 mg subcutaneous (SC) injection 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 every two weeks (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 once a week (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, GRADUATION 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 approximately 150 participants were planned to be enrolled in participating countries in protocol Version 1. Approximately 40 centers in approximately 8 countries worldwide were planned to participate in this study. Due to a lower than expected screen failure rate at the end of the enrollment period, a total of 192 participants have been enrolled in a total of 38 centers in 8 countries worldwide that participate 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 magnetic resonance imaging (MRI) protocol (including T2*-weighted gradient−recalled echo and fluid−attenuated inversion recovery). 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 an approved 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 as detailed in the Protocol (version 3.0), 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 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 opt for the two-year extension of GRADUATION, 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. 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). Participants who opt for the two-year extension of GRADUATION will receive the final dose of study drug at Week 207. Final PD and efficacy assessments will be performed one week later at Week 208. Eligible participants may qualify for continued access or ongoing extension studies as outlined in the Protocol (version 3.0), 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).

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 the Protocol (version 3.0), Section 4.3.2.1.

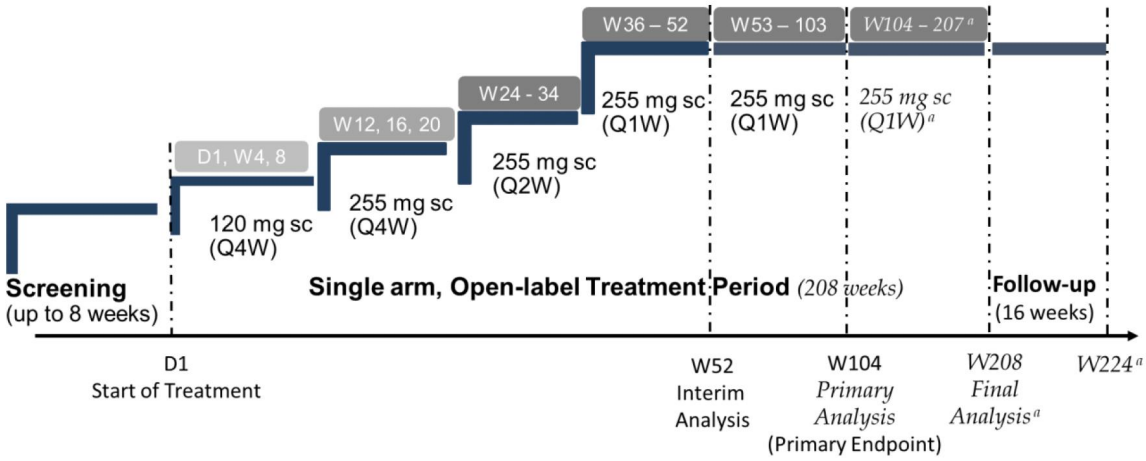
Participants will undergo brain MRI examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader (for more details regarding imaging-related criteria, see the Protocol (version 3.0), Section 4.1.2.2). Participants will also undergo standard 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 the Protocol (version 3.0), 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 the Protocol [version 3.0], Section 4.5.1).

An interim analysis will be conducted on the latest data cut available at the time of the primary analysis for GRADUATE I and GRADUATE II, and it will include descriptive analyses only. The primary analysis will be performed after database lock when the last participant has completed the Week 104 assessment or discontinued the study.

The study schema is shown in Figure 1.

Figure 1 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 two-year extension.

1.2.1 Treatment Assignment

Since this is a single-arm study, all participants will be assigned to the same treatment and no randomization is performed.

1.2.2 Independent Review Facility

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessment of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7-10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to next dosing or prior to the Week 104 visit (refer to the Protocol (version 3.0), 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.

1.2.3 Data Monitoring

An Internal Monitoring Committee (IMC) will be employed to monitor and evaluate participant safety throughout the study.

The incidence, severity, and nature of adverse events (AEs), serious adverse events (SAEs), amyloid-related imaging abnormalities (ARIA) – edema/effusion (ARIA-E) and amyloid-related imaging abnormalities – hemosiderin deposition (ARIA-H), and laboratory abnormalities will be assessed on a regular basis by the Sponsor's IMC, as documented in the IMC Charter.

The Sponsor Safety Scientist and the Study Clinical Scientist will review the SAEs periodically and submit IND safety reports to the regulatory agencies, Institutional Review Boards / Independent Ethics Committees, and the IMC for any unexpected or serious events (as well as to the iDMC for GRADUATE I/II if deemed necessary). The main scope of the IMC is to review accumulating safety data for gantenerumab under the Q1W dosing regimen. Through summary and review of study data, the IMC will help the study Clinical Scientist minimize subject exposure to undue risk. Starting from 8 months after first-patient-in, the IMC will meet approximately every 3 to 6 months to review summaries of overall rates of death, ARIAs, AEs, and SAEs.

