STATISTICAL ANALYSIS PLAN

for the Open Label Extension Period for Gantenerumab

DIAN-TU-001

A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive, and Clinical Endpoints in Dominantly Inherited Alzheimer's Disease

[redacted]

VERSION NUMBER AND DATE: V7.0, 07 DEC 2023

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V7.0 (Dated 07Dec2023) for Protocol DIAN-TU-001

[redacted]

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

[redacted]

[redacted]

Author: [redacted]

Version Number: 7

Version Date: 07Dec2023

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MODIFICATION HISTORY

	Significant Changes from Previous Authorized Version
[redacted]	Not Applicable – First Version
	Incorporate minor updates for efficacy parameters and add interim analysis details
	Correct protocol title
	Modified analysis population nomenclature and added details for DIAN-OBS selection of data for external controls; changed efficacy analyses to evaluate asymptomatic and symptomatic subjects separately; modified LME analysis to consider two slopes when double-blind gantenerumab data is included; modified set of analyses used to support the interim analysis, including identification of primary and secondary outcomes; added additional fluid biomarker to efficacy; re-ordered efficacy parameter presentation
[redacted]	Changed interim to have CDR Global and CDR Sum of Boxes as primary efficacy parameters, with primary analysis based on baseline asymptomatic subjects; add definition for concurrent and non-concurrent controls; updated definition for first and recurrent progression; added sensitivity models for

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
			primary interim parameters based on last post-baseline PiB-PET and based on concurrent / non-concurrent controls; changed MAC-Q and Tau PET to use internal controls only due to limited data for external controls; added figures to interim analysis; reference made to the Addendum of the Statistical Analysis Plan
[redacted]	[redacted]	[redacted]	Updated the model used for MTBR243 in Section 17, Table B from MMRM to LME; added MTBR243 to Section 16.2.3.3.
[redacted]	[redacted]	[redacted]	1. Add a mITT population definition based on CDR Global for the final analysis in section 5.3. **Rationale for this change:** Due to the unexpected pandemic, many participants were unable to travel to the study site for the PET scan, resulting in significant missing data, either at baseline or post-baseline. Therefore, a mITT population defined based on amyloid PET would exclude many participants from the final analysis, even though they had clinical/cognitive data. To maximize the data available for the clinical/cognitive analysis, an additional mITT population will be defined using CDR Global as the endpoint. 2. Change the external dataset used for the final analysis from DF17 to DF16 in section 5.4.1. **Rationale for this change:** Due to the early termination of the OLE study, the final analysis, including the data collected after

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			the interim analysis, will be conducted much earlier than the original timeline. As a result, the external dataset DF17, which was planned to be used for the final analysis, will not be available on time. To avoid further delays in the final analysis, the same external dataset DF16 will be used for the final analysis as well. 3. Reallocate certain secondary efficacy endpoints (initially listed in the no longer present section 16.2.1.2) as exploratory endpoints (now detailed in section 16.3). **Rationale for this change:** The interim analysis resulted in the early termination of the OLE study without a path for regulatory approval. Consequently, several secondary efficacy endpoints are not relevant and the final Clinical Study Report (CSR) will be abbreviated. **In summary,** these modifications do not impact any of the pre-specified statistical models outlined in this SAP, nor do they alter any primary or key secondary endpoints. They address challenges stemming from the pandemic and the premature termination of the OLE study. Consequently, they will not compromise the overall integrity of the trial. 4. Update Columbia Suicide Severity Rating Scale description and analysis (sections 12, 18.7.1) according to CRF.

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LIST OF ABBREVIATIONS/TERMS

Abbreviation/Term	Definition
[11C]PiB	[11C]-Pittsburgh Compound B (PiB) amyloid PET imaging tracer
AD	Alzheimer's Disease
ADA	Anti-Drug Antibody
AE	Adverse Event
AO	Age at onset
ARIA	Amyloid-related imaging abnormalities (includes those that occur both after treatment and during the natural history of untreated Alzheimer's disease)
ARIA-E	Amyloid-related imaging abnormality characterized by vasogenic edema, including both parenchymal and in leptomeningeal spaces
ARIA-H	Amyloid-related imaging abnormality characterized by hemorrhage, including microhemorrhage, macrohemorrhage (e.g., lobar hemorrhage) and superficial hemosiderin deposits
ATC	Anatomical Therapeutic Chemical
bpm	Beats per minute
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DIAD	Dominantly inherited Alzheimer's disease
DIAN-MCE	DIAN-Multivariate Cognitive Endpoint
DIAN-OBS	DIAN Observational
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENR	All Subjects Enrolled Set
EYO	Estimated Years to Symptom Onset
FAS	Functional Assessment Scale
FDG-PET	Fluorodeoxyglucose PET Imaging Tracer
ICF	Informed Consent Form
ISLT	International Shopping List Test
ISR	Injection Site Reaction
LME	Linear Mixed Effects

Abbreviation/Term	Definition
MAC-Q	Memory Complaint Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	Mixed-Effects Model for Repeated Measures
MMSE	Mini Mental Status Exam
MRI	Magnetic Resonance Imaging
NA	Not applicable
NfL	Neurofilament light chain
OLE	Open Label Extension
PET	Positron emission tomography
PT	Preferred Term
pTau	Phosphorylated Tau
Q2W	Every 2 weeks
Q4W	Every four weeks
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SUVR	Standardized Uptake Value Ratio
TEAE	Treatment Emergent Adverse Events
WAIS-R	Wechsler Adult Intelligence Scale - Revised
WHO	World Health Organization
WMS-R	Wechsler Memory Scale - Revised

[redacted]

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and biomarker data for the gantenerumab open label portion of the Protocol DIAN-TU-001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol amendment 12, dated November 10, 2021.

Details of the analyses presented for the Data Safety Monitoring Board (DSMB) meetings are presented in a separate DSMB SAP.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective for the final analysis of the Open Label Extension (OLE) is to determine if continued treatment with gantenerumab at its target dose can result in continued or complete removal of brain amyloid plaque using cerebral amyloid imaging using [^{11}C]-Pittsburgh Compound B (PiB) amyloid PET imaging tracer ([11C]PiB) Positron emission tomography (PET).

2.2. SECONDARY OBJECTIVES

The secondary objectives of the final analysis are as follows:

- The key secondary objective will be to evaluate the efficacy of gantenerumab in reducing disease progression and will be assessed for the following key secondary

[redacted]

efficacy outcome measures. Measures other than Clinical Dementia Rating (CDR) scales will be assessed as the annual rate of change and/or assessment of repeated measures:

- CDR - Sum of Boxes (CDR-SB)
- CDR Global
- DIAN-TU OLE Cognitive Composite
- Functional Assessment Scale (FAS)
- Mini-Mental State Examination (MMSE)
- Tau PET Binding Partial Volume Corrected Standardized Uptake Value Ratio (Tau PET SUVR)
- Cerebrospinal Fluid (CSF) phosphorylated Tau (pTau)-181
- Neurofilament Light chain (NfL) in CSF (CSF NfL)
- CSF Amyloid Beta1-42/40

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2.4. SAFETY OBJECTIVES

This study will assess safety and tolerability of SC gantenerumab up to 1500 mg Q2W in individuals at risk for DIAD. Safety endpoints used will be the incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and treatment discontinuations. Analysis will be on an intent-to-treat basis. Clinical laboratory evaluations, vital signs, and 12-lead ECGs will also be measured throughout the study. Amyloid-related imaging abnormalities (ARIA) are a safety endpoint in this study.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This SAP refers to the open label period of the trial following a Phase II/III double-blind, placebo-controlled study of potential disease modifying therapies in individuals with or at risk for dominantly inherited Alzheimer's disease (AD).

[redacted]

The double-blind period had two arms for each study drug, the active study drug and the blinded placebo for that study drug. Subjects were recruited from various sources, i.e., participating DIAN-observational (DIAN-OBS) study sites, DIAN-TU-001 trial sites, DIAN-TU-001 partner sites, the DIAN Expanded Registry study, and families identified by the sites. Mutation positive subjects who signed the informed consent form (ICF), met eligibility requirements and completed all baseline evaluations were randomized in a 3:1 ratio to receive either the active study drug or placebo for the active study drug. Eligible subjects were offered the opportunity to receive active drug for up to 3 years in an open label extension.

Mutation positive subjects who were administered either gantenerumab/placebo to gantenerumab or solanezumab/placebo to solanezumab were allowed to participate in the OLE for gantenerumab. All subjects participating in the OLE will receive gantenerumab. Dosing and titration for the OLE can be found in Section 1.5.2 of Appendix 3 of the protocol.

3.2. SCHEDULE OF EVENTS

Schedule of events for the OLE can be found in Appendix 3 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Two additional mITT populations, the OLE Gant All Gant exposure mITT and All Gant exposure mITT, will be used as supportive analysis populations for selected efficacy parameters, noting that linear models for these populations containing double-blind data will allow for the use of two slopes, one for double-blind baseline to open-label baseline and the second for open-label baseline through Year 3 of the open-label period. Parameters for analysis are included in this SAP based on OLE primary, secondary and exploratory endpoints and do not reflect all of the parameters identified for the analysis of the double-blind period.

4. PLANNED ANALYSES

The following analyses will be performed for the gantenerumab OLE for this study:

- Analyses for DSMB meetings
- Interim Analysis
- Final Analysis

4.1. DATA SAFETY MONITORING BOARD (DSMB)

A DSMB SAP, describing the methodology and the presentation of, and access to, results will be provided by [redacted] as a separate document.

4.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by [redacted] following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, and Sponsor Authorization of Analysis Sets.

Results from selected post hoc exploratory analyses which are not identified in this SAP but are deemed relevant to support the planned trial analyses will be documented and reported in the clinical study report (CSR); these results will be clearly identified as post hoc.

Exploratory analyses not performed for the study CSR such as exploratory biomarker analysis or OLE Baseline comparisons will be described by the Sponsor in a separate document. Analysis of pharmacokinetic parameters will be assessed by [redacted] and will be described in a separate document.

4.3. INTERIM ANALYSIS

An interim analysis for selected clinical/cognitive and biomarker endpoints will be conducted based on a datacut with all visits conducted through 31 March 2023, at which time it is projected that there will be a sufficient number of subjects with data collected at the Year 2 visit. The objectives of the interim are to determine if gantenerumab high dose and/or long term treatment result in clinical benefit and to determine whether the high dose of gantenerumab results in substantially increased amyloid removal compared to the double-blind period.

All visits up to the last visit contributing to interim efficacy assessments, including unscheduled visits, will be frozen at the time of the interim. All populations planned for final analysis will also be created for the interim, with the exception that external controls identified from DIAN-OBS may differ due to a different datacut being used for the interim and final analysis. A set of subject listings supporting parameters used for the interim analysis from the open-label database will be produced. Tables to be produced for the interim will be identified throughout the SAP, with analyses of efficacy described in Section 17 with references to the corresponding Section 16 where applicable.

Analysis of pharmacokinetic parameters will be assessed by [redacted] and will be described in a separate document.

5. ANALYSIS SETS

Agreement and documentation of mutation positive subjects included/excluded from each analysis set will be conducted prior to database lock for the OLE. Treatment groups for all analysis sets will be represented as follows and in the given order, noting that "Double-Blind Treatment Arm" will be displayed above the individual treatment columns:

- Placebo
- Solanezumab
- Gantenerumab
- Total

A set of controls will be used for efficacy analysis. The control groups are identified in the figures within Section 5.3 and are described within Section 5.4.

5.1. PROCESS FOR ANALYSIS SET ASSIGNMENT

- Analysis sets will be assigned based on SAP definitions. Subjects excluded from each analysis set and reason for exclusion will be prepared for the blind data review meeting prior to interim datacut and prior to database lock.
- After the data review meeting, any changes agreed upon during the meeting will be incorporated and the analysis sets will be finalized and signed off on by the Sponsor prior to the associated data transfer.

5.2. ALL SUBJECTS ENROLLED SET [ENR]

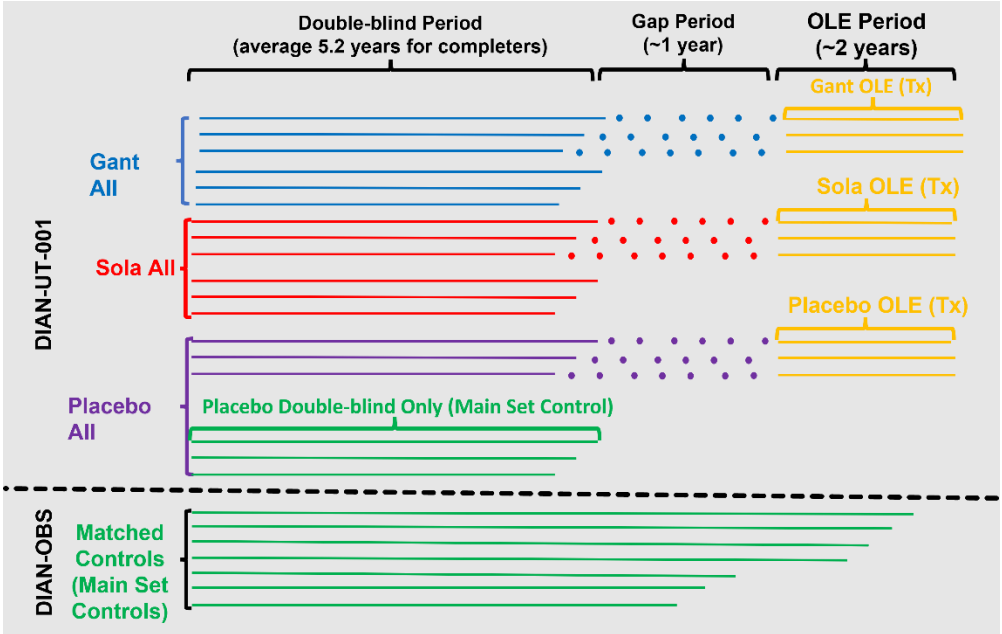
The all subjects enrolled (ENR) set will contain all mutation positive subjects who provided informed consent for the gantenerumab OLE.

