16.1.9 Documentation of Statistical Methods

The final approved Statistical Analysis Plan for this study is provided in the following pages.

- Statistical Analysis Plan v1.0, 18 Feb 2020

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2609-G000-202 Amendment 08
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease
Date:	18Feb2020
Version:	Final Version 1.0

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ApoE	Apolipoprotein E
BMI	body mass index
BP	blood pressure
CBB	CogState Brief Battery
C-CASA	Columbia- classification algorithm of suicide assessment
CDR	Clinical Dementia Rating
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	electrocardiogram
ED	early discontinuation
eCRF	electronic case report form
FAQ	functional assessment questionnaire
FAS	full analysis set
INR	international normalized ratio
ISLT	International Shopping List Task
LLT	Lower level term
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	mini-mental state examination
MRI	magnetic resonance imaging
OLE	open-label extension
PD	pharmacodynamic
PT	Preferred term

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SI	Système International
SOC	System organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TLG	tables, listings, and graphs
vMRI	Volumetric magnetic resonance imaging
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results from Open-label Extension (OLE) phase of study E2609-G000-202. This SAP is based on the protocol amendment 08 and "study" indicates OLE phase unless specifically described.

3.1 Study Objectives

3.1.1 Primary Objective(s)

- To assess the long-term safety and tolerability of daily dosing with elenbecestat (E2609) 50 mg in mild cognitive impairment (MCI)/Prodromal subjects and in subjects with mild to moderate dementia due to Alzheimer's disease (AD)

3.1.2 Secondary Objective(s)

- To explore the long-term effects of elenbecestat on clinical status by assessment of:
  a. The Mini-Mental State Examination (MMSE)
  b. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
- To explore the long-term effects of elenbecestat on:
  a. Volumetric magnetic resonance imaging (vMRI) including, but not limited to, total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume at 24 and 48 months of treatment in the Extension Phase.
  b. Plasma amyloid at 12, 24, 36, and 48 months of treatment in the Extension Phase

3.2 Overall Study Design and Plan

The Extension Phase allows eligible subjects to receive elenbecestat 50 mg for up to 48 months (4 years).

Subjects who are enrolled in the Core Study will have the option to participate in the Extension Phase provided that they complete the Core Study (which includes 18 months of double-blind treatment and 12 weeks of Follow-up Period) and satisfy the entry criteria for the Extension Phase. Subjects who discontinue from study drug during the Core Study are not eligible to participate in the Extension Phase.

Eligible subjects who choose to participate in the Extension Phase may enter the Extension Phase immediately following the completion of Visit 20 (ie, Visit 21 procedures may be completed on the same day as Visit 20). Subjects who are eligible to participate in the Extension Phase but

who do not transition to the Extension Phase on the day of Visit 20 may enter the Extension Phase any time within 4 weeks of Visit 20. The Medical Monitor must be contacted if Visit 21 is to occur more than 4 weeks after Visit 20. For all subjects, assessments performed at V20 may serve as baseline values for the Extension Phase (ie, results of assessments conducted at Visit 21) with exceptions of laboratory assessments and vital signs, which must be repeated if Visit 21 occurs more than 10 days from Visit 20.

During the Extension Phase, subjects will receive open-label elenbecestat 50 mg per day for up to 48 months. Subjects with pending International Normalized Ratio (INR) and serum pregnancy test results (females subjects of child bearing potential only) but who are otherwise qualified may begin OLE dosing at Visit 21; however, these subjects must discontinue study drug treatment immediately if either test result meet the exclusion criteria.

Safety assessments will be performed as described in Table 14 of the protocol. Subjects may discontinue from study drug for any reason. Subjects who complete 48 months of the Extension Phase treatment or who discontinue the study drug must comply with the Early Discontinuation Visit (within 7 days after the last dose of study drug) and the Follow-Up Visits (weeks 4 and 12 after the last dose of study drug).

The study will end when the last visit for the last subject has completed the Extension Phase.