2. STATISTICAL HYPOTHESES

No statistical hypotheses will be tested in this study. All analyses are descriptive or purely exploratory.

3. SAMPLE SIZE DETERMINATION

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 (CI) around its true value. With a standard deviation of 25.67 CL (see below), 150 participants are required to fulfill this criterion. However, due to a lower than expected screen failure rate at the end of the enrollment period, a total of 192 participants have been enrolled.

The standard deviation of amyloid reduction was estimated using amyloid PET data from the ongoing Studies WN25203 (hereafter referred to as “SCarlet RoAD”) and WN28745 (hereafter referred to as “Marguerite RoAD”) open label extension (OLE) periods (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 Marguerite RoAD OLE at Week 104 that was ongoing at the time the study protocol was written. A sample size increase may be considered if factors external to the study would warrant a change to the sample size assumption.

4. ANALYSIS SETS

The following analysis sets are defined:

Analysis Set	Definition
Intent to treat (ITT)	All enrolled participants (i.e., who gave informed consent, did not fail screening, and had at least one Amyloid PET scan with a valid quantitative measurement performed with either florbetaben or flutemetamol), whether or not the participant received the assigned treatment.
Safety-evaluable (SE)	All participants enrolled who received at least one dose of study treatment, whether prematurely withdrawn from the study or not.
MRI safety-evaluable (M-SE)	All participants of the SE analysis set who had at least one post-baseline MRI assessment.
Amyloid-PET-longitudinal	All participants in the ITT analysis set with a valid post-baseline quantitative amyloid PET measurement performed with either florbetaben or flutemetamol.
MRI modified intent-to-treat (MRI-mITT)	All participants in the ITT analysis set who had at least one valid volumetric MRI quantitative measurement.
MRI-longitudinal	All participants in the MRI-mITT with at least one valid post-baseline volumetric MRI quantitative measurement.

Opportunity for home dosing safety-evaluable (OH-SE)	All participants of the SE analysis set who did not discontinue study drug before week 26.
Home dosing by study partner safety-evaluable (H-SE)	All participants of the SE analysis set who received at least one dose of study treatment administered at home by caregiver / study partner.

ITT = intent to treat; H-SE = safety-evaluable with home dosing by study partner; M-SE = safety-evaluable with post-baseline MRI; MRI = magnetic resonance imaging; MRI-mITT = modified intent-to-treat with at least one valid vMRI measurement; OH-SE = safety evaluable with opportunity for home dosing by study partner; SE = safety-evaluable;.

5. STATISTICAL ANALYSES

Details of the interim and primary statistical analysis to be conducted on data collected from Day 1 through Week 104 are detailed in Section 5.1 through Section 5.8. Details of the final analyses planned for the optional two-year extension of the study until Week 208 will be described in a subsequent version of this SAP or in a separate document.

5.1 GENERAL CONSIDERATION

In the following sections, for all continuous variables for which descriptive statistics are indicated, the following statistics will be reported: the number of observations, the mean, median, standard deviation, and minimum and maximum. The 25th and 75th percentiles (Q1 and Q3) will also be reported for selected tables. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of participants.

For safety endpoints, the baseline is defined as the last available assessment prior to first study drug intake. For all other assessments, the baseline is defined as the last available assessment before or on the day of first study drug intake, unless specified otherwise.

All PD analyses and all clinical efficacy analyses will be performed on the ITT analysis set, unless specified otherwise. Safety analyses will be performed on the SE analysis set, except for analyses of MRI findings which will be performed on the M-SE analysis set and analyses of home administrations by study partner that will be performed on the SE, OH-SE, or H-SE analysis sets, as appropriate.

All analyses will be purely descriptive or exploratory without any formal hypothesis testing. For exploratory tests, a two-sided significance level of 5% will be used.

In general, missing outcome data will not be replaced or imputed unless specified otherwise. Number and percentage of missing data points will be reported for each visit for key endpoints of interest.

In statistical models using change from baseline of a given outcome measure as the dependent variable, participants with missing baseline outcome measure will be

excluded from the analysis. There will be no imputation of baseline value for outcome measures.

The impact of the COVID-19 pandemic on the study and its conduct will be monitored and the overall impact will be assessed and described in the Clinical Study Report.

5.1.1 Visit Windowing

The analysis of data will be undertaken using reporting windows. As all the endpoints in the study are collected at different time frequencies, different sets of reporting windows will be applied depending on the frequency of assessments. In case of more than one assessment within a time window, the assessment with the date closest to the target (scheduled) day will be selected.

For amyloid PET assessments, time windows will be used (Table 2). Because of visit windowing, data collected at an early termination visit will be summarized at the appropriate time in the trial. For participants who have discontinued treatment early, if a PET scan is performed more than 56 days after the date of last dose, the PET scan will not be used for the analysis.