5.3. MODIFIED INTENT-TO-TREAT [MITT]

The mITT analysis populations include all enrolled mutation positive subjects who receive any treatment post-baseline and have at least one assessment for the analysis primary parameter (PiB-PET SUVR for final analysis, CDR Global for both the interim analysis and the final analysis) prior to the associated treatment period (as a baseline assessment) and a post-baseline assessment. For analysis of clinical/cognitive endpoints or non-PET biomarker endpoints, the mITT population identified based on CDR Global should be used.

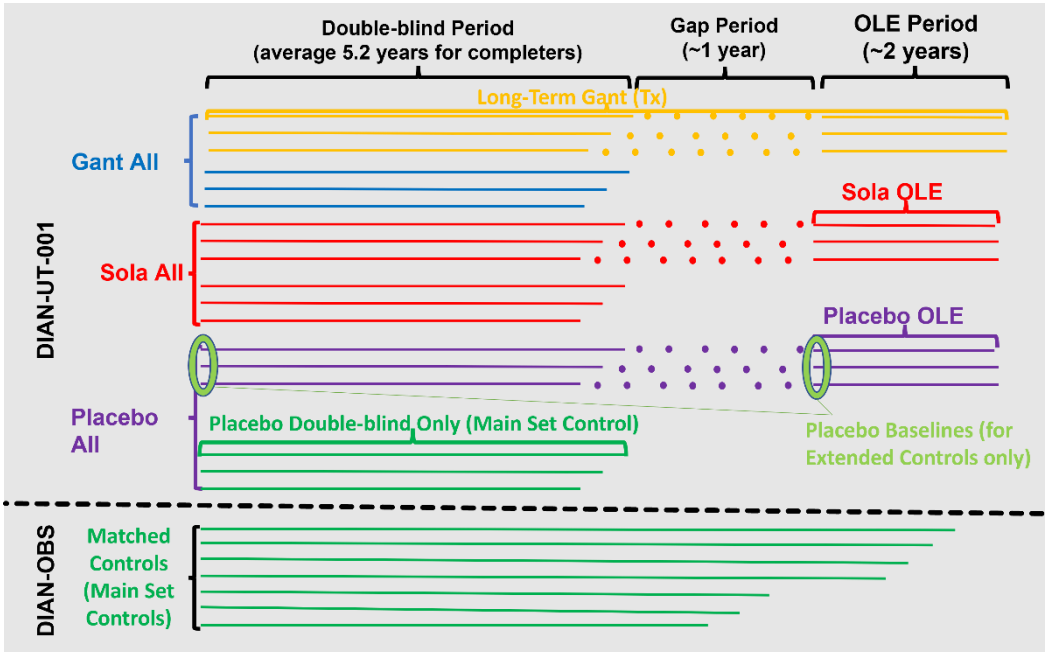
There will be three separate mITT populations:

1. OLE Gant mITT: Any subjects in the OLE meeting mITT criteria using OLE baseline (defined as the last assessment time for the analysis primary parameter prior to the first dose of OLE treatment) as the baseline reference point. Refer to figure below where the data contributing to the population is highlighted in yellow (and denoted with '(Tx)') for the OLE period, regardless of double-blind treatment, with controls (further described in Section 5.4) highlighted in green from both placebo double-blind only subjects and matched controls from DIAN-OBS.



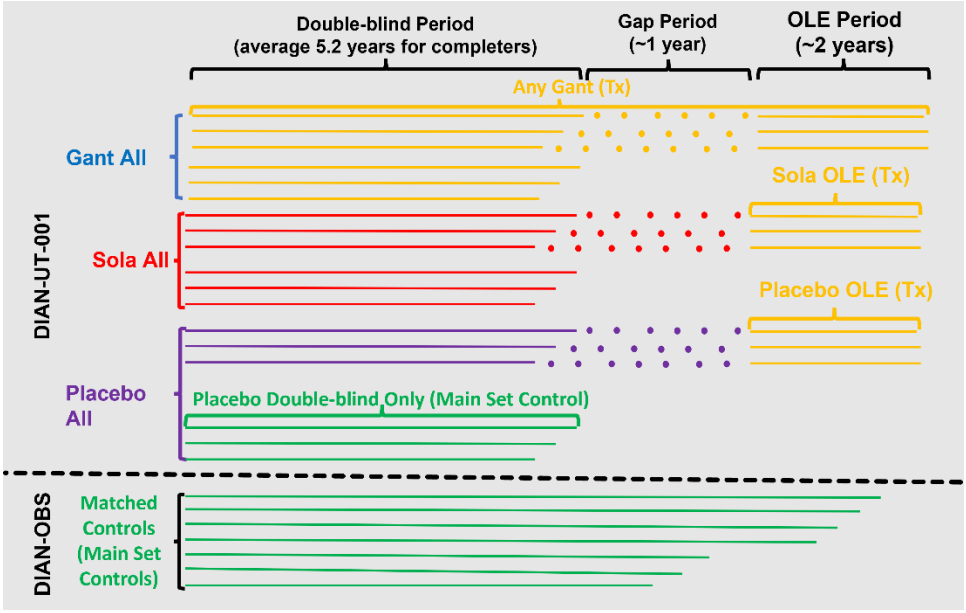
2. OLE Gant All Gant exposure mITT: Any subjects treated with gantenerumab in both the DB and OLE who meet mITT criteria using DB baseline as the baseline reference point. Refer to figure below where the data contributing to the population is highlighted in yellow (and denoted with '(Tx)') for subjects treated with gantenerumab in both DB and

OLE, with main set controls (further described in Section 5.4) highlighted in green from both placebo double-blind only subjects and matched controls from DIAN-OBS, and an additional set of extended controls (using DB and OLE baseline values for double-blind placebo subjects entering OLE) in a different shade of green to be added to the main set controls to form a second set of controls for the population.



3. All Gant exposure mITT: Any subjects treated with Gantenerumab in either DB or OLE who meet mITT criteria using the baseline associated with the first period of Gantenerumab exposure as the baseline reference point. Refer to figure below where the data contributing to the population is highlighted in yellow (and denoted with '(Tx)') any period of planned gantenerumab treatment, regardless of double-blind treatment, with controls (further described in Section 5.4) highlighted in green from both placebo double-

blind only subjects and matched controls from DIAN-OBS.



5.4. GROUPS OF CONTROLS

To facilitate the analysis, several groups of controls will be defined. It is acknowledged that data for the vast majority of subjects in the controls will represent a shorter duration than seen in subjects within OLE Gant All Gant exposure mITT.

5.4.1. EXTERNAL CONTROLS

External control subjects will be identified by [redacted] and approved by Washington University from the associated DIAN-OBS data freeze (DF16 for both the interim analysis and the final analysis) based on matched DIAN-TU inclusion/exclusion criteria used to select external controls as described in Section 7.2 of the double-blind SAP (including the use of Appendix II and Section 12.1.2 in that SAP to calculate EYO), with the exceptions of CDR Global being used rather than components of the DIAN-MCE and some variable selections in Table A below

differing from those used in the double-blind SAP. The exception to the convention is that subjects already selected for double-blind period as Eligible DIAN-OBS subjects will be retained with the same baseline visit as identified in the double-blind selection.

Table A: DIAN-TU-001 Exclusion Criteria Specified in Protocol Amendment 10 That Can Be Validated Using Information from the DIAN-OBS Database

DIAN-TU-001 Exclusion Criteria	Corresponding DIAN-OBS Available Information	DIAN-OBS Data Source	Variable Names in DIAN-OBS (the values to remove)
4.2.3	Subjects with recent health history of stroke, cerebral hemorrhage or transient ischemic attack.	UDS Form A5 Subject Health History (Item 2a/2b)	CBSTROKE (1) CBTIA (1) Eligibility Baseline MCH (5+)
4.2.4	Subjects with alcohol or drug dependence sufficient to meet DSM-IV criteria currently or within the past 1 year.	UDS Form A5 Subject Health History (Item 7a,7c)	ALCOHOL (1) ABUSOTHR (1)
4.2.6, 7, 8, 9, 10	Subjects with recent myocardial ischemic events, congestive heart failure or major cardiovascular procedures including angioplasty / endarterectomy/stent, cardiac bypass procedure, pacemaker	UDS Form A5 Subject Health History (Item 1a,1c,1d,1e,1f)	CVANGIO (1) CVBYPASS (1) CVCHF (1) CVHATT (1) CVPACE (1)
4.2.3, 11	Subjects with active atrial fibrillation or in treatment with anticoagulation	UDS Form A4 Subject Medications UDS Form A5 Subject Health History (Item 1b)	DRUGID (d00210 d00022) CVAFIB (1)
4.2.18	Subjects with clinically significant deficiency in B12 (recent diagnosis or in active treatment)	UDS Form Neurological Exam (Item 8, 9) UDS Form A5 Subject Health History (Item 5d)	NXSENSOR (2) and NXTENDON (2) and B12DEF (1)

When subjects meet the criteria above (per the respective DIAN-OBS data freeze corresponding to the analysis) to be included in the DIAN-TU-001 primary analysis, selected secondary, and selected sensitivity analyses, only their data from the point of eligibility and thereafter will be included.

5.4.2. Internal Set Controls

The internal set controls are defined as the placebo data from the double-blind period among subjects who did not enter the open-label extension.

5.4.3. Main Set Controls

The main set controls are defined as the external controls plus the internal set controls.

5.4.4. Extended Set Controls

The extended set controls are defined as the main set controls plus the double-blind baseline and OLE baseline values for subjects treated with placebo during the double-blind period who entered the OLE. This set will be an additional set used with the OLE Gant All Gant exposure mITT to add further long-term follow-up given that the two timepoints will differ by over four years for subjects added to this control group.

5.4.5. Concurrent Controls

Subjects in any control group will be identified as either concurrent or non-concurrent controls. The concurrent set of controls are defined as the internal set controls (including those in the extended set controls where applicable) and the external set controls where the point of eligibility occurs on or after the first dose of double-blind treatment in DIAN-TU-001. Based on this convention, the subject's baseline visit for internal set controls or point of eligibility for external

set controls will have occurred within the period during which DIAN-TU-001 subjects were treated (including the gap period between double-blind and open-label treatment).

5.4.6. Controls Applied to Individual Analysis Populations

Controls will be applied to the three mITT populations as follows, with the exception that Mixed Model for Repeated Measures (MMRM) analyses will be assessed against the internal set controls (when any controls are used) and parameters which are not assessed within DIAN-OBS will be assessed against the internal set controls:

- OLE Gant mITT: Evaluated against main set controls
- OLE Gant All Gant exposure mITT: Evaluated against main set controls (as primary set of controls) and also against extended set controls (as supportive set of controls)
- All Gant exposure mITT: Evaluated against main set controls

5.5. Safety Analysis Set [SAF]

The safety analysis population includes all subjects who have consented to participate and have received at least one dose of study drug in the gantenerumab OLE period.

6. General Considerations

All statistical analyses and summary information are to be generated according to this SAP. Any deviations from this SAP will be documented in the CSR.

For continuous variables, descriptive statistics such as the number of subjects (n), mean, standard deviation (SD) or standard error (SE), minimum, median, and maximum values will be reported. Lower and upper quartiles will be presented for select efficacy summaries. For categorical

variables, frequencies and percentages will be displayed. Subject data collected in the electronic case report form (eCRF) and other data sources will be presented in listings.

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of OLE study medication (where Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference date, then:

Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date, then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear partial or missing in the listings.

Similar variables will be created where needed for analysis based on using a reference start date as the day of first double-blind treatment. Study day will also be created for all controls where the reference date corresponds to the date of the visit to be used as the analysis baseline.

6.2. BASELINE

6.2.1. DOUBLE-BLIND BASELINE

Double-blind baseline is defined as the latest non-missing DIAN-TU-001 measurement taken prior to the double-blind study drug administration and will be consistent with the value identified as baseline during the double-blind analysis. Select imaging measures identified as failing after locking of the double-blind database a quality control during collection will be excluded from contributing to baseline.