4 DETERMINATION OF SAMPLE SIZE

Subjects who complete the Core Study will have the option to participate in the Extension Phase. There is no sample size calculation for the Extension Phase.

5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

5.1 Study Endpoints

5.1.1 Primary Endpoints

- Safety endpoints: adverse event (AE), vital sign, electrocardiogram (ECG), physical examination, clinical laboratory test, any relevant test of cognitive function to evaluate decline, and magnetic resonance imaging (MRI) parameter (microhemorrhage, vasogenic edema, and other clinically significant abnormalities).

5.1.2 Secondary Endpoints

Changes from Core Study and Extension Phase baselines in

- MMSE and FAQ at each visit assessed in the Extension Phase
- Plasma amyloid measurements at 12, 24, 36, and 48 months of Extension Phase treatment
- vMRI parameters including, but not limited to, total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume with up to 24 and 48 months of Extension Phase treatment

Due to the termination of the study, only change from Extension Phase baseline will be summarized and change from Core Study baseline will not be summarized. Percent change from Extension Phase baseline will be summarized if applicable.

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The OLE Safety Analysis Set (OLE-SAS) is the group of subjects who receive at least 1 dose of study drug during the OLE Phase.

The OLE Full Analysis Set (OLE-FAS) is the group of subjects who receive at least 1 dose of study drug during the OLE Phase and have baseline and at least 1 postdose efficacy assessment during the OLE Phase.

The OLE pharmacodynamics (PD) Analysis Set is the group of subjects who have baseline and at least 1 posttreatment PD measurement in the OLE Phase.

5.2.2 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition (OLE phase) electronic case report form (eCRF).

Study Completion: The number (percent) of enrolled and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (OLE phase) eCRF. The number (percent) will be presented for treatment group by core study treatment (placebo and elenbecestat total) and combined total; enrolled, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for

discontinuation, based on data reported on both the Subject Disposition (OLE phase) eCRF and Early Discontinuation (ED) from Study Drug (OLE phase) eCRF. The number (percent) will be presented for treatment group by core study treatment (placebo and elenbecestat total) and combined total; enrolled, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, pregnancy and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

5.2.3 Protocol Deviations

A listing of subjects with protocol deviations will be provided by subject along with the description of the protocol deviation. Protocol deviations will be identified prior to database lock.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the OLE-SAS will be summarized by treatment group by core study treatment (placebo and elenbecestat total) and combined total using descriptive statistics. Continuous demographic and baseline variables include age, weight, body mass index (BMI), Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog14), Clinical Dementia Rating (CDR) Sum of Boxes, MMSE, International Shopping List Task (ISLT) z-score (total recall, delayed recall), CogState Brief Battery (CBB) z-score (accuracy of one-back memory, accuracy of one-card learning, speed of one-back memory, speed of detection, speed of identification), and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, Apolipoprotein E4 *(ApoE4)* status (positive or negative), prior treatment with Acetylcholinesterase inhibitors (AChEIs) or memantine at OLE baseline (no or yes), clinical population (MCI/Prodromal AD, mild to moderate AD) at screening in Core Study, and CDR global score

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the case report form (CRF) will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (May 2014 or higher). All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Percent compliance will be calculated as follows:

Compliance=

$$\frac{\text{Total number of tablets dispensed} - \text{Total number of tablets returned}}{\text{Planned Total number of tablets to be taken}} \times 100\%$$

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

Not applicable.

5.3.3 Multiple Comparisons/Multiplicity

Since the primary objective of this study is about safety and tolerability, no multiplicity adjustment will be applied.

5.3.4 Examination of Subgroups

Not applicable.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

If any item is missing within the MMSE, and FAQ, then their respective total scores will be missing.

For plasma Ab(1-x), values >upper limit of quantification (ULOQ) or < lower limit of quantification (LLOQ) will be imputed using ULOQ or LLOQ respectively.

5.3.6 Other Considerations

Not applicable.