Table 2 Time Windows for Amyloid PET Endpoints

Visit	Target study day	Time window
Baseline	1	Up to day 1
Week 52	365	281, 449
Week 104	729	645, 813

For endpoints of home administration questionnaire (Caregiver or Patient), time windows will be applied (Table 3).

Table 3 Time Windows for Home Administration Questionnaire Endpoints

Visit	Target study day	Time window
Baseline	- (no baseline assessment planned)	- (no baseline assessment planned)
Week 36	253	2, 308
Week 52	365	309, 448
Week 76	533	449, 630
Week 104	729	631, 770

For cognitive and functional endpoints, time windows will be applied (Table 4)

Table 4 Time Windows for Cognitive and Functional Endpoints

Visit	Target study day	Time window
Baseline	1	Up to Day 1
Week 24	169	2, 266
Week 52	365	267, 448
Week 76	533	449, 630
Week 104	729	631, 770

5.2 PARTICIPANT DISPOSITION

The analysis of participant disposition will be based on the ITT analysis set. The number of enrolled participants will be tabulated by geographical region, country, and site.

The number of participants enrolled, treated with study drug, discontinued study drug, discontinued study, and completed study will be tabulated. Reasons for study drug discontinuations and for study discontinuations will be listed and summarized.

Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized. Separate tables will be provided for COVID-19-related major protocol deviations and reasons for COVID-19-related major protocol deviations.

5.3 PRIMARY ENDPOINT ANALYSIS

5.3.1 Definition of 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 centiloid (CL) conversion scale. For the purposes of analysis, the screening amyloid PET scan may be considered the baseline evaluation.

Brain amyloid load will be quantified in terms of Standardized Uptake Value Ratio (SUVR), defined as the ratio of the tracer uptake in a target region of interest (ROI) to the tracer uptake in a reference ROI. The target ROI is a weighted composite of the following regions (left and right), where each region is weighted by its own volume: frontal, temporal, parietal lobes, anterior and posterior cingulate gyri. The reference ROI is the whole cerebellum. The whole cerebellum region is represented by a weighted average of Cerebellum Ventral, Cerebellum Dorsal (left and right), and Cerebellar White Matter.

For each participant at each visit, SUVR will be linearly transformed to the standardized CL scale using the following formula:

$$CL = 175.6 \times SUVR_{WC}^{FBB} - 174.2$$

The CL variable is the current common standard in the scientific community.

5.3.2 Definition of Primary Estimand

The scientific question of interest is to assess the effect of the intended study treatment on the PD endpoint, change from baseline to Week 104 in brain amyloid load, in participants treated with SC gantenerumab, in the absence of a substantial impact of the COVID-19 pandemic and as if treatment discontinuation would not have occurred.

In alignment with the Addendum to ICH E9, the primary Amyloid PET estimand is thus described by the following attributes:

- **Target Population**:
  Early (prodromal to mild) AD population as identified by the inclusion and exclusion criteria, see the Protocol (version 3.0), Sections 4.1.1 and 4.1.2
- **Variable**:
  Change from baseline to Week 104 in amyloid PET CL
- **Treatment**:
  Prescribed study drug in a Q1W regimen, including up-titration to the target dose
- **Population-level summary**:
  Variable mean in the ITT analysis set
- **Intercurrent events (ICEs)**:
    - Substantial reduction in drug exposure due to the COVID-19 pandemic (defined as ≥4 missed dose-months)
    - Treatment discontinuation due to any reason

Considering that amyloid PET primarily aims at estimating the Pharmacodynamic effect of the drug, rather than a direct measure of clinical efficacy, reporting treatment effect estimated "as if there were no treatment discontinuations and no substantial reduction in exposure due to COVID-19 pandemic" (thus using a hypothetical strategy) addresses the scientific question of interest.

The ICE of substantial reduction in drug exposure due to the COVID-19 pandemic is defined as 4 or more dose-months (i.e., 16 weeks) of treatment missed due to COVID-19-related reason. One dose-month is defined as 4 weeks of dosing, i.e., one dose with a Q4W dosing frequency or two doses with a Q2W dosing frequency or four doses with a Q1W dosing frequency (at target dose). The threshold (4) on the number of missed dose-months was determined based on the following reasons:

- Based on the half-life of approximately 24 days of gantenerumab, plasma concentrations after 4 months' interruption at the target dose are expected to be below the concentration with the dose of 225 mg Q4W which was shown to be ineffective in SCarlet RoAD and Marguerite RoAD
- Comparability to the GRADUATE I and GRADUATE II studies which use the same cut-off.