6.2.2. OLE BASELINE

OLE Baseline is defined as the latest non-missing DIAN-TU-001 measurement taken prior to OLE study drug administration, using data from the OLE database where applicable. OLE baseline for specific assessments are as follows:

- OLE baseline for CDR Global and CDR-SB will be defined as the latest non-missing measurement prior to OLE study drug administration.
- For blood pressure, OLE baseline will further be defined as the latest time prior to OLE study drug administration where both systolic and diastolic blood pressure measurements are available.
- For laboratory assessments, OLE baseline will be defined as the values at Visit 1 of the OLE.
- OLE baseline measurements for height and weight will be derived from the values at Visit 1.

OLE Baseline will not be defined for subjects who never took the study drug. For assessments collected without a time measurement on the date of the first dose, the assessment can contribute

to OLE baseline if it was scheduled per protocol to take place prior to dosing.

Baseline for DIAN-OBS will be defined based on the first visit in which the subject met criteria as described in Section 5.4, noting that this visit will be identified at the time the subject is identified to contribute to the external controls.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

Summaries by visit will be based on the visit windows described in Section 6.4. Early discontinuation assessments of efficacy will be included at the annual visit when it occurs +/- 6 months relative to the visit, except in cases where a scheduled visit was conducted for the corresponding annual visit. Unscheduled visits that are not captured by analysis visit windowing will not contribute to by-visit analyses.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

Analysis visit windows will be applied based on the planned frequency of collection outlined in the protocol. Planned visit dates will be calculated from the date of the first OLE dose at V1 (Week 0). For data collected yearly, visit windows will begin 182 days prior to the planned visit date and end 182 days after the planned visit date. For data collected semi-annually, visit windows will begin 91 days prior to the planned visit date and end 91 days after the planned visit date. Safety/titration MRI's and measurements collected more frequently than a semi-annual basis (e.g., vital signs) will be summarized based on the nominal visit. If multiple measurements fall within the same visit window, the value closest to the planned visit timepoint per the protocol schedule of events will contribute to by-visit summaries, with the later visit to be used

in the case of a tie.

6.5. STATISTICAL TESTS

The default significant level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.6. COMMON CALCULATIONS

Scores for CDR Global and CDR-SB will be reported based on the value entered in the database and will not be recalculated.

For quantitative measurements, change from baseline will be calculated as post-baseline assessment - baseline assessment. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary.

EYO equals a subject's age at the clinical assessment minus this subject's estimated age at onset (AO). The details of the estimated AO are provided in the double-blind period SAP, Section 12.1.2, noting that Appendix III of this SAP will be used for analysis rather than the Appendix II in the double-blind SAP. CRF visit date will be used for the calculation of EYO to ensure a constant value across all tests within a visit.

6.7. SOFTWARE VERSION

All analyses, summary tables, figures, and data listings will be generated with SAS® version 9.4 or higher, or R, or with analysis code that has been appropriately validated.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Double-blind baseline CDR Global
  - CDR=0 (asymptomatic)
  - CDR>0 (symptomatic)
- OLE baseline CDR Global
  - CDR=0 (asymptomatic)
  - CDR>0 (symptomatic)
- Double-blind baseline PiB-PET SUVR
  - PiB-PET SUVR <= 1.25
  - PiB-PET SUVR > 1.25
- OLE baseline PiB-PET SUVR
  - PiB-PET SUVR <= 1.25
  - PiB-PET SUVR > 1.25
- Time since OLE baseline (in years; continuous)
- Time since double-blind baseline (in years; continuous)
- Double-blind baseline EYO (in years; continuous)
- OLE baseline EYO (in years; continuous)
- Post-baseline EYO (in years; continuous)

For external controls, baseline values will be identified as the last measurement at or prior to the first visit for the subject to be identified as contributing to the external controls.

7.2. MULTICENTER STUDIES

This platform study is conducted in three regions, USA/Australia/Canada, Europe, and the rest of the world. This study is being conducted at approximately 30 global sites. The homogeneity of treatment effects across investigational sites will be investigated using descriptive statistics.

When specified, statistical analysis will be adjusted for geographic region. Geographic region will be categorized as follows:

Geographic Region	Country
United States/Canada/Australia	United States, Canada and Australia
Europe	France, Spain, United Kingdom, as well as any European countries available from external controls.
Rest of World	The rest of world besides the above 2 regions, based on countries applicable to external controls.

7.3. MISSING DATA

There will be no imputation of missing data. Handling of missing data for specific efficacy endpoints is detailed in Sections 16.1.2 and 16.2.2.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

There will be no adjustments for multiplicity or multiple comparisons for the open label analysis as the study was powered based on the double-blind analysis.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analysis will be conducted as described within Section 16 for the primary variables, (key) secondary variables, and exploratory variables.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by [redacted]

9. DISPOSITION AND WITHDRAWALS

All mutation positive subjects who provide informed consent for the Gantenerumab OLE will be accounted for in this study period.

9.1. DISPOSITION

Subject disposition and withdrawals and study region will be presented for the ENR set, and presented separately by baseline asymptomatic and symptomatic status for the OLE Gant mITT population. In addition, visit attendance will be listed and summarized for each scheduled visit. Reasons for end of study and end of treatment will be presented in a listing. An additional listing will include subjects who did not meet one or more eligibility criteria.

Summaries for disposition will be presented for the interim analysis and will also identify the number of subjects who are active in the study as of the interim analysis datacut.

9.2. PROTOCOL DEVIATIONS

A summary will be provided to identify subjects who had important protocol violation(s) and a list will be provided for important protocol violation(s). The identification of the important protocol violation(s) will be discussed at the data review meeting prior to final database lock.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for each mITT population (along with their associated controls) and the SAF. No statistical testing will be carried out for demographic or other baseline characteristics. The univariate summary statistics, n, mean (SD), median, minimum and maximum will be calculated for the continuous variables. The following demographic and other baseline characteristics will be reported, where values will be presented as collected prior to double-blind treatment if the value was not collected in the open label database:

- Age (years) - calculated relative to date of consent for the OLE, based on date of birth as collected in the double-blind period
- Sex
- Race (where subjects can contribute to multiple race categories)
- Ethnicity
- OLE Baseline CDR Global
- OLE Baseline CDR-SB (summarized both as a continuous value and an ordinal value)
- OLE Baseline EYO
- Years of Education

- OLE Baseline Height
- OLE Baseline Weight

For the OLE Gant All Gant exposure mITT and All Gant exposure mITT populations, values for the double-blind period baseline for age, CDR Global, CDR-SB, EYO, height and weight will also be presented for subjects in the population who were randomized to gantenerumab during the double-blind period.

Demographic data will also be presented in a listing.

Demographic data will be summarized for the interim analysis for each mITT population and associated controls.

11. MEDICAL HISTORY

Updated Medical History information collected in the OLE eCRF will be listed for the SAF, and select family history as collected prior to the double-blind period will be summarized

- Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). The version will be established and documented prior to lock of the data and will be identified within footnotes.
- Family AD History as indicated by symptoms, history or diagnosis will be summarized by descriptive statistics and listed for the OLE Gant mITT and the SAF. Mutation gene types (PSEN1, PSEN2, and APP), APOE4 status (as positive/negative, as number of copies (0, 1, or 2), and by allele combinations), number and percentage of blood grandparents and parents, siblings, and children in a family with dementia will also be tabulated.

12. COLUMBIA – SUICIDE SEVERITY RATING SCALE (C-SSRS)

The OLE baseline C-SSRS score, as obtained using the Since Last Visit version of the form, will be summarized using descriptive statistics by severity rating scale for each category of Suicidal Ideation, Intensity of Ideation, and Suicidal Behavior for the SAF. C-SSRS scores will also be listed.

13. MEDICATIONS

Medications defined as concomitant medications (as identified below) will be presented for the SAF and coded using the World Health Organization (WHO) dictionary. The version will be established and documented prior to lock of the data and will be identified within footnotes. Medications will be classified and summarized by anatomical therapeutic chemical (ATC) drug class and by the WHO drug preferred name. Subjects who report use of more than one medication or multiple uses of the same medication will be counted once per medication code and once for all drugs taken within an ATC drug class.

Concomitant medications will also be summarized based on the number of subjects with changes to AD medication between the first and last dose of OLE treatment. The number of subjects will be presented along with the incidence of AD medications by WHO drug preferred name.

If the medication start date is missing or partial, the date will be compared as far as possible with the date of first dose of the OLE study drug. Medications will be assumed to be concomitant unless there is clear evidence (through comparison of partial dates and/or collected assessment of whether the medication started prior to the first dose of the study drug) suggesting the medication started prior to the first dose of study medication.

- 'Prior' medications are medications which have a start date prior to the first dose of OLE study drug and will include those medications which were identified as ongoing at the end of double-blind and re-entered onto an Ongoing Concomitant Medication page of the OLE eCRF form.
- 'Concomitant' medications are all medications which have a start date on or after the date of the first dose of OLE study drug.

All medications captured in the OLE eCRF concomitant medications form will be listed, ordered within subject by the medication start date. The listing will display the recorded term from the CRF and, adjacent to that, the preferred name that appears in the tables.

14. SUBSTANCE USAGE

Substance usage history was not re-assessed after double-blind baseline and will not be included in any OLE listings.

15. STUDY MEDICATION EXPOSURE

Duration of treatment in the OLE will be summarized as both total days and total weeks per subject and will be presented using the descriptive statistics including mean (SD), 25th percentile, median, 75th percentile, min and max for the SAF. Similarly, duration of total gantenerumab exposure spanning the double-blind and OLE periods, duration of gantenerumab exposure at the highest dose in the OLE and duration of gantenerumab exposure at the highest dose in either the double-blind or OLE period will be summarized.

The total number of administered doses (including both fully and partially administered) for each subject will be summarized overall and by dose levels using descriptive statistics. The cumulative OLE dose exposure will be summarized. A listing of OLE study drug administration

will be presented. In addition, percent compliance will be summarized during the OLE.

Study medication exposure will be summarized for the interim analysis.

15.1. DERIVATIONS

Duration of treatment from OLE baseline (days) = date of last OLE dose – date of first OLE dose +1

Total duration of treatment with gantenerumab from double-blind baseline (days) = (date of last double-blind dose – date of first double-blind dose) + (date of last OLE dose – date of first OLE dose) +1

Duration of treatment of gantenerumab at the highest OLE dose received (days) = date of last OLE dose – date of first OLE dose at the same dose level +1

Duration of treatment of gantenerumab at the highest dose received (days) = date of last dose at the highest level in either the OLE or double-blind periods – date of first dose at the same dose level +1

Percent compliance in the OLE = (number of OLE doses/ number of planned OLE dosing visits prior to treatment discontinuation) x 100, where the number of OLE doses combines dosing at the visit and the preceding Q2W dosing timepoint, where applicable, as a single dose

Cumulative OLE dose of gantenerumab = sum of all OLE doses, based upon the planned dose for any dose administered.

16. EFFICACY OUTCOMES

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY VARIABLE(S) & DERIVATION(S)

The primary efficacy variable is the change in amount of amyloid deposition as measured by [11C]PiB-PET. The composite PiB partial volume corrected standardized uptake value ratio (C-SUVR, the composite SUVR of precuneus, caudate, gyrus rectus, occipital cortex, parietal cortex, prefrontal cortex and temporal cortex) is used as the biomarker endpoint for amyloid deposition. Corresponding analyses based on conversion of SUVR to centiloid will be performed by Washington University.

16.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE(S)

There will be no missing data imputation for the primary efficacy variable.

16.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

The primary objective for the OLE is to determine if treatment with gantenerumab at its target dose can result in removal of brain amyloid plaque using cerebral amyloid imaging using [11C]PiB-PET.

The primary efficacy analysis will be performed for the OLE Gant mITT without the use of controls in the model. A Mixed-Effects MMRM analysis will be used to test if the change from the OLE baseline to the end of OLE in PiB-PET SUVR is significantly less than 0 for the OLE Gant mITT population. The MMRM will include the OLE baseline PiB-PET SUVR and visit (treated as categorical) as the fixed effects. An unstructured variance-covariance matrix will be

used to model the within-subject errors among the repeated measures. If the unstructured covariance structure matrix results in a lack of convergence, the following covariance structures will be assumed in sequence: heterogeneous Toeplitz, heterogeneous autoregressive, heterogeneous compound symmetry, and compound symmetry. The corresponding p-value and the 95% confidence interval for the estimated least squares mean change at each visit will be presented. If the upper bound of the 95% CI at the year 3 OLE visit is less than 0, it is concluded gantenerumab significantly removes amyloid plaque at year 3. In the case that a structured variance-covariance matrix is used to enable the model to converge, the "sandwich" estimator of the variance-covariance matrix will be employed by using the “empirical” option in the proc mixed procedure. P-values for within-subject change resulting from a one-sample t-test using least squares mean estimates and associated standard errors will be presented.

Descriptive statistics including number of observations, mean, SD, median, minimum, and maximum will be provided by visit. P-values for within-subject change resulting from a one-sample t-test using least squares mean estimates and associated standard errors will be presented. In addition, a listing of the primary endpoint will be presented.

