Statistical Analysis Plan H8A-MC-LZBE

A 24-Month, Phase 3, Multicenter, Placebo-Controlled Study of Efficacy and Safety of Solanezumab versus Placebo in Prodromal Alzheimer's Disease

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1. Statistical Analysis Plan: H8A-MC-LZBE: A 24-Month, Phase 3, Multicenter, Placebo-Controlled Study of Efficacy and Safety of Solanezumab versus Placebo in Prodromal Alzheimer's Disease

Solanezumab (LY2062430) Alzheimer's Disease

Study H8A-MC-LZBE is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study comparing solanezumab with placebo for 24 months in approximately 2450 subjects with prodromal Alzheimer's disease.

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Protocol H8A-MC-LZBE
Phase 3

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

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3. Revision History

SAP Version 1 will be approved prior to the first production data transfer.

4. Study Objectives

Table LZBE.4.1 shows the objectives and endpoints of the study.

Table LZBE.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess the hypothesis that solanezumab 400 mg Q4W will slow the clinical progression of prodromal AD over 24 months compared to placebo	ADAS-Cog_{14}: change from baseline over 24 months
Secondary To assess the effect of solanezumab vs placebo on the clinical progression of prodromal AD over 24 months	Changes from baseline to 24 months on ADCS-MCI-ADL, MMSE, MoCA, FAQ, NPI, CDR-SB, RBANS, and FCSRT
To assess the effect of solanezumab vs placebo on quality of life and health outcomes in prodromal AD over 24 months	Changes from baseline to 24 months on RUD-Lite, EQ-5D, QoL-AD
To assess the effect of solanezumab vs placebo on biomarkers in prodromal AD over 24 months	Changes from baseline to 24 months in florbetapir PET or CSF Aβ/tau, vMRI, plasma Aβ, plasma solanezumab, sample storage for biomarkers (where permitted); includes CSF collected via optional addendum
To assess the hypothesis that solanezumab will slow the accumulation of tau pathology over 12 and 24 months compared to placebo	Changes from baseline in neocortical tau deposits (collected in a subset of subjects using ^{18}F-AV-1451 PET as part of an addendum) over 12 and 24 months
To assess the hypothesis that change from baseline in accumulation of tau pathology over 12 and 24 months is associated with changes from baseline in cognition	Changes from baseline in neocortical tau deposits (collected in a subset of subjects using ^{18}F-AV-1451 PET as part of an addendum) and ADAS-Cog_{14}, over 12 and 24 months
To assess the hypothesis that change from baseline in accumulation of tau pathology over 24 months is associated with changes from baseline in function	Changes from baseline in neocortical tau deposits (collected in a subset of subjects using ^{18}F-AV-1451 PET as part of an addendum) and ADCS-MCI-ADL over 24 months
To assess the effect of pharmacogenomic factors on clinical and functional progression with solanezumab vs placebo in prodromal AD over 24 months	Changes from baseline in pharmacogenomics markers (where permitted) and clinical and functional scales

Objectives and Endpoints

Objectives	Endpoints
Exploratory	
To generate additional data for validation of the PACC score, a composite endpoint being used in another Lilly study	Changes from baseline in components of the MMSE, RBANS, and FCSRT over 24 months
To compare MMSE and MoCA scales	Changes from baseline in MMSE and MoCA over 24 months
To assess time to significant progression	Time to progression to CDR-SB score of 1.0, and significant change on other cognitive and functional measures

Abbreviations: Aβ = amyloid-β peptide; AD = Alzheimer's disease; ADAS-COG_{14} = 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment-Activities of Daily Living Inventory; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CSF = cerebrospinal fluid; EQ-5D = EuroQol 5-Dimensional Health-Related Quality of Life Scale; FAQ = Functional Activities Questionnaire; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; PACC = Preclinical Alzheimer's Cognitive Composite; PET = positron emission tomography; Q4W = every 4 weeks; QoL-AD = Quality of Life in Alzheimer's Disease (scale); RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RUD-Lite = Resource Utilization in Dementia-Lite; vMRI = volumetric magnetic resonance imaging.