5.3.3 Main Analytical Approach for Primary Endpoint

Descriptive summary statistics for the brain amyloid CL load at baseline, Week 52 and Week 104 as well as the change from baseline to Week 52 and to Week 104 will be produced on both the ITT and Amyloid-PET-longitudinal analysis sets. Descriptive summaries of the primary endpoint will present the mean, standard deviation, median, and minimum and maximum.

A Mixed Model for Repeated Measures (MMRM) analysis will be used to estimate the mean change in CL from baseline to Week 52 and to Week 104 on the ITT analysis set. The model will include the change from baseline in CL as the dependent variable, while adjusting for visit (as categorical), apolipoprotein E allele ε4 (APOE ε4) status (as categorical; carrier vs non-carrier), baseline CL, and baseline CL-by-visit. Visit will be treated as the repeated variable within a participant. An unstructured variance-covariance matrix will be applied to model the within-participant errors; in the case of non-convergence, compound symmetry will be used, together with a robust estimator of standard error ("sandwich" estimator).

In line with the primary estimand definition, data acquired after the ICE "Substantial reduction in drug exposure due to the COVID-19 pandemic" (as defined above) or more than 56 days from date of last dose will be excluded from the analysis and treated as missing for the primary analysis purposes.

There will be no data imputation for missing data. However, the MMRM model provides unbiased estimates and valid inference in the presence of missing data, under the MAR (missing at random) assumption.

The least squares means at Week 52 and at Week 104 will be estimated and presented with a 95% CI.

5.3.4 Sensitivity Analyses for Primary Endpoint

Impact of COVID-19

The following sensitivity analyses will be performed to evaluate the impact of the COVID-19 pandemic:

- Vary threshold on the number of missed doses due to the pandemic in the definition of "substantial reduction in drug exposure" ICE. The "substantial reduction in drug exposure" ICE is defined with a threshold of ≥ 4 dose- months. A sensitivity analysis will be performed using different thresholds: 1, 2, 3, 5, and 6 dose-months. All other aspects of the primary estimator remain the same.
- Ignore COVID-19 impact on missed doses. A sensitivity analysis will be performed where all available data points will be used, irrespective of whether or not a "substantial reduction in drug exposure" ICE occurred or not.

5.3.5 Supplementary Analyses for Primary Endpoint

The number and proportion of participants with values below or equal to the positivity threshold will be summarized for each assessment time point. CL zero is the mean amyloid burden for a typical population of young healthy controls, and 100 CL is the typical mean of a population with AD. The CL value of 24 is consistent with the diagnostic amyloid positivity threshold (Klunk et al. 2015; Navitsky et al. 2018) and will be used for the CL variable as defined for the primary analysis (see Section 5.3.2).

In order to account for the potential impact of missing values, a completers analysis will be performed, i.e., restricting the analysis at each visit to participants who completed the visit with non-missing data.

5.3.5.1 Subgroup Analyses for Primary Endpoint

The analysis of the primary endpoint will be repeated for subgroups of participants who received no home administrations of study drug by their study partner vs participants who received at least 1 home administrations by their study partner. The threshold of 1 administration may be varied for additional exploratory, data-driven analyses.

5.4 SECONDARY ENDPOINT(S) ANALYSIS(SES)

The secondary objective for this study is the study partner's confidence in his or her ability to perform the injection and their perception of the ease of injection, as well as the study partner's satisfaction with and convenience of home administration. The corresponding endpoints consist of the responses to the caregiver part of the home administration questionnaire (HAQ) up to Week 52 (for the interim analysis) and up to Week 104 (for the primary analysis).

The home administration questionnaire is to be completed as per Schedule of Assessments at site visits on Weeks 36, 52, 76, 104, early termination and unscheduled visits, and comprises a caregiver and a participant portion. The Caregiver portion of the HAQ is the secondary endpoint of the study. The participant portion of the HAQ will be analyzed as an exploratory endpoint (Section 5.5.3).

The home administration questionnaire comprises 4 items to be completed by study partner 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. Participants will complete satisfaction and convenience items with the same response options and recall period. Responses to this questionnaire may be captured electronically and transferred to the database directly from the core laboratory.

Descriptive summaries will be reported separately for each of the 4 items of the caregiver portion of the HAQ on the H-SE analysis set. Responses to each item are considered ordinal data: for each item and at each visit, the number of available

responses as well as the number and percentage for each response category will be reported. No imputation of missing data will be performed for this endpoint.

Descriptive tables will summarize the number of home administrations by study partner per participant as well as the reasons for the study partner not performing home-administrations. Reasons for switches in the person administering the study drug will be summarized as well. Graphical representations may be used to show the proportion of participants receiving administrations at home by study partner over time or to visualize the administrations by their study partner vs by a healthcare professional at home or at the site over time. The change from baseline in amyloid burden will be summarized as described in Sections 5.3.5.1 and 5.3.3 for participants who have had at least one home administration by their study partner vs those who have had none. These tables and figures will be based on the SE analysis set.