Figures of model estimated mean over time or spaghetti plots of individual data over time/EYO color-coded by treatment arms and doses will be presented as deemed necessary by Washington University team and may be included in CSR as needed.

16.1.4. SUPPLEMENTARY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

16.1.4.1. Amyloid Removal by Double-Blind Treatment

An MMRM analysis similar to the one described in Section 16.1.3 will be re-run to compare the change during the double-blind period in amyloid PET for participants on gantenerumab (only

their data in the double-blind period will be included) with the change from the OLE baseline for participants (only their data in the OLE period will be included) on solanezumab or placebo in the double-blind period using an MMRM model.

16.1.4.2. Amyloid Removal by CDR Global Status

The analysis described in Section 16.1.3 will be re-run with the OLE baseline CDR Global (in categories of baseline CDR=0 and baseline CDR >0) as a covariate to estimate the treatment effect for the subgroup Figures of model estimated mean over time or spaghetti plots of individual data over time/EYO (CDR=0 vs CDR >0) will be presented as deemed necessary by Washington University team and may be included in CSR as needed.

16.1.4.3. Gantenerumab Treatment Effects during the Whole Study Duration (Double-Blind + OLE)

To evaluate the treatment effect of gantenerumab during the whole study duration, the change from the double-blind baseline for subjects in the All Gant exposure mITT and for subject in the OLE Gant All Gant exposure mITT will be calculated for each post double-blind baseline visit and will be analyzed using the MMRM model (without controls) described in Section 16.1.3. The MMRM model will include the double-blind baseline value, the double-blind treatment arm (gantenerumab, solanezumab, placebo) as applicable per analysis population, visit, and the interaction between the double-blind treatment arm and visit as the fixed effects. The visit variable will be considered as categorical with the following categories: visit 1 (the ~1-year visit in the double-blind period), visit 2 (the ~2-year visit in the double-blind period), visit 3 (the ~4-year visit in the double-blind period), visit 4 (the OLE baseline visit), visit 5 (the ~1-year OLE visit), visit 6 (the ~2-year OLE visit), visit 7 (the ~3-year OLE visit). Subjects on gantenerumab or placebo during the double-blind period will contribute to all visits. Subjects on solanezumab during the double-blind period will not contribute to post-baseline values within the double-blind period. An unstructured variance-

covariance matrix will be used to model the within-subject errors among the repeated measures. If the unstructured covariance structure matrix results in a lack of convergence, the following covariance structures will be assumed in sequence: heterogeneous Toeplitz, heterogeneous autoregressive, heterogeneous compound symmetry, and compound symmetry. In the case that a structured variance-covariance matrix is used to enable the model to converge, the "sandwich" estimator of the variance-covariance matrix will be employed by using the “empirical” option in the proc mixed procedure.

The corresponding p-value for the difference from no change from baseline and the 95% confidence interval for the estimated least squares mean change at each visit will be presented.

The model described above will also be analyzed with the addition of the double-blind baseline CDR status (CDR=0 vs CDR >0) as a covariate, the two-way interactions of CDR status and the double-blind baseline PiB-PET SUVR, CDR status and treatment arm, and CDR status and visit, and the three-way interaction of CDR status, treatment arm and visit. If the model fails to converge, the model will be removed.

Figures of model estimated mean over time by the double-blind treatment arms or spaghetti plots of individual data over time/EYO by the double-blind treatment arms will be presented as deemed necessary by Washington University team and may be included in CSR as needed.

16.1.4.4. Proportion of Subjects Converted from Abnormal to Normal

To evaluate whether gantenerumab can decrease the accumulated amyloid plaque from abnormal level to normal level, the threshold of 1.25 will be used to define normal level vs abnormal level at the OLE baseline and at each post-baseline visit. A PiB-PET SUVR >1.25 is considered abnormal while a PiB-PET SUVR ≤1.25 is considered normal. A shift from OLE baseline to

each post-baseline visit, where missing values are replaced using last observation carried forward (allowing the baseline value to also be carried forward), and to the last post-baseline OLE measurement will be provided along with a corresponding Fisher's exact test. A supportive analysis of shifts at each post-baseline visit without carrying forward values will also be provided. This analysis will be conducted for the OLE Gant mITT population.

16.1.4.5. Evaluate the Association between Amyloid Reduction and Treatment Exposure

The total treatment exposure at each visit, defined as the cumulative OLE dose prior to the start of the associated visit, will be calculated for each subject. Linear mixed effects model will be used to estimate the association between amyloid reduction and the treatment exposure.
The change from baseline in PiB-PET SUVR will be the dependent variable and the total treatment exposure at each visit and the baseline PiB-PET SUVR will be independent variable. Random effects in intercept and total treatment exposure will be included in the model to account the correlation among the repeated measures. This analysis will be applied to the OLE Gant mITT population and will also be run with baseline covariates such as disease status (asymptomatic vs symptomatic) and EYO. When the disease status is included in the model, the interaction between disease status and total treatment exposure will also be included so that the treatment effect will be evaluated separately for each disease status.

Figures of individual amyloid removal vs individual total dose exposure will be presented as deemed necessary by Washington University team and may be included in CSR as needed. If the plot demonstrates a non-linear relationship, an ad-hoc non-linear mixed effects model will be used to estimate this non-linear relationship.

Figures of model estimated mean over time by high dose and low dose or spaghetti plots of

individual data over time/EYO by high dose and low dose will be presented as deemed necessary by Washington University team and may be included in CSR as needed.

16.2. SECONDARY EFFICACY

For details of the collection methods for each test please refer to the protocol. For each secondary efficacy variable, the direction of benefit with effective drug is listed below. These may be calculated as change from baseline or difference between drug vs. control.

16.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

16.2.1.1. Key Secondary Efficacy Variables

- Clinical Dementia Rating – Sum of Boxes (CDR-SB): Higher scores indicate worse performance.
- CDR Global: Higher scores indicate worse performance.
- DIAN-TU OLE Cognitive Composite (OLE Cognitive Composite)

Based on the four components, the DIAN-TU-001 OLE Cognitive Composite will be calculated using the following formula: $Y = (0.25)\frac{M-mean}{SD} + (0.25)\frac{W-mean}{SD} + (0.25)\frac{A-mean}{SD} + (0.25)\frac{D-mean}{SD}$, where, D represents the WMS-R Digit Span Backward Recall, A represents the Category Fluency (Animals) value, W represents the Wechsler Adult Intelligence Scale Digit Symbol Substitution Test value, and M represents the Mini Mental State Examination value. The mean (SD) for each of the four parameters will be calculated using the double-blind baseline data of the mutation positive subjects in the DIAN-TU-001 trial. Lower scores of each component indicate worse performance.

- Functional Assessment Scale (FAS): Higher scores indicate worse performance.
- Mini-Mental State Examination (MMSE): Lower scores indicate worse

performance.

- Tau PET Binding Partial Volume Corrected Standardized Uptake Value Ratio - Parietal Composite (Tau PET SUVR): The summary region is the average SUVR values for the postcentral gyrus, supramarginal gyrus, superior parietal cortex, inferior parietal cortex, precuneus, posterior cingulate, and isthmus cingulate regions. Expected to decrease with effective drug.
- CSF pTau181: Expected to decrease with effective drug.
- CSF NfL: Expected to decrease with effective drug.
- CSF Amyloid Beta1-42/40: Expected to increase with effective drug

16.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE(S)

Missing values in the clinical or cognitive assessments (such as MMSE, FAS etc.) are expected to be rare. If at any given visit, the number of missing items within a questionnaire is less than 30% of the total number of items, then the score for this component at this visit will be calculated as the sum of the non-missing items multiplied by the ratio of the total number of items to the number of the non-missing items (Doody, 2014). If the number of missing items is equal to or greater than 30%, then the score at this visit is considered missing (Doody, 2014).

If at any given visit, where all four components of the OLE Cognitive Composite are intended to be measured and one of the four components has missing scores, meaning less than 30% of the total components as described above, then the OLE Cognitive Composite will be calculated using only the other three components and with the method described in SAP Section 16.2.1.1. But the composite will be weighed by 1/3 instead of 0.25. If two or more components have missing scores, then the composite will be considered missing as well.

If at any given visit, only some of the four components are intended to be measured instead of all, then the composite score will not be calculated and will not be used in the analysis for these visits.

Values captured within the FAS as 'not applicable (e.g., never did)' (NA) will be treated as missing.

16.2.3. PRIMARY ANALYSIS OF KEY SECONDARY EFFICACY VARIABLES

16.2.3.1. Primary Analysis of CDR-SB

The primary analysis will be on the All Gant Exposure mITT, with other baseline covariates (such as baseline EYO) defined in the same way as baseline for the associated population. The recurrent progression is defined as any progression which is either the first increase in CDR-SB above baseline or any progression above the highest preceding post-baseline value identified as a progression, where progression above the preceding value must be observed at two consecutive measurements unless the progression occurs at the last measurement. Subjects without a progression event at their last measurement will be censored at the time of that measurement. The time-to-event is the time elapse between the two visits where the recurrent progression is observed, or the time since the baseline assessment for the first progression. Subjects can contribute multiple records to the analysis (i.e., once for each progression and potentially for censoring at the time of last measurement). The same definition will be applied to all controls as defined in Section 5.4. The Cox proportional hazards model employing the Andersen-Gill method (Prentice RL, 1981) with robust variance estimator will be used to compare the hazards of recurrent progression in CDR-SB between population and all controls. The model will include treatment group and baseline EYO as the fixed effects. Should the model produce a two-sided p-value less than 0.10, a sensitivity analysis will be conducted using the shared frailty method (add reference).

Analyses will be conducted separately for baseline asymptomatic and symptomatic subjects.

The same analysis will be applied to the OLE Gant mITT population and the OLE Gant All Gant exposure mITT populations, along with all controls. The analysis will also be conducted for each of the three mITT populations based on the baseline asymptomatic and symptomatic subjects presented separately. A Kaplan-Meier figure will be generated for baseline asymptomatic subjects for all three mITT populations and associated controls.

The spaghetti plots of individual data will be presented over time since baseline and over EYO for both the OLE Gant All Gant exposure mITT population and for all controls. These figures, including those described for CDR-SB in Section 3 of the Addendum to the Statistical Analysis Plan created by Washington University prior to the interim analysis, will be generated by Washington University team and may be included in CSR as needed.

16.2.3.2. Primary Analysis of CDR Global

The primary analysis will be on the All Gant Exposure mITT, with all the other baseline covariates (such as baseline EYO) defined in the same way as baseline for the associated population. The time to the first disease progression is defined as the time from the baseline to the first visit where CDR Global is greater than CDR Global baseline value, where a progression is considered an increase above baseline observed at two consecutive measurements unless the progression occurs at the last measurement. Subject without progression will be censored at their last measurement.

The Cox proportional hazards model will be applied to compare the hazards of disease progression in CDR Global between each of the three mITT population separately and all

controls. The models will include the treatment group (specifically gantenerumab and controls) and baseline EYO as the fixed effects.

Analyses will be conducted separately for baseline asymptomatic and symptomatic subjects. A Kaplan-Meier figure will be generated for baseline asymptomatic subjects for all three mITT populations and associated controls.

Spaghetti plot of EYO for each participant will be presented for each of the three mITT populations. Lines and data points will be coded by different color/symbol for different CDR groups (without progression, with progression) and doses. This figure will be generated by Washington University team.

16.2.3.3. Primary Analysis of OLE Cognitive Composite, FAS, MMSE, Tau-PET SUVR, CSF NfL and CSF MTBR243

The annual disease progression between the OLE Gant mITT population and all controls (with the exception of internal controls only for Tau-PET SUVR) will be compared using a linear mixed effects (LME) model. CSF NfL will be log transformed for the analysis. The LME model will include time since baseline (in years: treated as continuous), treatment group (the OLE Gant mITT and all control), interaction between the treatment group and time, and random intercepts and slopes for each subject as the random effects. The unstructured covariance will be used to model the covariance between random intercepts and random slopes and will be modelled separately for baseline asymptomatic and symptomatic subjects.

The same analysis will also be applied to the OLE Gant All Gant exposure mITT population and the All Gant exposure mITT populations, along with all controls. This model will be tested using linear splines, which fits two slopes with one prior to the OLE baseline and one after the OLE

baseline (the linear splines have a node at the OLE baseline) to account for the different dosing regimens in the DIAN-TU-001 gantenerumab exposure population; for the pooled controls, only one slope will be fitted since no treatment was administered at any point in time. The analysis will also be conducted for each population based on the baseline asymptomatic and symptomatic subjects presented separately.

Figures of model estimated mean over time by treatment arms or spaghetti plots of individual data over time/EYO by treatment arms will be presented as deemed necessary by Washington University team and may be included in CSR as needed. The plots will also be presented separately for baseline asymptomatic and symptomatic subjects at the OLE baseline.

