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

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
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STATISTICAL ANALYSIS PLAN VERSION HISTORY

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
[^{18}F]GTP1	Genentech Tau Probe 1
AD	Alzheimer's Disease
ADA	anti-drug antibody
ADAS-Cog	Alzheimer Disease Assessment Scale-Cognition
ADCS-ADL	Alzheimer Disease Cooperative Study Group-Activities of Daily Living
AE	adverse event
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
CSR	Clinical Study Report
C-SSRS	Columbia-suicide severity rating scale
DSST	Digit Symbol Substitution Test
EQ-5D	EuroQol 5-Dimension Questionnaire
FAQ	Functional Activities Questionnaire
iDMC	independent Data Monitoring Committee
IMC	Internal Monitoring Committee
ISR	injection site reaction
ITT	intent to treat
IxRS	interactive voice/web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NMPA	National Medical Products Administration
NPI-Q	Neuropsychiatric Inventory Questionnaire
OLE	open-label extension
PET	positron emission tomography
PD	Pharmacodynamic
PK	Pharmacokinetic
Q2W	Every two weeks
QoL-AD	Quality of Life-Alzheimer's Disease
RUD-Lite	Resource Utilization in Dementia-Lite
SAE	serious adverse events
SAP	Statistical Analysis Plan
SC	Subcutaneous
SUVR	standard uptake value ratio

ZCI-AD Zarit Caregiver Interview for Alzheimer's Disease

1. INTRODUCTION

This document describes the statistical analyses that will be reported in the Clinical Study Report (CSR) of Study WN42171 (hereafter referred to as "POSTGRADUATE"). This document will focus on the statistical methodology underlying the report that will include participant disposition, baseline demographics, descriptive efficacy and standard safety outputs along with the analysis sets.

This Statistical Analysis Plan (SAP) covers analyses planned for POSTGRADUATE study only. Analyses planned across the double-blind period in the pivotal parent studies WN29922 and WN39658 (hereafter referred to as "GRADUATE I" and "GRADUATE II", respectively), the open-label extension (OLE) period in the GRADUATE studies and POSTGRADUATE are described separately and not the subject of this SAP.

Analyses planned for the longitudinal amyloid positron emission tomography (PET) and tau-PET substudies are provided in Sections 5.7.6 and 5.7.7. The pharmacokinetic (PK) data and PK/PD modelling will be reported in the population PK report and are therefore not covered in this document. Similarly, health economic data (such as utility values derived from the EuroQoL–5 Dimensions [EQ-5D] and the Resource Utilization in Dementia Scale–Lite [RUD-Lite]) will be analyzed and reported separately from the CSR and are therefore not covered here. Similarly, the exploratory biomarker endpoints of changes in functional brain connectivity or changes in the integrity of white matter will be analyzed and reported separately from the CSR and are therefore not covered here.

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 the Data Analysis Plan Module 2 and 3.

The language used in this SAP supersedes that in the protocol and protocol synopsis. This SAP is based on Protocol version 4, issued on May 11, 2022.

1.1 OBJECTIVES AND ENDPOINTS

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

Table 1 Objectives and Corresponding Endpoints

Primary Objective(s)	Corresponding Endpoint(s)
• To evaluate the safety and tolerability of long-term gantenerumab administered by SC injection	• Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events • Physical examinations (including neurologic systems), vital signs, ECG, laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS) • Nature, frequency, severity, and timing of ARIA-E and ARIA-H • Nature, frequency, severity, timing, and outcomes of ISRs • Incidence of treatment discontinuations for adverse events • Incidence of adverse events of special interest
Secondary Objective(s)	**Corresponding Endpoints**
• To evaluate the efficacy of long-term gantenerumab administered by SC injection	Change over time in cognition and/or function, as measured by the following: • Clinical Dementia Rating (CDR) • Mini-Mental State Examination (MMSE) • Alzheimer Disease Assessment Scale-Cognition, Subscale 11 (ADAS-Cog11) and Alzheimer Disease Assessment Scale-Cognition, Subscale 13 (ADAS-Cog13) • Verbal Fluency Task • Coding • Functional Activities Questionnaire (FAQ) • Alzheimer Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL)
Exploratory Objective(s): Efficacy	**Corresponding Endpoints**
• To evaluate the efficacy of long-term gantenerumab administered by SC injection	Change over time in: • Health-related quality of life, as assessed by the Quality of Life-Alzheimer's Disease (QoL-AD) scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q)

	• Caregiver burden, as assessed by the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale • Elements of resource utilization, as assessed by the Resource Utilization in Dementia-Lite (RUD-Lite)
Exploratory Pharmacokinetic Objective(s)	**Corresponding Endpoints**
• To characterize the PK profile of gantenerumab administered by SC injection	• Plasma concentration of gantenerumab administered SC at specified timepoints
Immunogenicity Objective(s)	**Corresponding Endpoints**
• To evaluate the immune response to gantenerumab administered by SC injection	• Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study
Exploratory Biomarker Objective(s)	**Corresponding Endpoints**
• To evaluate the long-term effects of gantenerumab administered by SC injection	• Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants • Brain tau load over time, as measured by tau PET scan in a subset of participants • CSF markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau (t-tau), and phosphorylated tau (p-tau) • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures; changes in functional brain connectivity; or changes in the integrity of white matter in all participants • Blood and Plasma markers over time
Exploratory Health Status Utility Objective(s)	**Corresponding Endpoints**
• To evaluate the health status utility scores of participants treated with gantenerumab	• Health outcomes in participant and caregiver, as measured by EuroQol 5-Dimension Questionnaire (EQ-5D)

1.2 STUDY DESIGN

The POSTGRADUATE study is an open-label, multicenter, rollover study to evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab

in participants with AD who completed GRADUATE I or GRADUATE II, either the double-blind or OLE part, as applicable (parent study).