5.4 Safety Analyses

Safety analysis will be performed similarly to the Core Study. All safety analyses will be based on OLE-SAS. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (Columbia Suicide Severity Rating Scale(C-SSRS)), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as MMSE will be summarized by using descriptive statistics. The OLE baseline is used for all safety analyses.

5.4.1 Extent of Exposure

The extent of exposure to study drug will be summarized by categories of cumulative months as well as by categories of duration of exposure in 3-month intervals. The number and percent of

subjects for each exposure category will be presented for treatment group by core study treatment (placebo and elenbecestat total) and combined total. Duration of exposure is the number of months between the date the subject received the first dose of OLE study drug and the date the subject received the last dose of OLE study drug and will be summarized using descriptive statistics as continuous variable for treatment group by core study treatment (placebo and elenbecestat total) and combined total. Overall exposure (number of subject months) is defined as summation over all subjects' exposure durations in the OLE and will be summarized for treatment group by core study treatment (placebo and elenbecestat total) and combined total.

5.4.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 22.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerged during treatment in OLE, having been absent at pretreatment (Baseline) in OLE or

- Reemerged during treatment in OLE, having been present at pretreatment (Baseline) in OLE but stopped before treatment in OLE, or
- Worsened in severity during treatment in OLE relative to the pretreatment state, when the AE was continuous.

Only those AEs that are treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized for treatment group by core study treatment (placebo and elenbecestat total) and combined total. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

A subject data listing of all AEs leading to death will be provided.

The number (percent) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT for treatment group by core study treatment (placebo and elenbecestat total) and combined total. A subject data listing of all SAEs will be provided.

The number (percent) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for treatment group by core study treatment (placebo and

elenbecestat total) and combined total. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

The number (percent) of subjects with TEAEs with specific interest will be summarized by MedDRA SOC and PT for treatment group by core study assignment (placebo and elenbecestat total) and combined total.

The number (percent) of subjects with non-serious TEAEs will be summarized by MedDRA SOC and PT for treatment group by core study assignment (placebo and elenbecestat total) and combined total.

5.4.3 C-SSRS

The C-SSRS responses will be mapped to Columbia- classification algorithm of suicide assessment (C-CASA). The incidence of new or worsening suicidal ideation or suicidal behavior will be summarized for treatment group by core study treatment (placebo and elenbecestat total) and combined total. The clinical assessment of suicidal thinking and behavior will also be summarized for treatment group by core study treatment (placebo and elenbecestat total) and combined total. Categorical variables will be summarized by number (percentage) of subjects.

5.4.4 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters, the actual value and the change from baseline to each post-baseline visit will be summarized by visit for treatment group by core study treatment (placebo and elenbecestat total) and combined total using descriptive statistics. The end of treatment visit and 12 week Follow-up visit are also included, as appropriate. Qualitative parameters will be summarized using frequencies (number and percent of subjects), and changes from baseline to each post-baseline visit will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant post-baseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each post-baseline visit and at the end of treatment visit and 12 week Follow-up visit.

The Sponsor's Grading for Laboratory Values (Appendix 13.1) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a post-baseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV is defined as a post-baseline value with an increase from baseline to a grade of 3 or higher. The incidence of TEMAVs will be summarized for treatment group by core study treatment (placebo and elenbecestat total) and

combined total. When displaying the incidence of TEMAVs, each subject will be counted once in the laboratory parameter high and low categories, as applicable.

Lymphocyte subset parameters (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages], and regulatory T cells) will be summarized in the same manner as other laboratory parameters.

5.4.5 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic blood pressure (BP), pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit for treatment group by core study treatment (placebo and elenbecestat total) and combined total.

In addition, frequency counts of clinically notable vital signs will be summarized for treatment group by core study treatment (placebo and elenbecestat total) and combined total. Table 1 presents the clinical notable ranges.