16.2.3.4. Primary Analysis of CSF pTau181

To evaluate whether gantenerumab will continue to reduce the CSF pTau181 from OLE baseline, MMRM (without controls) will be used to test if the change from the OLE baseline to the end of OLE in CSF pTau181 is significantly less than 0 for the OLE Gant mITT population. The MMRM will include the OLE baseline CSF pTau181 and visit (treated as categorical) as the fixed effects. An unstructured variance-covariance matrix will be used to model the within-subject errors among the repeated measures. If the unstructured covariance structure matrix results in a lack of convergence, the following covariance structures will be assumed in sequence: heterogeneous Toeplitz, heterogeneous autoregressive, heterogeneous compound symmetry, and compound symmetry. The corresponding p-value and the 95% confidence interval for the estimated least squares mean change at each visit will be presented. If the upper bound of the 95% CI at the year 3 OLE visit is less than 0, it is concluded gantenerumab significantly remove amyloid plaque at year 3.

Figures of model estimated mean over time by treatment arms or spaghetti plots of individual data over time/EYO by treatment arms will be presented as deemed necessary by Washington University team and may be included in CSR as needed. The plots will also be presented separately for baseline asymptomatic and symptomatic subjects at the OLE baseline.

16.2.3.5. Primary Analysis of CSF Amyloid Beta1-42/40

To evaluate if treatment with gantenerumab increases CSF Amyloid Beta1-42/40, the MMRM as described in Section 16.2.3.4 will be applied for the OLE Gant mITT and the MMRM as described in Section 16.1.4.3 will be applied for the All Gant exposure mITT, with both asymptomatic and symptomatic subjects included within the same model.

16.2.4. SUPPLEMENTAL ANALYSIS OF KEY SECONDARY EFFICACY VARIABLES

16.2.4.1. Supplemental Analysis of CDR-SB

16.2.4.1.1. Subgroup Analysis for CDR SB

Each subject in the All Gant exposure mITT population and all controls will be categorized into 3 groups by comparing the baseline and the last available PiB SUVR values to 1.25: (1) Amyloid normal group (both the baseline and the last available PiB SUVR values <1.25); (2) Amyloid abnormal to normal group (the baseline PiB SUVR value>=1.25 and the last available PiB SUVR value <1.25); (3) The rest (not in groups (1) and (2)). The model described in Section 16.2.3.1 will be applied to the All Gant exposure mITT population and all controls to compare the hazard of progression in CDR SB among these 6 subgroups (i.e., 3 groups above assessed within baseline asymptomatic/symptomatic status).

A separate analysis will identify DIAN-TU-001 subjects as either PiB-PET SUVR normal or abnormal based upon the last post-baseline measurement for the subject. The model described in

Section 16.2.3.1 will be applied to the asymptomatic subjects in the All Gant exposure mITT population where treatment groups are replaced with the three groups of PiB-PET SUVR normal, PiB-PET SUVR abnormal, and external controls, with the normal and abnormal groups being compared to the external controls and to each other. The model will also be run with factors of the number of post-baseline PiB-PET normal values (as a continuous measure to replace the normal/abnormal status) and the interaction of that variable with the treatment groups.

The model described in Section 16.2.3.1 will be applied to the asymptomatic subjects in the All Gant exposure mITT population where treatment groups are replaced with the three groups of gantenerumab exposure, concurrent controls, and non-concurrent controls, with the gantenerumab exposure being compared to both sets of controls.

Figures of model estimated mean over time by treatment arms or spaghetti plots of individual data over time/EYO by treatment arms will be presented as deemed necessary by Washington University team and may be included in CSR as needed. The plots will also be presented separately for baseline asymptomatic and symptomatic subjects at the OLE baseline.

16.2.4.1.2. Cox Proportional Hazards Model for Time to First Disease Progression in CDR SB

The analysis models in Section 16.2.3.2 (Cox proportional hazards model) will be applied to CDR SB. The same analysis will be repeated for the OLE Gant mITT population with 4 treatment groups (subjects on gantenerumab in the double-blind period, subjects on solanezumab in the double-blind period, subjects on placebo in the double-blind period, and all control) and will be repeated for the six subgroups defined in the first paragraph in Section 16.2.4.1.1. The same analysis may also be conducted for subgroups defined in the second paragraph in Section 16.2.4.1.1.

16.2.4.1.3. LME Model for Annual Rate of Change

The annual disease progression between each mITT population and all controls will be compared using an LME model for each key secondary efficacy variable. The same model described in Section 16.2.3.3 will be used. Separate analyses of baseline asymptomatic and symptomatic subjects will also be made to determine if treatment before symptom onset is different from after symptom onset.

The same analysis will also be conducted for the six subgroups defined in the first paragraph in Section 16.2.4.1.1.

16.2.4.1.4. Exponential Disease Progression Model

The exponential disease progression model with EYO as the continuous time variable as presented below will be applied to CDR-SB. The model will be used to estimate the slowing of disease progression in the OLE Gant mITT population compared to all controls. Because the baseline values of the OLE Gant mITT population were obtained before the treatment, these values will be counted into all controls for estimating the disease progression over EYO.

Briefly, the model can be described as:

$$Y_{ijk} = (\beta + \mu_i) + \gamma_{1k} * e^{\left(\frac{EYO_{ij}+\delta_i}{\gamma_{2k}}\right)} + \varepsilon_{ijk}$$

Where, y_{ijk} denotes the assessment for subject i at visit EYO j in treatment arm $k = 1, 2$; treatment is a categorical variable with two categories: subjects the OLE Gant mITT population (only post OLE baseline data), and subjects in all controls (data in this category include: baseline data of the OLE Gant mITT population and data of all controls); β is the mean of the healthy period (e.g. EYO <=-15) and is assumed to be the same for all arms; γ_{1k} is the mean decline

from the healthy period to symptom onset (e.g. EYO=0); I is the indicator function with $I(k = 2) = 1$; μ_i and δ_i are the subject-level random effects and are assumed to follow a bivariate normal distribution; ε_{ijk} is the within- subject error and is assumed to follow a normal distribution $N(0, \sigma^2)$; and γ_{2k} represents the scale parameter of the treatment and all control group.

The null hypothesis is: $\gamma_{21} = \gamma_{22}$;

and the alternative is: $\gamma_{21} \neq \gamma_{22}$.

The same analysis will also be applied to the OLE Gant mITT population and the OLE Gant All Gant exposure mITT populations, along with all controls. The analysis will also be conducted for each population based on the baseline asymptomatic and symptomatic subjects presented separately.

The spaghetti plots of individual will be presented over time since baseline and over EYO for both the OLE Gant mITT population and all controls.

Figures of model estimated mean over EYO by treatment arms or spaghetti plots of individual data over EYO by treatment arms will be presented as deemed necessary by Washington University team and may be included in CSR as needed.

The same analysis will also be conducted for the six subgroups defined in the first paragraph in Section 16.2.4.1.1.

16.2.4.1.5. Logistic Disease Progression Model

The logistic disease progression model with EYO as the continuous time variable as presented

below will be applied to the CDR-SB. The model will be used to estimate the slowing of disease progression in the OLE Gant mITT population compared to all controls. Because the baseline values of the OLE Gant mITT population were obtained before the treatment, these values will be counted into all controls for estimating the disease progression over EYO.

Briefly, the model can be described as:

$$Y_{ijk} = (\beta + \mu_i) + \frac{\gamma_1}{1 + e^{\left(-\frac{(EYO_{ij} + \delta_i) - \gamma_{3k}}{\gamma_{2k}}\right)}} + \varepsilon_{ijk},$$

where, y_{ijk} denotes the assessment for subject i at visit j in treatment arm $k = 1, 2$; treatment is a categorical variable with two categories: subjects the OLE Gant mITT population , and subjects in all controls; β is the mean of the healthy period (e.g. EYO <=-15) and is assumed to be the same for all groups; γ_1 is the mean decline from the healthy stage to the disease stage (e.g. EYO>=0) and is assumed to be the same for all groups; γ_{3k} is the EYO point where the disease progressed to the middle point between the healthy stage and the disease stage; γ_{2k} is the scale parameter indicating the spread of the disease progression curve; ε_{ijk} is the within-subject error and is assumed to follow a normal distribution $N(0, \sigma^2)$; μ_i and δ_i are the individual level random effects to account for the correlation among the repeated measures and use an unstructured covariance matrix. The main assumption of this model is that after accounting for the between subject difference though the random effects, the disease progression from EYO to EYO is the same for both cross-sectional data (from different subjects) and longitudinal data (repeated measurements of the same individual).

The treatment effect will be estimated by comparing the EYO points where the disease progressed to the middle point between the healthy period (β) and the disease period ($\beta + \gamma_1$). The null hypothesis is: $\gamma_{31} = \gamma_{32}$;

and the alternative is: $\gamma_{31} \neq \gamma_{32}$.

The model will be used to estimate the slowing of disease progression in the OLE Gant mITT population compared to all controls.

If the model fails to converge, the random effect (δ_i) in EYO will be removed.

The model will also be used to compare OLE Gant mITT population and the OLE Gant All Gant exposure mITT populations, along with all controls.

Figures of model estimated mean over time by treatment arms or spaghetti plots of individual data over time/EYO by treatment arms will be presented as deemed necessary by Washington University team and may be included in CSR as needed.

The same analysis will also be conducted for the six subgroups defined in the first paragraph in Section 16.2.4.1.1.

16.2.4.1.6. Longitudinal Logistic Regression Model

For subjects in the All Gant exposure mITT, at each post-baseline visit including all the OLE visits, the CDR-SB value will be compared to that of the previous visit (rather than compared to highest value of previous visits), if the value of the later visit is larger than the previous one, the disease progression status is defined as 1; otherwise, the disease progression status is defined as 0. The same definition will be applied to all controls. Longitudinal logistic regression model will be applied to compare the odds of disease progression in CDR-SB between the All Gant exposure mITT and all controls. The model will include treatment group, time since baseline (continuous), interaction between the treatment group and time, and baseline EYO as the fixed

effects, and a subject-level random intercept will also be included to account for the within-subjects correlation among the disease progression status.

Baseline CDR status will also be included in the model along with the three-way interaction between time, treatment group, and CDR status to determine if treatment before symptom onset is different from after symptom onset.

16.2.4.2. Supplemental Analysis of the CDR Global

The analysis models described in Section 16.2.3.1 (Cox proportional recurrent event hazard model) and in Section 16.2.4.1.5 (Logistic disease progression model) will also be applied to CDR Global for both asymptomatic and symptomatic subjects together. Models described in Section 16.2.3.1 (Cox proportional recurrent event model) will also be applied separately for baseline asymptomatic and symptomatic subjects in each of the three mITT populations and all controls, with Kaplan-Meier figures presented for asymptomatic subjects.

Each subject in the OLE Gant All Gant Exposure mITT population and all controls will be categorized into 3 groups as defined in the first paragraph in Section 16.2.4.1.1. The model described in Section 16.2.3.1 (Cox proportional recurrent event hazard model) and in Section 16.2.3.2 (Cox proportional hazard model) will be applied to the OLE Gant All Gant Exposure mITT population and all controls to compare the hazard of progression in CDR Global among the 3 subgroups.

Each subject in the All Gant Exposure mITT population and external controls will be categorized as described in the second and third paragraphs in Section 16.2.4.1.1, with the analysis being applied to the primary parameter for CDR Global described in Section 16.2.3.2 (Cox proportional hazards model).

16.2.4.3. Supplemental Analysis of the OLE Cognitive Composite

The supplemental analysis of the OLE Cognitive Composite will follow the logistic disease progression model in Section 16.2.4.1.5 and the exponential disease progression model as described in Section 16.2.4.1.4.

16.2.4.4. Supplemental Analysis of the CSF Amyloid Beta1-42/40

The supplemental analysis of the CSF Amyloid Beta1-42/40 will follow the logistic disease progression model in Section 16.2.4.1.5 for the OLE Gant mITT and All Gant exposure mITT populations.

16.2.5. ANALYSIS OF REMAINING SECONDARY EFFICACY VARIABLES

The analyses for secondary clinical and cognitive tests will follow the LME model for the annual rate of change as described in Section 16.2.3.3, with ISLT and MAC-Q compared to internal controls only. Additionally for ISLT and MAC-Q, the OLE Gant mITT population will be evaluated to compare the annual rate of change among 3 groups: gantenerumab in the double-blind period, solanezumab in the double-blind period, and placebo in the double-blind period with the double-blind baseline as the baseline. The same analysis will be re-run with the double-blind baseline as the baseline and the OLE baseline as the first post-baseline visit, and the time variable will be the time since the double-blind baseline.

The analysis for remaining secondary fluid and imaging biomarkers will follow the analysis of the key biomarkers as described in Section 16.2.3.3 (the LME models). Fluid biomarker will also be assessed using the same MMRM models as described in Section 16.2.3.5.

For all these analyses, figures of model estimated mean over time by treatment arms or spaghetti plots of individual data over time/EYO by treatment arms will be presented as deemed necessary

by Washington University team and may be included in CSR as needed.