To protect study data integrity and to aid the assessment of the long-term effects of gantenerumab, treatment assignment information from the double-blind phase of the parent GRADUATE I or GRADUATE II studies will remain blinded to the Sponsor, investigator, and participant at least until database lock of the parent studies, which will happen while this study is ongoing.

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

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

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

- For participants who completed the double-blind part and did not enter the OLE part of GRADUATE I or GRADUATE II: The first administration of open-label study drug should take place approximately 2 weeks after the last efficacy and safety visit of the double-blind part of the parent study (GRADUATE I or GRADUATE II) and will be considered the OLE baseline visit (OLE Day 1).

- For participants who completed the double-blind part and the OLE part of GRADUATE I or GRADUATE II, the first administration of study drug in this study should take place approximately 2 weeks after the OLE Week 34 visit or the final dose visit in the GRADUATE I or GRADUATE II OLE. Participants who have a gap in their transition between the OLE part of the parent study (GRADUATE I or GRADUATE II) and this study, for unforeseen reasons, will roll over to this study continuing the schedule of activities as per their last visit in the OLE part of the parent study (GRADUATE I or GRADUATE II). Discussion with the Sponsor is recommended.

Participants with evidence of amyloid-related imaging abnormalities – edema/effusion (ARIA-E) on the last per-protocol study magnetic resonance imaging (MRI) scan report in GRADUATE I or GRADUATE II, either its double-blind or OLE part, as applicable, will be retained in GRADUATE I or GRADUATE II until the ARIA-E finding is resolved. They may then enroll in POSTGRADUATE. For those enrolling from the OLE part, the first

visit of the participants in POSTGRADUATE will be adapted according to the schedule of the visits of each participant in the parent study.

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

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

The dosing schedule and the schedule of activities will be different for participants, depending on whether they completed the OLE part of GRADUATE I or GRADUATE II study, which covers the up titration phase for the participants in the placebo arm, or if they completed only the double-blind part. Details are described in Appendix 1 of the study protocol.

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

Week 220 unless they are transitioning to an alternative gantenerumab OLE study that becomes available.

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

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

An interim analysis will be conducted at the time of the primary analysis for the GRADUATE parent studies, to support a potential filing of gantenerumab in case of positive read-out of the pivotal studies. The analysis will be considered strictly administrative and will not impact the conduct of the study, i.e., early termination for futility or efficacy will not be considered. The final analysis will take place after the last participant, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later.

China Enrollment Plan

Based on historical data, participant recruitment is expected to take longer in China; therefore, a specific China enrollment plan has been established in the GRADUATE parent studies.

In the GRADUATE I study, after completion of the global enrollment phase, additional participants are being enrolled in an extended China extension phase at China's sites in mainland China to investigate the consistency in treatment effect between the China subpopulation and the global population for the purpose of registration in China.

The global population will include all participants enrolled during the global enrollment phase (including participants enrolled at China's sites in mainland China, Hong Kong, and Taiwan, during that phase), and the China subpopulation will include all participants at China's sites (i.e., during both the global enrollment phase and the extended China enrollment phase).

Separate analyses will be performed for the global population and the China subpopulation. The analysis of the China subpopulation will be conducted and reported separately from the analysis detailed in this SAP.

Substudies

The substudies associated with POSTGRADUATE will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms. To date, two optional substudies are associated with POSTGRADUATE: a longitudinal amyloid PET substudy and a longitudinal tau PET substudy.

The amyloid and tau PET assessments will enable a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [^{18}F]GTP1 (Genentech Tau Probe 1; an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with AD.

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

1.2.1 Treatment Assignment and Blinding

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

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

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

operational assay group personnel, IxRS service provider, and independent Data Monitoring Committee (iDMC) members.

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

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

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

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

1.2.2 Independent Review Facility

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessments of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7-10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to the dosing visit that the MRI corresponds to (refer to Section 5.1.2 of the study protocol for additional details on MRI safety management).

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

In addition to any local reading according to local procedures and requirements, all MRI scans will be reviewed by an expert central reader within approximately 1 week of receipt and a report provided to the site. For the purposes of overall study relevant decisions and recommendations, results from the expert central reader will be used. Any time the central reader identifies a new MRI finding, the study center medical staff and the Sponsor will be rapidly notified (see Section 5.1.2 of the study protocol).

All MRI readings and volume measures will be conducted by the central reader.

1.2.3 Data Monitoring

The iDMC will evaluate participant safety on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, amyloid-related imaging abnormalities – hemosiderin deposition [ARIA-H], and injection site reactions [ISRs]), the iDMC will review all necessary cumulative data, including efficacy data if necessary, at regular intervals during the study. It is anticipated that these assessments will occur approximately every 3 months or as detailed in the iDMC charter. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, the safety risk management should be modified, the protocol should otherwise be amended, and enrollment should be held pending further safety evaluations).