5.5 EXPLORATORY ENDPOINT(S) ANALYSIS(SES)

The change from baseline in the continuous, exploratory endpoints listed below.

5.5.1 Amyloid PET Comparison to Data from GRADUATE I and GRADUATE II

The feasibility of using amyloid PET data from the pivotal ongoing GRADUATE I and GRADUATE II as an external control group will be explored for a comparison of measured amyloid reduction between dosing regimens. Such an analysis may be performed at the primary analysis of this study.

In case that it is feasible to compare the change from baseline to Week 52 and to Week 104 in deposited amyloid as measured by brain amyloid PET within this study with the change measured in GRADUATE I and GRADUATE II as external control, then this analysis will be reported separately. Pertinent descriptions of the planned analysis will be appended to this SAP as a separate document.

5.5.2 Clinical Efficacy Outcomes

Clinical efficacy outcomes of CDR-SOB, MMSE, ADAS-Cog, Verbal Fluency Task, Coding, and ADCS-ADL will be assessed and collected via electronic tablets. The number of participants with available results at each visit will be presented. For all these outcomes, the total score, the change and percent change from baseline (if applicable) will be summarized descriptively for all participants at each visit.

5.5.2.1 CDR

Clinical Dementia Rating Sum of Boxes (CDR-SOB) is a global scale covering both functional and cognitive domains.

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]).

5.5.2.2 MMSE

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a participant-based assessment.

5.5.2.3 ADAS-Cog11 and ADAS-Cog13

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.

The ADAS-Cog 11 and 13 will be used in this study. Individual item scores are based on errors and generally range from 1 to 5, although some items have smaller or larger score ranges. The ADAS-Cog 13 total score ranges from 0-85, with higher scores reflecting greater impairment. It takes approximately 45 min to administer the ADAS-Cog 13.

5.5.2.4 Verbal Fluency Task

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

5.5.2.5 Coding

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

5.5.2.6 ADCS-ADL

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

5.5.3 Home Administration Questionnaire (Patient)

As described in Section 5.4, the home administration questionnaire contains 2 items to be completed by participants. Participants will complete satisfaction and convenience items on a 4-point verbal Likert scale and respondents will be asked to consider their most recent at home administration in answering these questions. Responses to this questionnaire may be captured electronically and transferred to the database directly from the core laboratory.

5.5.4 Biomarker Analyses

5.5.4.1 Volumetric MRI Analyses

Analysis of volumetric MRI will be based on the MRI-mITT analysis set.

Volumetric MRI, for each brain region, will be summarized visit using descriptive statistics for the absolute volume at baseline and percent change from baseline at post-baseline visits. These summaries will be provided for both the MRI-mITT and the MRI-longitudinal analysis sets.

A MMRM analysis will be used to estimate the mean percent change from baseline to Week 104 (as well Week 48) in volumetric MRI for each brain region. The model will include the percent change from baseline in volumetric MRI as the dependent variable, while adjusting for visit (as categorical), baseline age, gender (as categorical), APOE ε4 status (as categorical; carrier vs. non-carrier) and disease stage (as categorical). Visit will be treated as the repeated variable within a participant. An unstructured variance-covariance matrix will be applied to model the within-participant errors; in the case of non-convergence, compound symmetry will be used, together with a robust estimator of standard error ("sandwich" estimator).

There will be no data imputation for missing data. However, the MMRM provides unbiased estimates and valid inference in the presence of missing data, under the MAR (missing at random) assumption.

The following brain regions will be considered:

- Whole brain volume
- Regional brain volumes
- Ventricular volume

Other exploratory analyses based on other brain regions may be reported separately.

In addition, exploratory biomarker analysis will be performed to assess change from baseline to Week 104 in functional brain connectivity, fiber tract integrity, and cerebral blood perfusion.

5.5.4.2 Plasma Biomarker Analyses

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

- p-tau
- Aβ1-42
- Neurofilament light chain (NFL)
- Glial fibrillary acidic protein (GFAP)

The plasma concentration of these biomarkers will be assessed. Analysis of plasma biomarkers will be based on the ITT analysis set. Biomarker data will be summarized for each assessment visit using descriptive statistics of absolute values as well as change from baseline values.

An MMRM analysis will be used to estimate the mean change from baseline to Week 104 (but also to Week 24, 36, 52, and 76) for each plasma biomarker. The model will include the change from baseline in the plasma biomarker as the dependent variable, while adjusting for visit (as categorical), APOE ε4 status (as categorical; carrier vs non-carrier), baseline biomarker and baseline biomarker-by-visit. Visit will be treated as the repeated variable within a participant. An unstructured variance-covariance matrix will be applied to model the within-participant errors; in case of non-convergence, compound symmetry will be used, together with a robust estimator of standard error ("sandwich" estimator). The MMRM model will be based on log-transformed biomarker data.