[redacted]

- [redacted].
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- [redacted].
- [redacted]
- [redacted]

[redacted]

[redacted]

16.4. EVALUATION OF THE ASSOCIATION BETWEEN AMYLOID REDUCTION AND CLINICAL/COGNITIVE CHANGES

To evaluate if amyloid reduction is associated with clinical/cognitive benefits, the following analysis will be conducted.

1. The correlation between the change in PiB-PET SUVR and the change in clinical/cognitive

endpoints of CDR SB and OLE Cognitive Composite will be evaluated using Spearman correlation. This correlation will be evaluated using the annual rate of change and the change from baseline to the end of OLE, respectively. The correlation will also be estimated for the subjects on double-blind gantenerumab treated group vs combined double-blind placebo and double-blind solanezumab treated group, or for subgroups defined below in item #2 (Amyloid normal group, Amyloid abnormal to normal group, and the rest). This analysis will be applied to the Gant OLE mITT and All Gant exposure mITT, respectively. Additionally, all controls will also be included to evaluate the correlation without any treatment.

2. Each subject will be categorized into 3 groups as defined in the first paragraph in Section 16.2.4.1.1. The LME model will be applied to the All Gant exposure mITT population and all controls to compare the annual rate of change among the 3 subgroups for key secondary efficacy variables.

Baseline PiB PET SUVR and baseline EYO will be included as covariates in these analyses when evaluating the correlation of the annual rate of change.

For all these analyses, figures of model estimated mean over time by treatment arms or spaghetti plots of individual data over time/EYO by treatment arms will be presented as deemed necessary by Washington University team and may be included in CSR as needed.

17. SUBSET OF ANALYSES AT THE INTERIM

The two objectives of the interim analysis are to determine if gantenerumab OLE treatment results in clinical benefit and determine the extent of amyloid removal compared to the double-blind period. The primary analyses for the interim will be the primary analysis of CDR Global

(in Section 16.2.3.2) and CDR-SB (in Section 16.2.3.1) applied to subjects who are asymptomatic at baseline for the All Gant Exposure mITT and main set controls.

The following subset of analyses will be conducted separately for baseline asymptomatic and baseline symptomatic subjects, except where noted for select imaging and fluid biomarker analyses, at the interim analysis and additional exploratory analyses will be conducted as needed, noting that focus will be on Year 2 findings in the absence of Year 3 findings, with any imputation for Year 3 excluded. These analyses will be conducted for the each of the three mITT populations and controls as specified for each model, unless the associated section describes the analysis as being conducted on select mITT populations, noting that when multiple models are described within a section, only the first one will be conducted for the interim unless otherwise specified. By-visit descriptive statistics during OLE will be displayed, overall and by OLE baseline symptomatic status, for each associated parameter, including each component of the OLE cognitive composite.

Table B: Interim Analysis Models

Endpoint	**Analysis Tier and Statistical Method**	**Objective**
CDR Global	Primary: 16.2.3.2: Cox proportional hazards time to first progression	To evaluate whether the treatment delays the disease progression
	Sensitivity: 16.2.4.2 (third paragraph): post-baseline PiB-PET SUVR normal	To evaluate whether normal / abnormal amyloid levels are associated with lower risk of first progression (delay of disease progression) in CDR Global compared to all controls
	Sensitivity: 16.2.4.1.1 (third paragraph): comparison to concurrent and non-concurrent controls	To evaluate whether the treatment delays the disease progression in CDR Global compared to the concurrent and non-concurrent controls
CDR-SB	Primary: 16.2.3.1: Cox recurrent event proportional hazards model	To evaluate whether the treatment is associated with lower risk of recurrent progression (delay of disease progression) in CDR-SB compared to all controls

Endpoint	Analysis Tier and Statistical Method	Objective
	Secondary: 16.2.3.3: LME model	To evaluate whether the treatment will slow down annual rate of change of CDR-SB compared to all controls
	Sensitivity: 16.2.4.1.1 (both analyses in second paragraph): post-baseline PiB-PET SUVR normal	To evaluate whether normal / abnormal amyloid levels are associated with lower risk of recurrent progression (delay of disease progression) in CDR-SB compared to all controls
	Sensitivity: 16.2.4.1.1 (third paragraph): comparison to concurrent and non-concurrent controls	To evaluate whether the treatment is associated with lower risk of recurrent progression (delay of disease progression) in CDR-SB compared to the concurrent and non-concurrent controls
OLE Cognitive Composite	Secondary: 16.2.3.3: LME model	To evaluate whether the treatment will slow down annual rate of change of OLE Cognitive Composite compared to all controls

Endpoint	**Analysis Tier and Statistical Method**	**Objective**
FAS	Secondary: 16.2.3.3: LME model	To evaluate whether the treatment will slow down annual rate of change of FAS compared to all controls
MMSE	Secondary: 16.2.3.3: LME model	To evaluate whether the treatment will slow down annual rate of change of MMSE compared to all controls
Amyloid PET SUVR	Secondary: 16.1.3: MMRM (asymptomatic and symptomatic combined)	To evaluate whether gantenerumab can stop or reverse amyloid plaque growth during the OLE period for all participants
	Secondary: 16.1.4.1: MMRM (asymptomatic and symptomatic combined)	To compare the gantenerumab treatment effect during OLE period by the double-blind treatment (gantenerumab, combination of solanezumab and placebo)
	Secondary: 16.1.4.2: MMRM	To evaluate whether gantenerumab can stop or reverse amyloid plaque growth during the OLE period for asymptomatic and symptomatic separately

Endpoint	Analysis Tier and Statistical Method	Objective
	Secondary: 16.1.4.3: MMRM	To evaluate the treatment effect of gantenerumab in reducing or reversing amyloid plaque growth during the whole study duration for all participants treated with gantenerumab in double-blind, overall and for asymptomatic and symptomatic separately
	Secondary: 16.1.4.4: Fisher's exact test	To evaluate whether treatment with gantenerumab is associated with a shift from baseline abnormal to post-baseline normal
MAC-Q	Secondary: 16.2.3.3: LME model	To evaluate whether the treatment will slow down annual rate of change of MAC-Q compared to internal controls
Tau PET SUVR	Secondary: 16.2.3.3: LME	To evaluate whether gantenerumab can reverse the annual rate of amyloid plaque growth compared to internal controls

Endpoint	**Analysis Tier and Statistical Method**	**Objective**
FDG-PET SUVR	Secondary: 16.2.3.3: LME	To evaluate whether gantenerumab can reverse the annual rate of amyloid plaque growth compared to all controls
CSF Amyloid Beta1-42/40	Secondary: 16.2.3.5: MMRM (asymptomatic and symptomatic combined)	To evaluate whether the treatment will show an increase from baseline in CSF Amyloid Beta 42/40
CSF Total Tau	Secondary: 16.2.3.5: MMRM (asymptomatic and symptomatic combined)	To evaluate whether the treatment will show a decrease from baseline in CSF Total Tau
CSF pTau217	Secondary: 16.2.3.5: MMRM (asymptomatic and symptomatic combined)	To evaluate whether the treatment will show a decrease from baseline in CSF ptau217
CSF MTBR243	Secondary: 16.2.3.3: LME model	To evaluate whether the treatment will slow down annual rate of change of MTBR243 compared to all controls

Kaplan-Meier figures will be created for asymptomatic subjects for each of the three mITT populations and associated controls for both the CDR Global time to first progression and CDR-SB time to recurrent progression. Figures of model estimated mean over time by treatment arms with spaghetti plots of individual data over time of CDR-SB will be provided for asymptomatic subjects for each of the three mITT populations.

The following biomarkers are considered the most relevant to the mechanism of action of gantenerumab: Tau PET SUVR, CSF pTau217 and CSF MTBR243. Analyses using LME and MMRM of additional CSF biomarkers, additional clinical/cognitive parameters, and select plasma biomarkers which are not listed in Table B will be assessed as exploratory analyses by Washington University, with planned analyses to be described in the Addendum of the Statistical Analysis Plan written and signed prior to the availability of data to Washington University, and associated items will not be run by [redacted] for the interim analysis. Analyses of CDR-SB described in Sections 16.2.4.1.4 (exponential disease progression model), 16.2.4.1.5 (logistic disease progression model), and 16.2.4.1.6 (longitudinal logistic regression model) may also be assessed as exploratory analyses by Washington University and will not be run by [redacted] for the interim analysis. Any exploratory analyses, including those planned as noted above, will be included in any reports written to summarize the interim analysis only when considered relevant and will be identified as exploratory analyses.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

18.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA SOC and PT. The version will be established and documented prior to lock of the data and will be identified within footnotes.

An AE is defined as any untoward medical occurrence in a clinical trial subject, regardless of whether it is considered to be drug related. AEs will be recorded and assessed as to whether they are TEAEs. TEAEs are defined as events that first occur or worsen (increase in severity) after the first dose of the OLE study drug. The onset date/time of an AE will be compared to the date/time of first dose of the OLE study drug to determine if the AE is treatment emergent or not. If the AE onset date is missing or partial, the date will be compared as far as possible with the date of first dose of the OLE study drug. AEs will be assumed to be treatment-emergent unless there is clear evidence (through comparison of partial dates and/or collected assessment of whether the AE started prior to the first dose of the study drug) suggesting the AE started prior to the first dose of OLE study medication.

An overall summary of TEAEs will be presented with the number and percentage of subjects having a TEAE, number of TEAEs by severity, number of subjects with a TEAE by highest severity, a TEAE related to study treatment, an injection site reaction TEAE, a serious TEAE, a

TEAE leading to treatment discontinuation, a TEAE leading to study discontinuation, and an AE with an outcome of death. An overall summary of TEAEs will also be presented by dose level.

Subjects experiencing more than one TEAE by SOC and PT will only be counted once at the preferred terminology level in AE frequency tables, but each unique TEAE will be included in the total number of TEAEs (where provided) for each SOC and PT. The overall summary for SOC and PT will be presented overall. A separate table summary will also be reported by dose level.

In summaries presented by SOC and PT, SOC will be sorted by alphabetical order within SOC, then PT.

A listing will include TEAEs and Non-TEAEs. Events ongoing from the double-blind period and events reported in the open label period will be listed separately

18.1.1. ALL TEAEs

18.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of OLE study medication with a missing severity will be classified as severe.

18.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as “Definite”, “Probable/Likely”, “Possible”, “Unlikely”, “Definitely Not” (decreasing severity of relationship). A “related” TEAE is defined as a TEAE with a relationship to study medication as “Definite”, “Probable/Likely” or

"Possible" to study medication. TEAEs with a missing relationship to study medication will be regarded as related to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

18.1.2. TEAEs Leading to Treatment Termination

TEAEs that lead to treatment termination will be presented by a listing. TEAEs leading to treatment termination are those which are recorded as "Drug Withdrawal" for action taken with study treatment on the OLE AE page of the eCRF. The subject's ID number, the TEAE that caused treatment termination, and date of withdrawal will be included in the listing.

18.1.3. TEAEs Leading to Study Discontinuation

TEAEs that lead to study discontinuation will be presented by a listing and are determined using the question "Did the AE cause the subject to discontinue from the study?" on the OLE AE page of the eCRF. The subject's ID number, the TEAE that caused the study discontinuation, and date of discontinuation will be included in the listing.

18.1.4. Serious Adverse Events

An SAE is any AE which meets any of the following criteria:

- Death of subject
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Important medical event requiring medical or surgical intervention to prevent

serious outcome

- Congenital anomaly/birth defect
- Suspected Hy's Law Case
- Other (otherwise medically significant)

The SAE will be presented by a listing. The subject's ID number, SOC, PT and verbatim term and SAE onset/stop date will be included in the listing. Treatment Emergent SAEs will be summarized by SOC and PT.

18.1.5. INJECTION SITE REACTIONS (ISRS)

Injection site reactions related to study treatment will be recorded as injection site reactions on the AE CRF page, with signs and symptoms (e.g., swelling, redness) collected separately. The signs and symptoms associated with ISRs will be coded in the same manner as other AEs and will be summarized separately from other events, with summaries by SOC and PT consistent with the overall summary of AEs.

18.1.6. OTHER CAUSES OF ADVERSE EVENTS

The other causes of AEs include:

- AE involving the injection/infusion site
- AE occurring due to administration of PIB
- AE occurring due to administration of FDG
- AE occurring due to administration of [^{18}F] AV-1451 Tau PET

The relationship of an AE to these causal factors will be presented in the same manner as described for relationship to study drug. The other causes of AEs will be summarized by cause and by relationship.

18.2. DEATHS

A listing of all deaths will be provided.

18.3. SAFETY MRI EVALUATIONS

The number and percentage of subjects with MRI scan (including annual, safety, and dose titration MRIs) conducted will be summarized by visit for each type of MRI finding during the OLE. Summaries will also display the number of subjects with a new finding and those with any post-baseline finding for each type of MRI finding.

ARIA can occur as either cerebral edema (ARIA-E) or as hemorrhages (ARIA-H), typically microhemorrhages, but larger hemorrhages and frank infarction have also been reported. MRI scans will be analyzed for ARIA changes at the Mayo Clinic Aging and Dementia Imaging Laboratory. The number of microhemorrhages (ARIA-H, including both hemorrhages and hemosiderin deposits) and size of areas of edema (ARIA-E) will be monitored at entry and throughout the trial.