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

Final decisions will rest with the Sponsor.

In the event the iDMC which reviews safety in both the parent studies (GRADUATE I and GRADUATE II) and POSTGRADUATE is no longer required (for instance after the unblinding of the parent studies) evaluation of participant safety may be taken over by the Sponsor's Internal Monitoring Committee (IMC), with details documented in an IMC Charter.

1.2.4 ARIA Management

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

with asymptomatic ARIA-E with a BGTS ≥4 or symptomatic ARIA-E and discontinued for participants with more than 15 ARIA-H or with disseminated leptomeningeal hemosiderosis. In this study, ARIA management rules are based on the Bioclinica 5-point severity score (renamed as Severity Scale of ARIA-E (SSAE) since the writing of the study protocol) and treatment is interrupted for asymptomatic ARIA-E with a Bioclinica score ≥4 or symptomatic ARIA-E of any severity with CNS symptoms attributable to ARIA-E in the judgement of the investigator and discontinued for ARIA-H with disseminated leptomeningeal hemosiderosis. Disseminated leptomeningeal hemosiderosis is defined as more than three focal leptomeningeal hemosiderosis cumulatively.

2. STATISTICAL HYPOTHESES

All analyses provided in this document are descriptive, thus no statistical hypothesis will be tested in these analyses.

3. SAMPLE SIZE DETERMINATION

The sample size will be determined by the number of participants who complete the parent studies (GRADUATE I and GRADUATE II) and enroll in this study. The sample size is expected to be no more than approximately 2032 participants.

4. ANALYSIS SETS

The following analysis sets are defined:

Analysis Set	Definition
All enrolled participants	All enrolled participants (i.e.; who signed the informed consent form and are marked as enrolled in IxRS), whether or not the participant received the assigned treatment.
ITT (intent to treat)	All enrolled participants, who received at least one dose of study drug. Participants will be analyzed by the treatment they were randomized to in the parent studies.
Safety-evaluable (SE)	All participants enrolled who received at least one dose of study drug in this study or in the OLE part of the parent studies. Any participant randomized to placebo in the parent studies who received at least one dose (any dose) of active drug during the double-blind treatment in the parent studies will be summarized as having received the active drug in the parent studies.
MRI safety-evaluable (M-SE)	All participants in the safety-evaluable analysis set who had at least one post-baseline safety MRI scan.
Immunogenicity	All enrolled participants with at least one ADA assessment.
MRI modified intent-to-treat (MRI-mITT)	All participants in the ITT analysis set who had at least one valid volumetric MRI quantitative measurement.
CSF modified intent-to-treat (CSF-mITT)	All participants in the ITT analysis set who had at least one valid quantitative cerebrospinal fluid (CSF) measurement.

Amyloid PET modified ITT (aPET-mITT)	All enrolled participants of the ITT analysis set who consented to the Amyloid PET substudy, did not withdraw consent before enrolment in the substudy and had at least one amyloid PET scan with a valid quantitative measurement.
Tau PET modified ITT (tPET-mITT)	All enrolled participants of the ITT analysis set who consented to the Tau PET substudy, did not withdraw consent before enrolment in the substudy and had at least one tau PET scan with a valid quantitative measurement.

ITT = intent to treat; SE = safety-evaluable; M-SE = MRI safety-evaluable.

5. STATISTICAL ANALYSES

5.1 GENERAL CONSIDERATION

The purpose of this study is to assess the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed GRADUATE I or GRADUATE II.

The period of the POSTGRADUATE study and the OLE period from the parent studies will henceforth be referred to as the OLE period. Data from the OLE period, i.e., from OLE baseline (see Section 5.1.1 below for definition) to the end of study, will be summarized. Consequently, for participants who completed the OLE part of the parent studies and gave informed consent for the POSTGRADUATE study, the data collected in the OLE period of the parent studies will be included in the CSR of POSTGRADUATE. This will ensure that data from baseline and uptitration are included in the analyses for all participants of POSTGRADUATE. Participants of the OLE period of the parent studies without informed consent to POSTGRADUATE cannot be included in the analyses for the CSR of POSTGRADUATE and will instead be included in the analyses within the parent studies' CSRs.

All analyses will be purely descriptive and no imputation of missing data will be performed. For continuous data, descriptive statistics of mean, standard deviation, median, 1st and 3rd quartile as well as minimum and maximum and number of available data will be provided. For categorical data, number and frequency will be provided for each category as well as the number of available data.

All analyses of safety endpoints will be based on the SE analysis set unless mentioned otherwise while all analyses of efficacy endpoints will be performed for the ITT analysis set. The immunogenicity analysis set will be used for immunogenicity analyses.

Results will be shown separately based on previous treatment in the GRADUATE parent studies GRADUATE I and GRADUATE II, and by participation / non-participation in the OLE part of the parent studies and overall. For analyses using the ITT analysis set, this will be the treatment as randomized in the parent studies; for analyses using the SE analysis set, this will be the treatment actually received in the parent studies.

The results are shown separately by participation / non-participation in the OLE part of the parent studies to mitigate the introduction of bias into the overall results. The non-inclusion of participants who discontinued during the OLE part of the parent studies and do not have an informed consent to POSTGRADUATE introduces an immortal time bias in certain analyses for this group of participants for the OLE part of the parent studies. The separation is further required due to different ARIA management rules in the parent studies and this study.