There will be no data imputation for missing data. However, the MMRM provides unbiased estimates and valid inference in the presence of missing data, under the MAR (missing at random) assumption.

Other exploratory plasma biomarkers may be reported separately.

5.6 SAFETY ANALYSES

Descriptive statistics will be used to analyze all safety data collected in SE analysis set, unless otherwise specified. Safety data collected during the safety follow-up will also be included but may be summarized in separate tables. Safety analyses will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, MRI findings, changes in vital signs and ECGs, changes in C-SSRS scores and immunogenicity.

5.6.1 Extent of Exposure

Exposure to study drug information will be descriptively summarized overall and by dose level as follows:

- Treatment duration (in weeks)
- Total cumulative study drug dose (mg)
- Total number of study drug administrations
- Medication errors

5.6.2 Adverse Events

All verbatim Adverse Events (AE) terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version that is current at the time of the analysis (Version 24.1 or higher), and AE intensity will be graded according to the scale defined in Table 2 in Section 5.3.3 of the study protocol (mild/moderate/severe). The frequency of each AE preferred term will be defined as the number of participants experiencing at least one occurrence of the event. Each table will present the overall number and percentage of participants experiencing at least one AE and the total number of AEs reported. Percentages will be based on the number of participants in the SE analysis set. In summary tables, AEs will be sorted by body system (also referred to as System Organ Class, in decreasing order of overall incidence), then by preferred term (in decreasing order of overall incidence). The summary tables will be restricted to treatment-emergent AEs, i.e., AEs that occur on or after the day of first study drug, and to those AEs with onset no later than 17 weeks after last dose of study drug. Non-treatment-emergent AEs (with onset before the first dose) will be listed, and AEs occurring more than 17 weeks after the last dose will be summarized.

The following safety information will be summarized for treatment-emergent AEs:

- AEs, AEs by greatest intensity, AEs related to study drug, AEs related to radioligand
- SAEs, SAEs by greatest intensity, SAEs related to study drug
- AEs leading to discontinuation of study drug
- AEs leading to dose modification (dose interruption, dose reduction, or delayed up-titration). Delayed up-titration at any given visit is defined as the simultaneous occurrence of the following two tickboxes in the eCRF Adverse Events form:
  - Action taken with Gantenerumab due to AE/SAE: Dose Not Changed
  - Was dose regimen modified from protocol schedule? Yes
- AEs resulting in death
- Injection site reaction (ISR) signs and symptoms
- Systemic injection reactions (AEs with eCRF tickbox “systemic injection reaction” selected)
- Hypersensitivity AEs
- AEs associated with medication errors, AEs of medication errors

The impact of the COVID-19 pandemic on the safety data will be assessed by reviewing the following:

- Confirmed or suspected COVID-19 AEs
- AEs associated with COVID-19
- Potential long COVID-19 symptoms

The following data handling rules will be applied for all AE summary tables:

- Events that are missing both at onset and at end dates will be considered to have started after the first dose of study drug and the duration will be set to missing.
- If the onset date is missing, and the end date is on or after the first dosing date or unresolved or missing, then the event will be considered to have started after the first dose of study drug.

The following data handling rules will also be applied for specific tables:

- An AE will be included in the summary table of AEs leading to study drug discontinuation if the "action taken with Gantenerumab due to SAE/AE" drop-down menu on the AE eCRF is checked "drug withdrawn".
- In the summary table of AEs by intensity, if a participant has more than one occurrence of an event, the event with the most severe intensity will be counted. If the intensity of an AE is missing, then the AE will be included only in the total number of events column, and not in the count of participants with the event by intensity.
- In summary tables of AEs related to study drug, if a participant has more than one occurrence of an event, the related event will be counted if applicable. If the relationship of an AE is missing, then the AE will not be included.

5.6.3 MRI Safety Findings

ARIA-E and ARIA-H are identified risks associated with gantenerumab. According to the study protocol, 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., dose 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.

Since not all ARIA MRI findings qualify as AE, ARIA analyses will be mainly based on ARIA MRI findings. ARIA AEs will also be reported. Based on MRI data, the incidence, severity (based on the Barkhof Grand Total Score [BGTS]), and timing of ARIA-E and the incidence and timing of ARIA-H will be summarized overall and also by APOE ε4 genotype (by number of alleles) and by dose level. The timing of ARIA-E and ARIA-H

may be summarized by descriptive statistics and Kaplan-Meier methods. Recurrence of ARIA-E will be summarized overall and also by APOE ε4 genotype (by number of alleles). ARIA-E associated with CNS symptoms (see Section 5.6.3.1) and with serious CNS symptoms will be summarized by APOE ε4 genotype. Temporal co-occurrence of ARIA-E and ARIA-H will be summarized overall and also by APOE ε4 genotype. Temporal co-occurrence is defined as an MRI scan showing new ARIA-H that occurs between ARIA-E onset and resolution (inclusive), irrespective of the brain region.