Table 1: Clinical Notable Ranges for Vital Signs

Vital Sign	**Criterion for Low**	**Criterion for High**
Pulse (bpm)	< 40	> 120
Temperature (°C)	< 36	> 38
Weight (kg)	< 45	> 100
Systolic BP	< 90	> 160
Diastolic BP	< 50	> 100

5.4.6 Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit for treatment group by core study treatment (placebo and elenbecestat total) and combined total. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; abnormal, clinically significant) to each post-baseline visit and to the end of treatment visit and the 12 week Follow-up visit.

In addition, the number (percentage) of subjects with at least 1 post-baseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 msec

- QTcF interval >480 mse
- QTcF interval >500 msec

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 msec
- QTcF interval increases from baseline >60 msec

5.4.7 Safety MRI

Vasogenic Edema and white matter disease will be summarized by visit for treatment group by core study treatment (placebo and elenbecestat total) and combined total. Shift table for the total number of microhemorrages will be presented by visit for treatment group by core study treatment (placebo and elenbecestat total) and combined total. Other abnormalities will be presented in subject data listing.

5.4.8 Other Safety Analyses

Comprehensive neurological examination results will be summarized by visit for treatment group by core study treatment (placebo and elenbecestat total) and combined total.

Dermatology findings will be presented in subject data listing.

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include MMSE.

5.5 Efficacy Analyses

There is no primary efficacy analysis for this study. Secondary analyses will be based on OLE-FAS as specified in Section 5.2.1. The analyses using OLE baseline are summarized by treatment group by core study treatment (placebo, elenbecestat 50 mg R, elenbecestat 50 mg Total) and combined total. Elenbecestat 50 mg R group are the subjects initially randomized to 50 mg group in Core Study. Elenbecestat 50 mg Total group are the subjects ever exposure to 50 mg in Core Study.

5.5.1 Primary Efficacy Analyses

There is no primary efficacy endpoint.

5.5.2 Secondary Efficacy Analyses

The secondary efficacy endpoints in this SAP are:

- Change from OLE baseline in MMSE and FAQ scores

- Change / percent change from OLE baseline in total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume with up to 24 and 48 months as measured by vMRI

The actual value and change (percent change, if applicable) from baseline will be summarized using descriptive statistics for OLE baseline. Due to the termination of the study, the summary statistics will not be presented graphically.

Due to the termination of the study, the relationship between efficacy endpoints and biomarker endpoints will not be explored using correlation analysis.

5.5.3 Other Efficacy Analyses

No other efficacy analyses are planned for this study

5.6 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

The OLE PD Analysis Set will be used for the summaries and analyses of PD biomarkers. The same summary groups as for efficacy are used for PD analyses.

5.6.1 Pharmacokinetic Analyses

Not applicable.

5.6.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

The secondary endpoint from PD marker in this SAP is:

- Percent Change from baseline in plasma amyloid measurements

The actual value and percent change from OLE baseline will be summarized using descriptive statistics for OLE baseline. Due to the termination of the study, the summary statistics will not be presented graphically.

5.7 Other Analyses

No other analyses are planned.

6 INTERIM ANALYSES

No interim analyses in OLE phase.

7 CHANGES IN THE PLANNED ANALYSES

Due to the termination of the study, the following analyses, as described in the protocol, will not be performed.

- Summary statistics of change from Core Study baseline in MMSE, FAQ, vMRI parameters, and PD biomarkers
- Figures of change from baseline in MMSE, FAQ, vMRI parameters, and PD biomarkers
- Correlation analysis for the relationship between efficacy endpoints and biomarker endpoints

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Definition of baseline

The OLE baseline value is defined as the most recent value reported just before first dosing in OLE (for safety, efficacy and PD).

8.2 Algorithms for Efficacy Parameters

This section describes each efficacy parameter, in particular, the algorithms and missing data handling procedure to derive the totals scores if applicable.