Frequencies and percentages of ARIA-E will be summarized by dose (all doses), by visit, and for the highest post-baseline value. Frequency and percentage of ARIA-H will be summarized by dose separately for ARIA-H Microhemorrhages and ARIA-H Superficial Siderosis, with summarizes separated for those associated with ARIA-E and those which are not. The number of ARIA-H and ARIA-E will be categorized (1, 2 to 4, 5+, or no presence). The size of ARIA-E, where present, will be summarized using mean (SD) by visit. A summary of time to ARIA-E resolution will be presented. ARIA-E resolution corresponds to the first MRI following a new post-baseline ARIA-E finding where no definite findings are observed and is calculated as the date of the MRI with no findings – the date of the MRI with AREA-E +1 day. If a subject has

more than one ARIA-E that resolves, the largest duration per subject will be used for the summary of time to ARIA-E resolution. A listing of all ARIA-E findings will be produced for all subjects who have an incidence of ARIA-E at any assessment. The listing will include the number of definite findings for ARIA-E, the size of ARIA-E, the number of days since treatment start, the current active drug dose, and the number of days since start of the current active drug dose. In addition, the frequencies and percentages of the following findings will be summarized in separate tables by visit and for the highest post-baseline value:

- Large cortical infarctions
- Small cortical infarctions
- Subcortical infarctions
- Acute ischemia infarctions
- Other findings (frequencies and percentages only, including for individual sub-categories)

MRI findings will be listed. Details for other findings will be listed separately for all subject with other MRI findings at any assessment. The listing will include number of definite other findings, a description of the other findings, number of days since treatment start, current active dose and the number of days since start of the current active dose.

18.4. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for hematology, chemistry and urinalysis. Presentation of results for drug-specific laboratory parameters including gantenerumab levels and anti-gantenerumab antibodies are described in Section 18.7.2. A list of expected laboratory assessment visits can be found in the protocol Appendix 3, Section 3.2. Table C identifies the laboratory parameters and order of parameters to be included in table summaries.

Table C: Laboratory Parameters

Chemistry	Hematology	Urinalysis
ALT (SGPT)	Basophils	Bilirubin
AST (SGOT)	Basophils %	Blood
Albumin-QT	Eosinophils	Clarity
Alkaline Phosphatase-QT	Eosinophils %	Color
Calcium (EDTA)	Hematocrit	Glucose
Cholesterol (High Performance)	Hemoglobin	Ketones
Creat Cir, Cockroft & Gault	Lymphocytes	Leukocyte Esterase
Creatinine Kinase	Lymphocytes (%)	Nitrate
Creatinine (Rate Blanked)	MCH	Protein
Direct Bilirubin	MCHC	Specific Gravity
GGT	MCV	Urobilinogen
LDH	Monocytes	pH
Magnesium	Monocytes (%)	
Phosphorus	Neutrophils	
Serum Chloride	Neutrophils (%)	

Chemistry	**Hematology**	**Urinalysis**
Serum Glucose	Platelets	
Serum Potassium	RBC	
Serum Sodium	WBC	
Serum Uric Acid		
Total Bilirubin		
Total Protein		
Triglycerides		
Urea Nitrogen		

Presentations will use SI Units. Clinical laboratory parameters will be summarized descriptively at each measurement time. Mean and mean change from baseline values will be presented at each study visit for continuous parameters. Change from baseline will be calculated as post-baseline assessment - baseline assessment. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary. If a laboratory parameter has a value "< x", where x is a numerical number, then the value "x/2" will be assigned to the parameter. If a laboratory parameter has a value "> x", then the value "1.1x". will be assigned to the parameter.

The following summaries will be provided for laboratory data:

- Observed values and change from baseline by visit for Chemistry, Hematology and Urinalysis (quantitative measurements)
- Observed values for categorical Urinalysis measurements
- Shifts from OLE baseline to annual post-baseline visit for Chemistry, Hematology and Urinalysis
- Shifts from OLE baseline to markedly abnormal value for Chemistry and Hematology
- Listing of subjects with markedly abnormal results for Chemistry, Hematology and Urinalysis
- Listing of all observed values for Chemistry, Hematology and Urinalysis

18.4.1. Laboratory Reference Ranges and Markedly Abnormal Criteria

For each visit, laboratory results will be classified as low (L), normal (N), and high (H) according to the laboratory-supplied normal range. The shift from baseline will be presented for each annual post-baseline visit.

A laboratory value is considered Critically High or Critically Low if it exceeds a pre-defined threshold as set by the laboratory vendor. All values for a parameter will be listed for a subject when at least one value for that parameter is identified as Critically High or Critically Low by the laboratory vendor.

18.5. ECG Evaluations

ECG evaluations are not scheduled after the OLE Baseline measurement. Therefore, no table summaries of ECG findings will be produced for the OLE. Any data collected during the OLE

will be included in a listing of ECG findings sorted by subject, visit and parameter. Potential parameters to be included in the listing if collected include:

- PR Interval (msec)
- QRS Interval (msec)
- QTcF Interval (msec) [derived]
- QTcB Interval (msec) [derived]
- HR (bpm)
- Overall assessment of ECG (Investigator's judgment):
  - Normal
  - Abnormal, Not Clinically Significant (ANCS)
  - Abnormal, Clinically Significant (ACS)

18.6. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (ºC)
- Weight (kg)
- Height (cm)

The following summaries will be provided for vital signs data:

- Observed values and change from baseline by visit (blood pressure, heart rate, respiratory rate and temperature)
- Incidence of post-baseline markedly abnormal values (blood pressure, heart rate, respiratory rate and temperature)
- Observed values and change from baseline by visit for Weight
- Observed values for Height
- A listing of all vital sign data will be presented for the OLE.

18.6.1. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria in Table D.

Table D: Post-Baseline Markedly Abnormal Vital Sign Criteria

Variable	Unit	Low	High
Systolic Blood Pressure	mmHg	≤ 90 mmHg AND decrease from baseline ≤ 20 mmHg	≥ 180 mmHg AND increase from baseline ≥ 20 mmHg
Diastolic Blood Pressure	mmHg	≤ 50 mmHg AND decrease from ≤ 15 mmHg	≥ 105 mmHg AND increase from baseline ≥ 15 mmHg

Variable	Unit	Low	High
Heart rate	bpm	≤ 50 bpm AND decrease from baseline ≤ 15 bpm	≥ 120 bpm AND increase from baseline ≥ 15 bpm
Body temperature	˚C	NA	≥ 38.3 ˚C AND increase from baseline ≥ 0.8 ˚C

18.7. OTHER SAFETY ASSESSMENTS

18.7.1. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

C-SSRS score observed at any post-baseline assessment will be summarized using descriptive statistics for categories of Suicidal Ideation, Suicidal Behavior, as well as for the individual questions associated with each category. Treatment-emergence of suicidal ideation and suicidal behavior during OLE will also be summarized. Responses for each of the 12 corresponding questions will also be listed.

18.7.2. ANTI-DRUG ANTIBODIES TO GANTENERUMAB

Frequencies and percent of Anti-Drug Antibodies (ADA) to Gantenerumab will be summarized for evaluable subjects at baseline prior to first gantenerumab exposure (in either double-blind or open-label period) by positive/negative status and post baseline by the following categories:

- Treatment-emergent ADAs
  - Treatment-induced ADAs- defined as a subject with a negative or missing baseline ADA result and at least one positive post-baseline ADA result.

- Treatment-enhanced ADAs- defined as a subject with a positive ADA result at baseline who has one or more post-baseline titer results that are >2.5-fold greater than the baseline titer result.

- No treatment-emergent ADAs
  - Negative ADAs
  - Treatment Unaffected ADAs- defined as a subject with a positive ADA result at baseline and where all post-baseline titer results are less than or equal to the baseline result.

All ADA results will be listed by subject, visit, specimen type and parameter. For subjects with a treatment emergent positive ADA, all adverse events will be listed with along with results from the most recent ADA and the most recent positive ADA.

19. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments
- Physical Examination
- Pregnancy Report
- Volumetric MRI, fluid biomarkers, PET scan data, clinical efficacy parameters, and cognitive efficacy parameters which are not included in Section 16.

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

20. REFERENCES

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Doody, R. (2014). Phase 3 trials of solanezumab for mind-to-moderate Alzheimer's disease. *New England Journal of Medicine, 370*, 311-321.

Prentice RL, W. B. (1981). On the regression analysis of multivariate failure time data. *Biometrika, 68*, 373-379.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

[redacted] OUTPUT CONVENTIONS

1. ABBREVIATIONS

RTF Rich text file format

2. INTRODUCTION

This document applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures. These standards should be used in the absence of customer specific standards.

3. OUTPUT FILE NAMING CONVENTIONS

File names should only consist of uppercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

As far as possible, output files should be in RTF format, although .DOC files are also permitted.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('T' for table, 'L' for listing and 'F' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (e.g., T14_3_01_1.RTF).

4. PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter.

The page orientation will be landscape.

Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.

The number of columns per page (linesize) should be 134 for Letter.

The number of rows per page (pagesize) should be 51 for Letter.

5. FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No **bolding**, underlining, *italics* or subscripting should be permitted. Super-scripts should be avoided. Single spacing should be used for all text.

6. HEADER INFORMATION

Headers should be defined as follows:

- On the left side of the header, the following will represent the top three lines:
  - Washington University
  - Protocol DIAN-TU-001
  - Gantenerumab OLE, [delivery name as either Dry Run or Final]
- On the right side of the header, the following will represent the top two lines, with the third line being blank:
  - Confidential
  - Page X of Y (where Y is the total number of pages for the output)

- The header values as shown above should be placed at the top of the page (same place on each page)
- A blank line should appear between the header and the output title.
- The output identification number and title should appear, centered, in the next set of rows.
- The output population should appear, centered, below title row(s). The population should be spelled out in full.
- The following row should be a continuous row of underscores ('_') (the number of underscores should equal the linesize).
- Mixed case should be used for titles.
- The output titles should be designed so that they are arranged consistently through all outputs. For example, content (e.g., Vital Signs) followed by metric (e.g., Change from Baseline) e.g., Vital Signs – Change from Baseline.
- Titles should not contain quotation marks or footnote references.
- The column headings should be underlined with a row of underscores ('_')
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- Column headings containing numbers should be centered.
- In general, the population count should appear in the column header in the form "(N=XXX)".
- "Statistic" should be the column header over n, Mean, SE, n (%) etc.
- As a rule, all columns should have column headings.

7. TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank.
- The left-hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.
- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- Listings of adverse events, concomitant medications, injection site reactions etc. should be sorted in chronological order, with earliest event or medication coming first.
- The treatment column order should be Placebo, Solanezumab, Gantenerumab, Total, with all columns other than Total having a value of Double-Blind Treatment Arm that is a merged field over the treatment group names.
- If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
- All listing outputs should be sorted (preferably by Subject Number) and will not reference double-blind treatment.
- Do not use superscripts and subscripts.
- Exponentiation will be expressed using a double asterisk, i.e., mm3 will be written as mm**3.

- The width of the entire output should match the linesize.

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum).
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:

Minimum and maximum: N
Mean and median: N + 1
SD or SE: N + 2

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100 as a value and padded with blank space if the percent is less than 100. An example is given below:

  77 (100.0%)
  50 (64.9%)
  0 (0.0%)

- Percentages will be reported to no decimal places, except percents <100% but >99.5% will be presented as '>99%' (e.g., 99.6% is presented as >99%); and percents < 0.5% will be presented as '<1%' (e.g., 0.4% is presented as <1%).

Rounding will be applied after the <1% and >99% rule, noting that due to the small number of subjects this rule is only expected to be applicable for summaries of total number of administered doses by dose level.

e.g., (<1%)
(6.8%)
(>99%)

- Where counts are zero, no percentage will be displayed.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2).

Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values

- A "0" should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in a subject listing.

8. FOOTNOTE INFORMATION

Footers should be defined as follows:

- A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page.
- Table footnotes should be defined using compute statements in the proc report and

should appear directly after the body of the table.

- The program path (starting with sponsor) and name should appear as footnote 1 at the bottom of the page and be left aligned, while the date/time stamp should appear right aligned on the same line.
- Footnotes should be left-aligned.
- Footnotes should be in sentence case.
- Only "typewriter" symbols are permitted – e.g., "*", "$", "#", "@", "&" and "+".
- The choice of footnote symbols should be consistent. E.g., if you have the footnote "# indicates last observation carried forward" for one table, the same symbol and footnote should indicate LOCF for all tables.
- If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.

Ordering of footnotes should be as follows:

1.) Symbols
2.) Abbreviations and definitions
3.) Formulae
4.) Specific notes

- Common notes from table to table should appear in the same order.
- The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

9. PROGRAMMING INSTRUCTION

Programming instructions must appear in blue font at the end of each table or listing shell.