MRI findings other than ARIA will also be summarized.

The summaries of MRI safety findings will be produced using the SE analysis set with at least one post-baseline MRI (M-SE, see Section 4).

5.6.3.1 CNS Symptoms Temporally Associated with ARIA-E MRI Findings

CNS symptoms temporally associated with ARIA-E are defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings. CNS symptoms experienced by the participant that are new or worsened since the last MRI without ARIA-E are collected in a CNS Symptoms Request Form before the MRI takes place at a visit. To identify CNS symptoms temporally associated with ARIA-E MRI findings, the following definitions will be used:

NEW CNS symptoms: If there is any AE reported in the eCRF with “Reported on the MRI CNS symptoms request form” = Y that is [new since date of most recent MRI scan showing no ARIA-E findings] AND is [ongoing or ends between the date of most recent site visit prior to date of MRI scan showing new ARIA-E (MRI) and date of MRI scan showing ARIA-E resolution (MRI)] then ARIA-E should be classified as associated with CNS symptoms

OR

WORSENED CNS symptoms: If there is any AE reported in the eCRF with “Reported on the MRI CNS symptom request form” = Y that is [started before the date of most recent MRI scan showing no ARIA-E findings] AND is [ongoing or ends between the date of most recent site visit prior to date of MRI scan showing new ARIA-E (MRI) and date of MRI scan showing ARIA-E resolution from MRI data] AND [there is an increase in severity grading] then ARIA-E should be classified as associated with CNS symptoms.

The CNS symptoms temporally associated with ARIA-E MRI findings will be listed and summarized by treatment group and within this also by APOE ε4 genotype (by number of alleles).

5.6.4 Laboratory Data

Laboratory data will be summarized for each assessment visit using descriptive statistics of absolute values and change from baseline values. In addition, the frequency of participants with abnormal laboratory values will be summarized.

5.6.5 Vital Signs

Vital signs assessments include systolic blood pressure, diastolic blood pressure, and pulse rate measured throughout the study. Vital sign measurements will be summarized for each assessment visit using descriptive statistics of absolute values and change from baseline values. In addition, the frequency of participants with abnormal results will be summarized.

5.6.6 ECGs

ECG data will be summarized for each assessment visit using descriptive statistics of absolute values and change from baseline values for the following parameters:

- Heart rate
- QRS duration
- RR interval
- PR interval
- QT interval
- QT corrected using Bazett's formula (QTcB) and QT corrected using Fridericia's formula (QTcF)

In addition, ECG overall interpretations will be summarized by visit.

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

The C-SSRS is an assessment tool used to assess the lifetime suicidality of a participant (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality.

The highest post-baseline suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent will be summarized. In addition, change from baseline to worst post-baseline assessment in suicidality categories will be summarized.

5.6.8 Safety of Home Administration by the Study Partner

Descriptive analyses will be performed to assess the safety of home administrations of study drug by the study partner. These will compare data at a participant level and at an injection level.

Participant Level

On the participant level, a descriptive table will show:

- Number and frequency of participants with at least one home administration by study partner
- Number and frequency of participants who changed the study partner during the study (overall)
- Number and frequency of participants with different overall number of changes in study partner
- Total number of home administrations by study partner per participant (descriptive statistics)
- Percentage of possible home administrations by study partner (i.e., number of actual home administrations by study partner divided by maximum possible number) per participant (descriptive statistics)
- Percentage of participants who received home administration by study partner at each visit (starting from Week 26, excluding planned in-clinic visits; line plot)
- First week with home administration by study partner
- Heat map of administrations by study partner or HCP at home or at site

The summaries above will be presented for the SE, OH-SE, and/or the H-SE analysis set as appropriate.

Furthermore, participants will be grouped in the following way:

- Participants who have had no home administrations by their study partner
- Participants who have been dosed at home by their study partner at least once

The threshold of 1 home administration by study partner may be varied for additional exploratory, data-driven analyses.

For these two groups, demographic data and baseline characteristics will be summarized as described in Section 5.7.2. Furthermore, demographics and characteristics of all study partners will be summarized.

An AE overview table will summarize the AE profile by group. Selected AE tables of ISRs, systemic injection reactions, and hypersensitivity will provide the frequency of these events by group. Additionally, medication errors will also be summarized descriptively by group.