5.1.1 Definition of Baseline

The first dosing visit in the OLE will be considered as baseline (OLE Day 1). The last available assessment made before or on OLE Day 1 will be considered the baseline assessment if occurring within 12 weeks before or on OLE Day 1 and prior to first dose for standard-of-care examinations or within 6 months for C-SSRS, cognitive scale results and MRI scans. For ADA data, baseline will be the baseline value of the parent studies to ensure that the baseline value is before any dose of the investigational product.

5.2 PARTICIPANT DISPOSITION

The analysis of participant disposition will be based on all enrolled participants (see analysis sets in Section 4). The number of participants enrolled will be tabulated by country and site. Participant disposition (the number of participants enrolled, treated, and completing the study) will be tabulated. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be 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 ENDPOINTS ANALYSIS

5.3.1 Definition of Primary Endpoints

The primary objective for this study is to evaluate the safety and tolerability of long-term gantenerumab administered by SC injection on the basis of adverse events (AEs), physical examinations, vital signs, ECGs, laboratory tests, C-SSRS, ARIA-E and ARIA-H, ISRs, treatment discontinuations for AEs, and incidence of AEs of special interest.

The corresponding primary endpoints are:

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

- Nature, frequency, severity, timing, and outcomes of ISRs
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

The analytical approaches are described in pertinent subsection for each endpoint below.

5.3.2 Main Analytical Approach for Primary Endpoint(s)

All these safety analyses will be performed in the SE analysis set, except for analyses of ARIA-E or ARIA-H, CNS symptoms temporally associated with ARIA events or other MRI safety findings that will be based on the M-SE analysis set.

Participants will be analyzed according to the previous treatment they actually received in the parent studies and by participation / non-participation in the OLE part of the parent studies.

Descriptive statistics will be used to analyze all safety data collected in the study in the SE analysis set, unless otherwise specified.

Safety analyses will provide summaries of exposure to study treatment, adverse events, changes in laboratory test results (including shift tables), MRI findings, changes in vital signs and ECGs, and changes in C-SSRS scores as described in pertinent sections below.

5.3.3 Adverse Events

All verbatim AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version that is current at the time of the analysis (Version 25.0 or higher), and AE severity will be graded according to the scale defined in Table 3 in Section 5.3.3 of the study protocol (mild/moderate/severe). For each displayed participant group, 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 (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 or worsen on or after the day of first OLE dose, with onset no later than 14 weeks after last dose. Non-treatment-emergent AEs (AEs ongoing at OLE Day 1 with onset before the first OLE dose) and AEs occurring more than 14 weeks after the last dose will be listed.

The following safety information will be summarized:

- AEs, AEs by intensity, AEs related to study drug
- AEs with fatal outcome

- Serious AEs (SAEs), SAEs by intensity, SAEs related to study drug
- AEs leading to discontinuation of study treatment
- AEs leading to dose modifications (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 Event form:
    - Action taken with open label gantenerumab due to SAE/AE: Dose Not Changed
    - If Dose not changed, was open label dose regimen modified from protocol schedule due to SAE/AE? Yes
- Injection site reaction (ISR) signs and symptoms
- Systemic injection reactions (AEs with "systemic reaction" selected)

Protocol-specified adverse events of special interest (AESI) will be listed.

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 onset and 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 open label gantenerumab" 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 the summary table 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 in the count of participants with the event by relationship

5.3.4 Magnetic Resonance Imaging Safety Findings

ARIA-E and ARIA-H are identified risks associated with gantenerumab. Sites were asked to capture ARIA findings as AEs in the POSTGRADUATE eCRF if they met any of the following criteria:

- Symptomatic ARIA-E (onset or worsening of CNS symptom[s] attributable to ARIA-E MRI findings in the judgement of the investigator), 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

Not all ARIA MRI findings qualify as AE. ARIA analyses will be mainly based on ARIA MRI findings. ARIA AEs will also be reported. ARIA analyses will be restricted to ARIAs documented during this study or the OLE part of the parent studies.

Based on MRI data, the incidence, severity (based on the Bioclinica severity scale (see Appendix 2) and 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. For participants from the OLE part of the parent studies, only ARIA-E severity measured by the BGTS is available for events that occurred during the OLE part of the parent studies. The timing of ARIA-E and ARIA-H may be summarized by descriptive statistics. Recurrence of ARIA-E within this study or the OLE part of the parent studies will be summarized. ARIA-E with associated and attributable CNS symptoms (see Section 5.3.4.1) and serious associated and attributable CNS symptoms will be summarized overall and also by APOE ε4 genotype (by number of alleles). 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.

5.3.4.1 CNS Symptoms Temporally Associated with and Attributable to ARIA-E MRI Findings

CNS symptoms temporally associated with and attributable to ARIA-E are defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings and considered by the investigator to be attributable to ARIA-E. 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. To identify CNS symptoms temporally associated with and attributable to 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 this study's CNS Symptom Collection Form' = Yes 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)] AND has the question "Is this AE attributable to ARIA-E?" answered with Yes in the eCRF AE page, then ARIA-E should be classified as associated with attributable CNS symptoms

OR

WORSENED CNS symptoms: If there is any AE reported in the eCRF with 'Reported on this study's CNS Symptom Collection Form' = Yes 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] AND has the question "Is this AE attributable to ARIA-E?" answered with Yes in the eCRF AE page, then ARIA-E should be classified as associated with attributable CNS symptoms.