FAQ: The Functional Assessment Questionnaire (FAQ) is composed of 10 activities. Each activity is rated as 0 = Normal, 1 = Has difficulty but does by self, 2 = Requires assistance, 3 = Dependent, 8 = Not Applicable. The Total Score is the sum of the 10 activities. If any activity is missing then the Total Score is missing. Activities marked as "Not Applicable", are not use in the computation of the Total Score. However, in order to account for "Not Applicable" activity(s), the Total Score is weighted as follows;

Total Score = Total Score x 30 / (30 minus 3 times the number of activities marked "Not Applicable")

ISLT: The International Shopping List Task (ISLT) is a verbal learning and episodic memory test assessing both immediate and delayed recall. Number of correct responses is used as the score in both tests and transformed to Z-score, respectively.

CBB: The CogState Brief Battery (CBB) is a computer-based battery comprising 4 cognitive tests:

Detection – a simple reaction time test. Speed of response is the measure.
Identification – a simple choice reaction time test. Speed of response is the measure.
One Card Back – a simple working memory test. Accuracy of response is the measure.
One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

CDR: The Clinical Dementia Rating (CDR) scale is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

MMSE: The Mini Mental State Examination (MMSE) is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects. MMSE is composed of 30 questions grouped into domains. For each of the MMSE domains add the correct responses. If a domain has missing data then the domain is missing. From the domains compute the six items as show in Table 3. If any domain is missing then the item is missing. The MMSE Total Score (range 0 to 30) = sum of the six items. If any item score is missing then the Total Score is missing.

Table 3: MMSE Domains and Items

Domain	Score Range	Item	Score Range
1. Orientation to Time	0 to 5	1. Orientation to Time	0 to 5
2. Orientation to Place	0 to 5	2. Orientation to Place	0 to 5
3. Registration	0 to 3	3. Registration	0 to 3
4. Attention and Calculation[a]	0 to 5	4. Attention and Calculation	0 to 5
5. Recall	0 to 3	5. Recall	0 to 3
6. Naming	0 to 2	6. Language (Sum of Naming, Repetition, Comprehension, Reading, Writing, and Drawing)	0 to 9
7. Repetition	0 to 1		
8. Comprehension	0 to 3		
9. Reading	0 to 1		
10. Writing	0 to 1		
11. Drawing	0 to 1		
		Total Score	**0 to 30**

[a] Spell WORLD Forward, then Backward score is only used if Attention and Calculation score is not available

ADAS-cog$_{14}$: The Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items) (ADAS-cog$_{14}$) is composed of 14 items, see Table 4.

Table 4: ADAS-cog$_{14}$ Items and Algorithm for derivation of Item Scores and Total Score

Item	Algorithm	Handling Missing Data	Score Range
1. Word Recall	Total the number of "No" responses for each trial. The subscore is the sum the scores from trials 1, 2, and 3, divide by 3.	If a trial is missing or partially done then trial score is missing. If a trial score is missing then the subscore is missing	0 to 10
2. Commands	Total the number of "No" responses from the 5 tasks	If any task is missing then the subscore is missing	0 to 5
3. Constructional Praxis	Count the number of "No" responses. The subscore is 0 = all 4 drawings correct 1= 1 figure drawn incorrectly 2= 2 figures drawn incorrectly 3= 3 figures drawn incorrectly 4= 4 figures drawn incorrectly 5= no figures drawn, scribbles, parts of forms	If any task is missing then the subscore is missing	0 to 5
4. Delayed Word-Recall	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 10
5. Naming Objects / Fingers	Total the number of "No" responses. The subscore is 0= 0-2 "no" responses 1= 3-5 "no" responses 2= 6-8 "no" responses 3= 9-11 "no" responses 4= 12-14 "no" responses 5= 15-17 "no" responses	If any response is missing then subscore is missing	0 to 5
6. Ideational Praxis	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 5
7. Orientation	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 8
8. Word Recognition	For each trial, total the number of "1" responses. If the total is 12 or less, then the trial score = total. If the total is > 12 then trial score=12. The subscore is the sum the scores from trials 1, 2, and 3, divide by 3.	If a trial is missing or partially done then trial score is missing. If a trial score is missing then the subscore is missing	0 to 12
9. Remembering Test	The subscore is	If the response is	0 to 5