Injection Level

On the injection level, each single injection of study drug from Week 26 onwards (after the scheduled training of study partners at the site) will be grouped in the following way:

- Home administration by study partner

- Home administration by Health Care Professional (HCP)
- In clinic administration by study partner
- In clinic administration by HCP

The frequency of medication errors, ISRs, systemic injection reactions, and hypersensitivity will be summarized descriptively for home administrations by study partner vs. the combined group of all other administrations. The denominator in the calculations of percentages is here the number of administrations in each group (not the number of participants).

Other comparisons between home administrations by the study partner and other groups may be added.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

The summary of study conduct will include a description of the following items:

- Number of participants enrolled
- Number of participants included in each analysis set
- Number and percentage of participants who prematurely withdrew from the study or from study treatment (including the reasons for discontinuation and the distribution of these discontinuations by time-windowed visit)
- Incidence of major protocol deviations – overall and by four main categories (inclusion criteria, exclusion criteria, medication and procedural)
- Number of participants with home nursing

Major protocol deviations and premature withdrawals will be listed.

5.7.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, sex, medical history) will be summarized descriptively for the ITT population.

Exposure to AD concomitant medication (including post-baseline initiation or change in dose) will be summarized for the ITT population.

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.

5.7.3 Concomitant Medications

The following medication concept of interest has been identified:

- Antiplatelet therapy

The Medication terms (based on WHO ATC-Coding standard) used to identify the medication of interest will be listed (by WHO ATC Coding class).

In addition, medications administered to treat ARIA-Es, CNS symptoms associated with ARIA-E MRI findings and ISRs will be summarized separately by WHO ATC Coding class and preferred term. Summaries and listings will be provided for all previous and all concomitant medications.

5.7.4 Summaries of COVID-19 Impact on the Trials

GRADUATION is ongoing during the COVID-19 pandemic. Consequently, to monitor the potential impact of the pandemic on the trials, we will provide a specific set of descriptive analyses related to COVID-19 for the ITT analysis set (see Section 4), including:

- Demographic and Baseline Characteristics in Participants with Confirmed/Suspected COVID-19
- COVID-19 AEs (see Section 5.6.2)
- COVID-19 related Protocol Deviations (see Section 5.2)
- Missed dose-months due to COVID-19
- Study discontinuations due to COVID-19
- Site actions

5.7.5 Immunogenicity Analyses

Immunogenicity analyses include the evaluation for antibodies against gantenerumab (anti-drug antibody [ADA]), including the determination of antibody titers. The results of the confirmatory assay will be presented as a frequency table summarizing baseline and post-baseline results.

A listing of participants with positive ADA status per confirmatory assay and titer result will be provided.

5.7.6 Biomarker Analyses

Please see Section 5.5.4.

5.7.7 Pharmacokinetic and Pharmacodynamic Endpoint Analyses

Gantenerumab plasma concentration will be descriptively summarized by nominal time/visit.

Population PK and PK-PD modeling analyses that include assessing the influence of dosing frequency on PK-PD model performance will be reported separately in a modeling and simulation report and are therefore not covered in this document.

5.8 INTERIM ANALYSES

5.8.1 Planned Interim Analyses

An interim analysis will be conducted at the time of the primary analysis for GRADUATE I and GRADUATE II, to support a potential filing of gantenerumab in case of positive read-out of the pivotal studies. The analysis will be considered strictly descriptive and will not impact the conduct of the study, i.e., early termination for futility or efficacy will not be considered. As this study is open-label and no formal hypothesis testing is planned, the interim analysis is considered of an administrative nature and will not have an impact on the final study results (e.g., in terms of alpha spending).

The last patient last visit for GRADUATE I and GRADUATE II is expected for 23 September 2022. To allow for cleaning and other data management processes, the clinical cut-off date for GRADUATION will be set to 30 June 2022. All participants who were enrolled in the study by the time of the cut-off date will be included in the interim analysis. This is expected to comprise approximately 192 participants and of those approximately 180 participants are expected to have had the opportunity to complete the Week 52 assessment.

The following will be included in the interim analysis and analyzed according to the methods specified in the pertinent sections:

- Participant disposition (see Section 5.2)
- Demographics and baseline characteristics (see Section 5.7.2)
- Change in amyloid burden from baseline to Week 52 (see Section 5.3)
- Caregiver portion of the home administration questionnaire (see Section 5.4)
- Extent of exposure (see Section 5.6.1)
- Adverse events (see Section 5.6.2)
- MRI safety findings (see Section 5.6.3)
- Laboratory data (see Section 5.6.4)
- Vital signs (see Section 5.6.5)
- ECG data (see Section 5.6.6)
- C-SSRS (see Section 5.6.7)
- Immunogenicity analyses (see Section 5.6.8)
- Pharmacokinetics analyses (see Section 5.7.7)
- Safety of Home Administration by study partner (see Section 5.6.8).

The interim analysis will be performed by the Sponsor and reported in an interim CSR.

6. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

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