Programming instructions, where necessary, should follow the table or listing shells in blue font, beginning with the words "Programming Note" followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For tables, treatment groups will be represented as follows and in the given order, noting that "Double-Blind Treatment Arm" will be displayed above the individual treatment columns:

- Placebo
- Solanezumab
- Gantenerumab
- Total

PRESENTATION OF VISITS

For outputs, OLE visits will be represented as follows and in that order (Note: refer to protocol for full list of OLE visits), noting that listings will display visits (including unscheduled visit) in date order:

Long Name (default)	**Short Name**
Baseline (OLE Visit 1)	BL (V1)
Week 4 (OLE Visit 2)	W4 (V2)
Week 8 (OLE Visit 3)	W8 (V3)
…	…
Week 48/52 (OLE Visit 14) *Note: due to a protocol amendment, assessments for year 1 occurring at either week 48 or week 52 will be displayed with the format above	W52 (V14)
…	…
Week 156 (Visit 40)	W156 (V40)
Early Termination	ET
Safety MRI 1 (120 mg)	OSM1
…	…
Safety MRI 11 (stable dose 5 MRI)	OSM11

Summaries and/or models including external and/or double-blind data may display timepoints based on the anticipated duration from treatment start or observational period start, such as Month 6 or Year 1, rather than using visit identifiers.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Missing dates will not be imputed. Note that conventions below will not be applied to items which are on CRF pages to capture ongoing events/medications from the double-blind period, as all such records will be considered as starting prior to OLE.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known/Partial / Missing	If start date < OLE study med start date, then not TEAE If start date > study med start date, then TEAE If start date = study med start date with AE start time present and < med start time, then not TEAE If start date = study med start date with AE start time present and >= med start time, then TEAE If start date = study med start date with AE start time missing and AE noted as starting prior to OLE treatment, then not TEAE If start date = study med start date with AE start time missing and AE noted as not starting prior to OLE treatment, then TEAE

START DATE	STOP DATE	ACTION
Partial, but known components show that it cannot be on or after study med start date	Known/Partial / Missing	Not TEAE
Partial, could be on or after study OLE med start date OR Missing	Known	If stop date < OLE study med start date, then not TEAE If stop date >= OLE study med start date, then TEAE
	Partial, could be on or after OLE study med start date OR Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < OLE study med start date, assign as prior If start date >= OLE study med start date, assign as concomitant
Partial, could be on or after OLE study med start date OR Missing	Known	If stop date < OLE study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial, could be on or after OLE study med start date OR Missing	Assign as concomitant

APPENDIX 3. THE MEAN AGE AT ONSET FOR EACH MUTATION

If a subject's mutation type is listed below, the mean mutation AO is used to define the subject EYO. If the mutation type is not listed, the estimated AO is set to the subjects' parental AO. If, in addition, the parental AO is unavailable, the estimated AO is set to the subjects' secondary degree relatives' AO.

Table E: The Mean Mutation Ago at Onset

Gene	Mutation	Mean Mutation AO	Standard Error (SE)	# of Available AO
APP	Ala692Gly	45.8	1.8	5
APP	Asp678Asn	58.8	0.7	3
APP	Asp678His	52.6	1	17
APP	Glu693Gly	57	1	3
APP	Ile716Phe	34.7	1.8	7
APP	Ile716Thr	37	0	2
APP	Ile716Val	56.3	3.2	7
APP	Leu723Arg	46	1.1	4
APP	Leu723Pro	42	2	2
APP	Lys724Asn	53.5	1.5	2
APP	Thr714Ala	53.6	1.4	19
APP	Thr714Ile	36.5	1.5	4
APP	Val715Ala	49.4	1.7	7
APP	Val715Met	47.8	3.7	5
APP	Val717Gly	50	2.7	5
APP	Val717Ile	50.2	0.7	136
APP	Val717Leu	45.8	0.9	41
APP	Val717Phe	43.6	1.2	19
PSEN1	Ala231Val	56	1.8	7
PSEN1	Ala246Glu	50.1	1.2	15
PSEN1	Ala260Gly	53.5	2.2	13
PSEN1	Ala260Val	34	1.2	5

Gene	Mutation	Mean Mutation AO	Standard Error (SE)	# of Available AO
PSEN1	Ala275Val	46.5	1	8
PSEN1	Ala285Val	46.5	0.5	2
PSEN1	Ala396Thr	52.5	8.8	4
PSEN1	Ala426Pro	43.8	1.1	19
PSEN1	Ala431Glu	40.4	0.4	97
PSEN1	Ala431Val	44		1
PSEN1	Ala434Thr	41		1
PSEN1	Ala79Val	60.1	1.3	52
PSEN1	Arg269Gly	48.3	0.7	3
PSEN1	Arg269His	58.3	1.8	18
PSEN1	Arg278Ile	52.6	1.3	7
PSEN1	Arg278Lys	44.7	2	3
PSEN1	Arg278Ser	39		1
PSEN1	Asn135Asp	35.2	0.4	12
PSEN1	Asn135Ser	34.3	0.8	10
PSEN1	Asn135Tyr	36.2	2.8	4
PSEN1	Cys410Tyr	46.9	1.1	18
PSEN1	Cys92Ser	55.5	3	6
PSEN1	Gln222His	39.8	1.7	4
PSEN1	Gln223Arg	34.8	1.5	4
PSEN1	Glu120Asp	45.9	1.4	14
PSEN1	Glu120Asp	45.9	1.4	14
PSEN1	Glu120Asp	45.9	1.4	14
PSEN1	Glu120Gly	37	1.3	5
PSEN1	Glu120Lys	39		3
PSEN1	Glu123Lys	59	3	2
PSEN1	Glu184Asp	42.3	0.9	18
PSEN1	Glu184Gly	49.2	4.2	6
PSEN1	Glu273Lys	47.5	1.5	2
PSEN1	Glu280Ala	38.6	2.4	6
PSEN1	Glu280Gly	44.1	2.2	13
PSEN1	Glu280Lys	56.4	2.4	5

Gene	Mutation	Mean Mutation AO	Standard Error (SE)	# of Available AO
PSEN1	Gly206Ala	54.6	1.1	75
PSEN1	Gly206Asp	37.3	1.3	8
PSEN1	Gly206Ser	37.3	1.5	3
PSEN1	Gly206Val	50.6		5
PSEN1	Gly209Arg	52.1	2	7
PSEN1	Gly209Glu	49.3	1.6	10
PSEN1	Gly209Val	41.2	0.9	21
PSEN1	Gly217Arg	45	0.6	18
PSEN1	Gly266Ser	39.3	1.9	4
PSEN1	Gly378Glu	36.5	1.7	6
PSEN1	Gly378Val	42.4	0.9	5
PSEN1	Gly384Ala	34.8	1.4	5
PSEN1	Gly394Val	43.5	0.6	4
PSEN1	His163Arg	45.7	0.5	63
PSEN1	His163Tyr	54.2	1.7	18
PSEN1	His214Asn	51.5	2.2	4
PSEN1	His214Asp	55		1
PSEN1	His214Tyr	54	4	2
PSEN1	Ile143Met	48.2	2.2	6
PSEN1	Ile143Phe	53.4	1.2	8
PSEN1	Ile143Thr	31.6	1	7
PSEN1	Ile143Val	51	2.1	3
PSEN1	Ile168del	44	1	2
PSEN1	Ile202Phe	52	2	5
PSEN1	Ile213Leu	43.4	3.1	5
PSEN1	Ile213Phe	33		1
PSEN1	Ile213Thr	50	0.6	3
PSEN1	Ile229Phe	39	2.9	3
PSEN1	Ile238Met	57.7	2.4	9
PSEN1	Ile249Leu	55.4	1	7
PSEN1	Ile416Thr	49.7	2.3	12
PSEN1	Ile439Ser	55		1
PSEN1	Leu113Gln	33		1

Gene	Mutation	Mean Mutation AO	Standard Error (SE)	# of Available AO
PSEN1	Leu113Pro	42.2	2.1	5
PSEN1	Leu153Val	35.6	0.5	9
PSEN1	Leu166Arg	38	6	2
PSEN1	Leu171Pro	42.3	0.2	3
PSEN1	Leu173Phe	43.2	2.3	5
PSEN1	Leu174Arg	48.7	1.6	7
PSEN1	Leu174Met	57.6	2	16
PSEN1	Leu219Pro	50	2.1	9
PSEN1	Leu226Arg	48.1	1	7
PSEN1	Leu235Pro	32.3	0.9	6
PSEN1	Leu235Val	47.7	1.2	15
PSEN1	Leu250Ser	51.1	3.5	10
PSEN1	Leu250Val	50.5	0.5	2
PSEN1	Leu262Phe	53.3	4.3	10
PSEN1	Leu271Val	49.8	1.8	11
PSEN1	Leu282Arg	43.8	3.4	4
PSEN1	Leu282Phe	51	2	2
PSEN1	Leu282Val	46.5	2.5	4
PSEN1	Leu286Pro	39.5	0.8	8
PSEN1	Leu286Val	45.7	0.9	34
PSEN1	Leu381Val	43.5	7.4	4
PSEN1	Leu392Pro	36	0	3
PSEN1	Leu392Val	43.2	1	5
PSEN1	Leu424Arg	30.5	0.5	2
PSEN1	Leu424His	39	0	2
PSEN1	Leu85Pro	25.5	2.5	2
PSEN1	Lys239Asn	56.7	3.1	9
PSEN1	Met139Ile	35.8	0.5	12
PSEN1	Met139Thr	49.5		2
PSEN1	Met139Val	39.9	0.8	24
PSEN1	Met146Ile	43.4	1.1	29
PSEN1	Met146Leu	39	0.8	29
PSEN1	Met146Val	40.1	0.7	7

Gene	Mutation	Mean Mutation AO	Standard Error (SE)	# of Available AO
PSEN1	Met233Leu	39.1	1.4	14
PSEN1	Met233Thr	33	1.3	7
PSEN1	Met233Val	26.3	1	7
PSEN1	Met84Val	54.7	1.6	13
PSEN1	Phe105Leu	51.2	4	5
PSEN1	Phe105Ser	50.1	0.6	5
PSEN1	Phe175Leu	54.7	4.2	10
PSEN1	Phe176Val	57	3.5	3
PSEN1	Phe177Ser	30.3	0.3	11
PSEN1	Phe283Leu	45.3	1.5	6
PSEN1	Phe386Ile	49.9	2.2	7
PSEN1	Phe386Leu	45	2.5	8
PSEN1	Phe386Ser	33.7	0.3	3
PSEN1	Pro117Ala	35.8	2.4	10
PSEN1	Pro117Arg	36.3	0.6	6
PSEN1	Pro117Leu	30.6	1.2	9
PSEN1	Pro117Ser	31	1.2	3
PSEN1	Pro264Leu	48.5	0.9	38
PSEN1	Pro267Leu	53.5	1.7	5
PSEN1	Pro284Leu	32		1
PSEN1	Pro436Gln	27.5		2
PSEN1	Pro436Ser	47	3	2
PSEN1	Pro88Leu	44		2
PSEN1	Ser169Leu	31	0.8	10
PSEN1	Ser169Pro	33.3	0.9	4
PSEN1	Ser170Phe	29.5	1.2	13
PSEN1	Ser178Pro	41.2	1.7	5
PSEN1	Ser212Tyr	45.6	2	9
PSEN1	Ser230Asn	57.2	0.7	6
PSEN1	Ser290Cys	40.8	0.7	22
PSEN1	Thr116Asn	37.4	0.7	7
PSEN1	Thr116Ile	41.3	1.8	12
PSEN1	Thr119Ile	59.9	3.3	15

Gene	Mutation	Mean Mutation AO	Standard Error (SE)	# of Available AO
PSEN1	Thr147Ile	25.8	1.3	2
PSEN1	Thr245Pro	42.6	1	5
PSEN1	Thr291Pro	33		1
PSEN1	Trp165Cys	50	2.9	3
PSEN1	Trp165Gly	36	1.2	4
PSEN1	Tyr115Cys	45.1	1.7	17
PSEN1	Tyr115His	36.1	1.8	4
PSEN1	Tyr154Asn	37		1
PSEN1	Tyr256Ser	27.5	2.5	2
PSEN1	Tyr288His	45.7	1.7	4
PSEN1	Val261Ile	41.8	6.2	2
PSEN1	Val261Leu	40.3	0.3	3
PSEN1	Val261Phe	34	1.2	3
PSEN1	Val272Ala	31.6	1.5	9
PSEN1	Val89Leu	44.8	2.5	5
PSEN1	Val96Phe	42.5	1.9	4
PSEN2	Asn141Ile	53.7	0.6	40
PSEN2	Met239Ile	50.2	2.3	12
PSEN2	Met239Val	63.1	6.1	8
PSEN2	Thr122Pro	46.8	0.9	5
APP	Ala713Thr	65.4	2.4	17
PSEN2	Arg71Trp	53		1

* Note: For mutations where the fourth character is a '0', a corresponding mutation value that excludes that '0' will be assigned the same Mean Mutation AO.