Instructions	0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	missing then subscore is missing	
10. Comprehension	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
11. Word Finding Difficulty	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
12. Spoken Language Ability	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
13. Executive Function (Maze)	The subscore is based on the total number of seconds to complete the task and/or whenever the task was stopped due to 2 errors being made, as follows; 0 = 0-30 seconds 1 = 31-60 seconds 2 = 61 – 90 seconds 3 = 91 – 120 seconds 4 = 121-239 seconds 5 = 240 seconds or at least 2 errors	If the response is missing then the subscore is missing	0 to 5
14. Number Cancellation	Adjusted Score = Total # correct targets crossed off <u>minus</u> Total # incorrect targets crossed off <u>minus</u> Total # times reminded of task. Then use Adjusted Score to determine the subscore as follows; <u>Adjusted Score</u> = <u>Subscore</u> ≥23 = 0 18-22 = 1 13-17 = 2 9-12 = 3 5-8 = 4 ≤4 = 5	If any component of the adjusted score is missing then the subscore is missing	0 to 5
Total Score	Total Score = sum of the subscores above	If any subscore is missing then Total Score is missing	0 to 90

8.3 Definition of visit windows

The protocol specified visits/weeks and corresponding time windows used for visit-wise analyses are presented in terms of days relative to the first dose in the OLE.

Different assessments may have different visit schedules. A general rule for determining a time window for each scheduled visit is to split the two consecutive scheduled visits in the middle point of the two consecutive visits. For example, the time window for visit X is from the middle point between visit (X-1) and X (exclusive) to the middle point between visit X and (X+1) (inclusive). The time window for the first post-baseline visit is from the next day of the first dose. . The details will be specified in the programming specification.

In addition, the following visits will be assigned separately (for MMSE, FAQ, and safety endpoint) if last dose date is not missing.

- Last on treatment: the last post-baseline assessment on or before last dose date.
- End of treatment: the earliest assessment on or after last dose date and before last dose date + 56 days (inclusive)
- 12 week Follow-up: the closest assessment to last dose date + 84 days after last dose date + 57 days (inclusive)

The assessments after last dose date + 8 days (inclusive) will not be included in the visit-wise analyses except end of treatment visit and 12 week Follow-up visit (the analysis flag should not be “Y”). If last dose date is missing, the assessment at early discontinuation from study drug, follow-up visits and unscheduled visits on or after early discontinuation from study drug or follow-up visits will not be included in the visit-wise analyses.

For biomarker endpoints, the following allowance after last dose date will be used. The assessments out of each allowance will not be included in the visit-wise analyses.

- Plasma Ab(1-x): last dose days + 5 days (inclusive)
- vMRI: no limitation (all assessments will be included)

If last dose date is missing, the assessment at early discontinuation from study drug, follow-up visits and unscheduled visits on or after early discontinuation from study drug or follow-up visits will not be included in the visit-wise analyses for Plasma Ab(1-x).

If there are multiple assessments for one analysis visit, the following rules will be applied in order to select one assessment.

1. Pick the closest assessment to the target day
2. Pick the assessment at scheduled visit than unscheduled visit

3. Pick the earliest assessment within the same visit (day)

8.4 Definition of duration of treatment and duration of exposure

The duration of treatment will be calculated using the following equation.

- Duration of treatment = date of last dose of study drug – date of first dose of study drug + 1

The duration of exposure will be calculated using the following equation.

- Duration of exposure = date of last dose of study drug – date of first dose of study drug + 1

If drug interruption occurs, then the drug interruption duration will be subtracted to calculate duration of exposure. For both duration, if the date of last dose of study drug is missing, the date of early discontinuation from study drug will be used instead. If the date of early discontinuation from study drug is also missing, the date of completion or discontinuation will be used instead.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS v 9.3 or later.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study tables, listings, and graphs (TLG) shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

No references.

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 1.