The CNS symptoms temporally associated with and attributable to ARIA-E MRI findings will be listed and summarized overall and also by APOE ε4 genotype (by number of alleles). The same summary and listing will be produced for all CNS symptoms temporally associated with (but not necessarily attributable to) ARIA-E MRI findings.

5.3.5 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 patients with abnormal laboratory values will be summarized.

5.3.6 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 patients with abnormal results will be summarized.

5.3.7 ECGs

ECG data will be summarized by previous treatment group and participation / non-participation in the OLE part of the parent studies 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

In addition, ECG overall interpretations will be summarized by previous treatment group, participation / non-participation in the OLE part of the parent studies and visit.

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

The C-SSRS is a 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.

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent will be summarized by previous treatment group and participation / non-participation in the OLE part of the parent studies. In addition, change from baseline to worst post-baseline assessment in suicidality categories will be summarized by previous treatment group and participation / non-participation in the OLE part of the parent studies.

5.4 SECONDARY ENDPOINTS ANALYSES

According to the study protocol, section 6.5, the secondary efficacy analyses are planned to use all enrolled participants to investigate both the long-term efficacy and potential disease modifying effect of long-term gantenerumab. However, all analyses in this SAP will be restricted to efficacy endpoints collected under this study or during the OLE part of the parent studies and will be purely descriptive. No estimands will be defined.

Analyses of long-term effect of the study drug (across the double-blind and open label phases from the parent Study [GRADUATE I or GRADUATE II]) as well as efficacy analyses of delayed start of treatment are not subject to this SAP and will be described elsewhere.

5.4.1 Secondary Efficacy Endpoints

The secondary objective for this study is to evaluate the efficacy of long-term gantenerumab administered by SC injection on the basis of change over time in cognition, function, and other outcomes as measured by the following:

- Clinical Dementia Rating (CDR)
- Mini-Mental State Examination (MMSE)
- Alzheimer Disease Assessment Scale-Cognition, Subscale 11 (ADAS-Cog11) and Alzheimer Disease Assessment Scale-Cognition, Subscale 13 (ADAS-Cog13)
- Verbal Fluency Task
- Coding
- Functional Activities Questionnaire (FAQ)
- Alzheimer Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL)

Descriptive statistics will be provided for each of these endpoints, summarizing absolute values and change from baseline for each assessment time point by previous treatment group and participation / non-participation in the OLE part of the parent studies.

5.4.1.1 Clinical Dementia Rating

The CDR-Global Score (CDR-GS) characterizes a participant's level of impairment according to the following categories: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The CDR-Sum of Boxes (CDR-SOB) score is a detailed quantitative general index that provides more information than the CDR-GS in participants with mild dementia (Berg 1988; Morris et al. 2001, O'Bryant et al. 2010) and is scored from 0 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 caregiver).

Descriptive statistics will be provided for the CDR-SOB and the CDR-GS.

5.4.1.2 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. The score ranges from 0 to 30, with lower values indicating a greater impairment.

5.4.1.3 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 participant-based assessment that measures learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations. 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 to 85, with higher scores reflecting greater impairment. It takes approximately 45 minutes to administer the ADAS-Cog 13.

5.4.1.4 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).

5.4.1.5 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.

5.4.1.6 FAQ

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities. The FAQ is a 30-point scale, the higher the score the worse the performance.

5.4.1.7 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 to 78, with higher scores indicating better functioning.

5.5 EXPLORATORY ENDPOINTS ANALYSIS

The exploratory efficacy analyses will be based on the ITT analysis set and will be restricted to efficacy endpoints collected under this study or during the OLE part of the parent studies. Therefore, analyses of long-term effect of the study drug (across the double-blind and open label phases from the parent study [GRADUATE I or GRADUATE II]) are not subject to this SAP and will be described elsewhere.

5.5.1 Exploratory Efficacy Endpoints

The exploratory efficacy objective is to evaluate the efficacy of long-term gantenerumab administered by SC injection in terms of change over time in:

- Health-related quality of life, as assessed by the Quality of Life-Alzheimer's Disease (QoL-AD) scale
- Behavioral and neuropsychiatric symptoms of AD, as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Caregiver burden, as assessed by the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale

- Elements of resource utilization, as assessed by the Resource Utilization in Dementia-Lite (RUD-Lite)

The RUD-Lite will be used in this study for informing pharmacoeconomic evaluations and will be reported separately. For the other endpoints, descriptive statistics will be provided for these endpoints by previous treatment group, participation / nonparticipation in the OLE part of the parent studies and assessment time point.

5.5.1.1 QoL-AD

The QoL-AD was developed to assess quality of life (QoL) in participants who have dementia (Logsdon et al. 1999, 2002). The QoL-AD consists of 13 items covering aspects of participants' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. The total score is the sum of the 13 items and ranges from 13 to 52, with higher scores indicating better health-related QoL. In this study, the QoL-AD will be administered in a standardized, structured interview format to participants by investigative staff in order to gather participant responses about QoL. The caregiver will also complete the caregiver version of the questionnaire to enable proxy responses from the caregiver.