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	< LLN – 10.0 g/dL < LLN – 100 g/L < LLN – 6.2 mmol/L	< 10.0 – 8.0 g/dL < 100 – 80 g/L < 6.2 – 4.9 mmol/L	< 8.0 g/dL < 80 g/L < 4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	< LLN – 3.0 x 10^9/L < LLN – 3000/mm^3	< 3.0 – 2.0 x 10^9/L < 3000 – 2000/mm^3	< 2.0 – 1.0 x 10^9/L < 2000 – 1000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Lymphocytes	< LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	< 800 – 500/mm^3 < 0.8 – 0.5 x 10^9/L	< 500 – 200/mm^3 < 0.5 – 0.2 x 10^9/L	< 200/mm^3 < 0.2 x 10^9/L
Neutrophils	< LLN – 1.5 x 10^9/L < LLN – 1500/mm^3	< 1.5 – 1.0 x 10^9/L < 1500 – 1000/mm^3	< 1.0 – 0.5 x 10^9/L < 1000 – 500/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	< LLN – 75.0 x 10^9/L < LLN – 75,000/mm^3	< 75.0 – 50.0 x 10^9/L < 75,000 – 50,000/mm^3	< 50.0 – 25.0 x 10^9/L < 50,000 – 25,000/mm^3	< 25.0 x 10^9/L < 25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	< LLN – 3 g/dL < LLN – 30 g/L	< 3 – 2 g/dL < 30 – 20 g/L	< 2 g/dL < 20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
AST	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN – 16 mmol/L	< 16 – 11 mmol/L	<11 – 8 mmol/L	< 8 mmol/L
Bilirubin (hyperbilirubinemia)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN
Calcium, serum-low (hypocalcemia)	< LLN – 8.0 mg/dL < LLN – 2.0 mmol/L	< 8.0 – 7.0 mg/dL < 2.0 – 1.75 mmol/L	< 7.0 – 6.0 mg/dL < 1.75 – 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Calcium, serum-high (hypercalcemia)	> ULN – 11.5 mg/dL > ULN – 2.9 mmol/L	> 11.5 – 12.5 mg/dL > 2.9 – 3.1 mmol/L	> 12.5 – 13.5 mg/dL > 3.1 – 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	> ULN – 300 mg/dL > ULN – 7.75 mmol/L	> 300 – 400 mg/dL > 7.75 – 10.34 mmol/L	> 400 – 500 mg/dL > 10.34 – 12.92 mmol/L	> 500 mg/dL > 12.92 mmol/L
Creatinine	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN
GGT (γ-Glutamyl transpeptidase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: > ULN – 160 mg/dL > ULN – 8.9 mmol/L	Fasting glucose value: > 160 – 250 mg/dL > 8.9 – 13.9 mmol/L	> 250 – 500 mg/dL; > 13.9 – 27.8 mmol/L; hospitalization indicated	> 500 mg/dL; > 27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	< LLN – 55 mg/dL < LLN – 3.0 mmol/L	< 55 – 40 mg/dL < 3.0 – 2.2 mmol/L	< 40 – 30 mg/dL < 2.2 – 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	< LLN – 2.5 mg/dL < LLN – 0.8 mmol/L	< 2.5 – 2.0 mg/dL < 0.8 – 0.6 mmol/L	< 2.0 – 1.0 mg/dL < 0.6 – 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L hospitalization indicated	> 7.0 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Potassium, serum-low (hypokalemia)	< LLN – 3.0 mmol/L	< LLN – 3.0 mmol/L; symptomatic; intervention indicated	< 3.0 – 2.5 mmol/L hospitalization indicated	< 2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L hospitalization indicated	> 160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	< LLN – 130 mmol/L	N/A	< 130 – 120 mmol/L	< 120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	> 300 – 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 – 1000 mg/dL >5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	> ULN – 10 mg/dL ≤ 0.59 mmol/L without physiologic consequences	N/A	> ULN – 10 mg/dL ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dL > 0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

SIGNATURE PAGE

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