5.5.1.2 NPI-Q

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

5.5.1.3 ZCI-AD

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

5.6 OTHER SAFETY ANALYSES

5.6.1 Extent of Exposure

Exposure to study drug information will be summarized descriptively as follows:

- Treatment duration (in weeks)
- Total number of administrations
- Total cumulative dose (mg)
- Number of participants with any dose administration, separately for each dose level

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 by previous treatment group and participation / non-participation in the OLE part of the parent studies:

- 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 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

Demographic and baseline characteristics (such as age, sex, race, disease stage at enrolment in the parent studies, stratification factors as reported in IxRS at randomization in the parent studies, APOEe4 status (carrier vs non-carriers and APOe4 allele's status), presence and cumulative number of ARIA-H (during the screening and double-blind part of the parent studies), history of ARIA-E in the double-blind part of the parent studies, and use and non-use of background therapy for AD at OLE baseline, participation in POSTGRADUATE PET substudies) will be summarized descriptively for the ITT and SE analysis sets.

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.

5.7.3 Summaries of COVID-19 Impact on the Trials

The POSTGRADUATE study is ongoing during the COVID-19 pandemic. Consequently, to monitor the potential impact of the pandemic on the trial, we will provide a specific set of descriptive analyses related to COVID-19 by previous treatment arm and participation / non-participation in the OLE part of the parent studies for the ITT analysis set (see Section 4), including:

- Demographic and Baseline Characteristics in Participants with Confirmed/ Suspected COVID-19 (see Section 5.7.2)
- COVID-19 AEs (see Section 5.3.3)
- COVID-19 related Protocol Deviations (see Section 5.2)
- Missed doses due to COVID-19

- Study discontinuations due to COVID-19
- Remote scale administrations

5.7.4 Immunogenicity Analyses

Immunogenicity analyses include the evaluation for antibodies against gantenerumab (i.e., ADAs), including the determination of antibody titers if appropriate. The immunogenicity analysis set will consist of all participants with at least one ADA assessment. The results of the confirmatory assay will be presented as a frequency table summarizing results at parent study baseline and during this study or the OLE part of the parent studies.

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

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

5.7.5 Biomarker Analyses

Biomarker data will be summarized for each assessment visit using descriptive statistics of absolute values as well as change from baseline values. Plasma biomarker reports will be based on the ITT analysis set. All analysis including CSF biomarkers will be based on the CSF-mITT analysis set. The following pharmacodynamic biomarkers will be analyzed:

- Cerebrospinal Fluid (CSF):
  - Total tau (tTau)
  - Phosphorylated tau (pTau 181)
  - Neurogranin
  - Neurofilament (NFL)
- Plasma:
  - Phosphorylated tau (pTau 181)
  - Amyloid-beta 42 (Abeta-42)
- MRI-derived measurements, including:
  - Volumetric changes in whole brain, ventricles, hippocampus, cortical gray or other structures

In addition, other exploratory biomarkers will be reported separately.

5.7.6 Amyloid PET Substudy

The main objective of the POSTGRADUATE longitudinal amyloid PET substudy is to assess changes in brain amyloid load (as measured by florbetaben or flutemetamol) over time during the treatment with gantenerumab.

The analyses described here are restricted to analyses of data assessed during this study or during the OLE part of the parent studies. Analyses across the double-blind part of the parent studies and this study will be reported separately and are not subject of this SAP. This document will focus on amyloid PET data assessed during this study or during the OLE part of the parent studies.

5.7.6.1 Brain Amyloid Load Analysis

Two amyloid PET ligands are allowed in this substudy according to country and site availability: florbetaben and flutemetamol. However, the same ligand has to be used for the same participant throughout the study. For all participants, the ligand that is used has to remain the same as that used previously (e.g., if a participant has been enrolled in the parent study (GRADUATE I or GRADUATE II) with a positive florbetaben PET scan, only florbetaben will be allowed and used for the longitudinal follow-up scans for this participant in this study).

Centiloid mapping will be completed for the Standard Uptake Value Ratio (SUVR) data from the two amyloid PET ligands. The aPET-mITT analysis set will be used to summarize amyloid load in centiloid by descriptive statistics for each assessment time point as well as the change from baseline by previous treatment.

5.7.6.2 General Considerations on Amyloid PET Statistical Analyses

The baseline assessment will be the last amyloid PET scan before or on OLE Day 43 (time window for day 1 is +42 days) that was performed within 6 months before OLE Day 1.

With the Centiloid endpoint, data from both tracers will be pooled and analyzed together. Separate analysis by tracer with the Centiloid endpoint may also be conducted as appropriate.

Missing values will not be imputed.

Visit Windowing

The analysis of amyloid PET data will be undertaken using reporting windows as defined in

Table 2. 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. The time windows are based on study days, defined as days on study since first OLE dose, with the day of first OLE dose being study Day 1 and the day before first dose being study Day -1

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 (early termination visit expected 14 days after last dose, followed by time window per protocol for early termination is ±42 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	-183, 43
Week 52	365	281, 449
Week 104	729	645, 813
Week 156	1093	1009, 1177
Week 208	1457	1373, 1541

Details for Definition of Variable

The Centiloid variable will be used rather than the original SUVR, because it allows data to be combined from different tracers, by mapping SUVR values to a standardized scale. The Centiloid variable is the current common standard in the scientific community.

The primary SUVR measure of interest is computed using a weighted composite target region and whole cerebellum as reference region. The weighted composite target region is composed of (both left and right side):

- frontal lobe,
- parietal lobe,
- temporal lobe lateral,
- cingulum posterior and
- anterior cingulate gyrus

Each region is weighted by its own volume. The Centiloid conversion is a linear transformation of SUVR with tracer-specific parameters that are given below in Table 3:

Centiloid Equation:

$$CL = SlopeCL \times SUVR + InterceptCL$$

CL=Centiloids; SlopeCL=slope; SUVR=standard uptake value ratio of the target region; InterceptCL=intercept.

The pertinent values for the two tracers are:

Table 3 Primary Centiloid Equation Parameters

Tracer	Reference	Slope	Intercept
Florbetaben-F18	whole cerebellum	175.6	-174.2
Flutemetamol-F18	whole cerebellum	143.5	-141.1

5.7.6.3 Summaries of Conduct of Substudy

The summary of study conduct will include a description of the following items by previous treatment arm:

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

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

Premature study drug discontinuation and study or substudy discontinuation, as well as reasons for discontinuations, will be summarized and listed.

The outputs will be performed on the Amyloid ITT analysis set.

5.7.6.4 Summaries of Demographic and Baseline Characteristics

Demographic and baseline characteristics of the participants who participate in this substudy will be summarized for the amyloid ITT analysis set as described in Section 5.7.2.

5.7.6.5 Safety Analyses

The safety analyses for the participants in the amyloid PET substudy will be conducted as part of the main study (POSTGRADUATE or OLE part of the parent study) safety analyses. There will not be a separate analysis of participants in this substudy.

5.7.6.6 Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim analyses for administrative reasons which may include efficacy, safety, and biomarker outcomes. No interim analysis of the substudy is planned for the time of the completion of parent studies.

5.7.7 Tau PET Substudy

The main objective of the POSTGRADUATE longitudinal tau PET substudy is to assess changes in brain tau load (as measured with [18F]GTP1) over time during treatment with gantenerumab.

The analyses described here are restricted to analyses of data assessed during this study or during the OLE part of the parent studies. Analyses across the double-blind part of the parent studies and this study will be reported separately and are not subject of this SAP. This document will focus on tau PET data assessed during this study or during the OLE part of the parent studies.

5.7.7.1 Brain Tau Load Analysis

The substudy is performed with an intravenous (IV) injection of a minimum of 185 MBq (5 mCi) and up to 259 MBq (not more than 7 mCi) of [^{18}F]GTP1 and imaging for a 30-minute scan, beginning 60 minutes following injection per PET scan.

The Tau ITT analysis set will be used to summarize tau burden in SUVR by descriptive statistics for each assessment time point as well as the change from baseline by previous treatment.

5.7.7.2 General Considerations on Tau PET Statistical Analyses

The baseline assessment for tau PET is scheduled for the OLE Day 1 visit (+42 days). Note that the results of the tau PET scan do not need to be available before dosing.

The last tau PET scan available within 6 months before OLE Day 1 and up to OLE Day 43 will be considered the baseline assessment.

Visit Windowing

For tau PET assessments, due to the long time between scheduled assessments, time windows, as defined in Table 4, will be used.

Table 4 Time Windows for Tau PET Endpoints

Visit	Target study day	Time window
Baseline	1	-183, 43
Week 52	365	281, 449
Week 104	729	645, 813
Week 156	1093	1009, 1177
Week 208	1457	1373, 1541

Details for Definition of Variable

Statistical analyses will be conducted on tau PET Median Standardized Uptake Value Ratios (SUVR) in the following four target regions of interest. In composite target regions, each region is weighted by its own volume.

- A temporal composite target region. This region is composed of (both left and right):
  - anterior and posterior superior temporal gyrus,
  - posterior temporal lobe,
  - fusiform gyrus,
  - middle and inferior temporal gyrus.
- A medial temporal composite region not including the hippocampus, composed of (both left and right):
  - Amygdala,
  - Parahippocampus,
  - Anterior medial and lateral temporal lobe.
- Frontal lobe (both left and right)
- Parietal lobe (both left and right)

The inferior cerebellar grey matter will be used as reference region for the calculation of median SUVRs for all four target regions considered.

5.7.7.3 Summaries of Conduct of Substudy

The summary of study conduct will include a description of the following items by previous treatment arm:

- Number of participants enrolled
- Number of participants included in each substudy analysis set

- Number and percentage of participants who prematurely withdrew from the study, substudy or from study treatment (including the reasons for discontinuation and the distribution of these discontinuations by time-windowed visit)
- Number and percentage of participants who completed treatment, the substudy, the study
- Incidence of protocol deviations – overall and by four main categories (inclusion criteria, exclusion criteria, medication and procedural)

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

Premature study drug discontinuation and study or substudy discontinuation, as well as reasons for discontinuations, will be summarized and listed.

The outputs will be performed on the Tau ITT analysis set.

5.7.7.4 Summaries of Demographic and Baseline Characteristics

Demographic and baseline characteristics of the participants who participate in this substudy will be summarized for the Tau ITT analysis set as described in Section 5.7.2.

5.7.7.5 Safety Analyses

The safety analyses for the participants in the tau PET substudy will be conducted as part of the main study (POSTGRADUATE or OLE part of the parent study) safety analyses. There will not be a separate analysis of participants in this substudy.

5.7.7.6 Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim analyses for administrative reasons which may include efficacy, safety, and biomarker outcomes. No interim analysis is planned for the substudy for the time of the completion of parent studies.

5.8 INTERIM ANALYSES

5.8.1 Planned Interim Analyses

A first interim analysis will be conducted at the time of the primary analysis for the parent pivotal studies GRADUATE I and GRADUATE II, to support a potential filing of gantenerumab in case of positive read-out of the pivotal studies. A second interim analysis may be conducted for an update on safety data in the filing dossier. The analyses will be 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 all analyses are descriptive, the interim analyses are considered of an administrative nature and will not have an impact on the final study results.

The following will be included in the interim analyses:

- Participant disposition (see Section 5.2)
- Demographics and baseline characteristics (see Section 5.7.2)
- Extent of exposure (see Section 5.6.1)
- Adverse Events (see Section 5.3.3)
- MRI safety findings (see Section 5.3.4, excluding analyses of time to onset or time to recurrence of ARIA, and analyses by dose level. Not all analyses will be run by APOE ε4 genotype.)
- Laboratory data (see Section 5.3.5)
- Vital signs (see Section 5.3.6)
- ECG data (see Section 5.3.7)
- C-SSRS data (see Section 5.3.8)

Immunogenicity analyses may also be performed at the interim analysis.

No interim analyses of efficacy data will be done.

5.8.2 Optional Interim Analyses

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more additional interim analysis(es) which may include efficacy, safety, and biomarker outcomes.

6. SUPPORTING DOCUMENTATION

Refer to Appendix 1 and Appendix 2 below.

Appendix 1 Changes to Protocol-Planned Analyses

All analyses in this SAP will be restricted to data collected under this study or during the OLE part of the parent studies and will be purely descriptive. No estimands will be defined.

Analyses of any long-term effect of the study drug (across the double-blind and open label phases from the parent study [GRADUATE I or GRADUATE II] and this study) are not subject to this SAP and will be described elsewhere.

Appendix 2 Bioclinica Severity Score

In order to determine the radiological severity of an ARIA-E event, the Bioclinica 5-point scale (Bracoud et al. 2017) will be used which has been renamed as Severity Scale of ARIA-E (SSAE) since the writing of the protocol. Please note that in addition to the 5-point scale being used for this study, a 3-point scale also exists.

Table 1 below details the definition of both the 5-point and 3-point severity scales.

Table 1 Bioclinica 3-Point and 5-Point Scale Definition

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

N/A = not applicable.

7. REFERENCES

Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull 1988;24:637-9.

Bracoud L, Fiebach JB, Purcell DD, et al. Validation of a simple severity scale for assessing AREIA-E. Alzheimers Dement 2017;13(Part 5):P253-4.

Clark LJ, Gatz M, Zheng L, et al. Longitudinal verbal fluency in normal aging, preclinical, and prevalent Alzheimer's disease. Am J Alzheimers Dis Other Demen 2009;24:461-8.

Columbia-Suicide Severity Rating Scale (C-SSRS; Columbia Protocol). The Columbia Lighthouse Project [resource on the Internet]. 2016 [Accessed: 28 July 2022]. Available from: https://cssrs.columbia.edu/

Connor DJ, Sabbagh MN. Administration and scoring variance on the ADAS-Cog. J Alzheimers Dis 2008;15:461-4.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.

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

Ihl R, Ferris S, Robert P, et al. Detecting treatment effects with combinations of the ADAS-Cog items in patients with mild and moderate Alzheimer's disease. Int J Geriatr Psychiatry 2012;27:15-21.

Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci 2000;12:233-9.

Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment (4th revised edition). New York: Oxford University Press, 2004.

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

Logsdon RG, Gibbons LE, McCurry SM, et al. Assessing quality of life in older adults with cognitive impairment. Psychosom Med 2002;64:510-9.

Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's disease assessment scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11(Suppl 2):S13-21.

Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001;58:397-405.

O'Bryant SE, Lacritz LH, Hall J, et al. Validation of the new interpretive guidelines for the Clinical Dementia Rating scale Sum of Boxes score in the National Alzheimer's Coordinating Center database. Arch Neurol 2010;67:746-9.

Pasquier F, Lebert F, Grymonprez L, et al. Verbal fluency in dementia of frontal lobe type and dementia of Alzheimer type. J Neurol Neurosurg Psychiatry 1995;58:81-4.

Pfeffer RI, Kurosaki TT, Harrah CH Jr, et al. Measurement of functional activities in older adults in the community. J Gerontol 1982;37:323-9.

Rozzini L, Chilovi BV, Conti M, et al. Conversion of amnestic mild cognitive impairment to dementia of Alzheimer type is independent to memory deterioration. Int J Geriatr Psychiatry 2007;22:1217-22.

Vellas B, Andrieu S, Sampaio C, et al., for the European Task Force Group. Endpoints for trials in Alzheimer's disease: a European Task Force Consensus. Lancet Neurol 2008;7:436-50.

Wechsler D. Wechsler Adult Intelligence Scale−Fourth Edition (WAIS−IV). San Antonio, TX: NCS Pearson, 2008.

Zarit SH, Zarit JM. The memory and behavior problems checklist and the burden interview. Gerontology Center, The Pennsylvania State University, 1990.

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