5. Study Design

5.1. Summary of Study Design

Study H8A-MC-LZBE (LZBE) is a multicenter, randomized, double-blind, parallel, placebo-controlled Phase 3 trial comparing solanezumab with placebo for 24 months in approximately 2450 subjects with prodromal Alzheimer's disease (AD). Subjects who meet entry criteria will be randomized in a 1:1 ratio to receive an infusion of solanezumab 400 mg or placebo once every 4 weeks. Subjects will be randomized by site and by use of florbetapir positron emission tomography (PET) scanning or cerebrospinal fluid (CSF) for study eligibility. The primary hypothesis being tested in Study LZBE is that solanezumab will slow the clinical progression of AD as compared with placebo in subjects with prodromal AD.

In addition, participants in the ^{18}F-AV-1451 tau imaging addendum will be included in an interim analysis designed to assess the relationship between ^{18}F-AV-1451 tau PET and solanezumab treatment.

Three months after the end of the double-blind treatment period (or 4 months after the last dose in case of early discontinuation), subjects will come to a follow-up visit for biomarker and safety assessments.

5.2. Determination of Sample Size

Power and sample size calculations have been based on the analysis of the primary objective using an effect size calculation of treatment difference at the end of the study.

To calculate power, an expected decline in 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog$_{14}$) at 2 years of 4.41 points for placebo-treated subjects and 3.21 points for solanezumab-treated subjects was used, with a common standard deviation of 8 (Doraiswamy et al. 2014). This is equivalent to a difference of 1.2 points over 2 years, with an effect size = 0.15. Based on these assumptions and a 25% discontinuation rate, 1225 randomized subjects per arm (919 completers per arm) or 2450 total randomized subjects will have approximately 89% power to detect a significant treatment difference at 2 years using a 2-sided significance level of 0.05.

Subjects who are randomized but not administered treatment may be replaced to ensure that enough subjects complete the study.

5.3. Method of Assignment to Treatment

Subjects who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign a vial containing double-blind investigational product to each subject. Site personnel will confirm the correct vial has been located by entering a confirmation number found on the vial into the IWRS.

To achieve between-group comparability, the randomization will be stratified by site and by use of florbetapir PET scanning or CSF for study eligibility.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter Lilly).

On 10 January 2017, approximately 6 months after the first subject entered the LZBE study, the study was discontinued due to sponsor decision. After careful review of additional data analyses from the solanezumab Phase 3 EXPEDITION3 (H8A-MC-LZAX) study in subjects with mild dementia due to AD, Lilly did not find sufficient scientific evidence that solanezumab would likely demonstrate a meaningful benefit to subjects with prodromal AD as defined by the LZBE study protocol. The study was not stopped for safety reasons. Based on EXPEDITION3 results, there were no new safety signals identified.

The 26 randomized subjects in the study are to be discontinued from the double-blind treatment period at the early discontinuation visit and are requested to return to the follow-up visit (Visit 301) 4 months after the last dose according to the protocol. The study DBL will happen at the end of the trial after the last subject has completed the follow-up visit. A synopsis report with attachments will summarize the study results for the early discontinued study and this statistical analysis plan will pre-specify analyses for the study synopsis.

In general, no analyses will be conducted to address any primary, secondary, or exploratory efficacy objectives because sufficient data will not be available for reliable efficacy evaluation in this early discontinued study. Safety data will be listed or summarized. No statistical comparison of treatment effect will be conducted.

All analyses will follow the intent-to-treat (ITT) principle unless otherwise specified. An ITT analysis is an analysis of data by the groups to which subjects are assigned by random allocation, even if the subjectdoes not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. When change from baseline is assessed, subjects will be included in the analysis only if both a baseline and a postbaseline measure are available. Unless otherwise defined, a baseline measure is the last non-missing observation collected prior to the first infusion of study medication. Endpoint is the last non-missing postbaseline measurement.

6.2. Handling of Dropouts or Missing Data

6.2.1. Handling of Missing Items for Scales

If any of the individual items for the ADAS-Cog or Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment-Activities of Daily Living Inventory (ADCS-MCI-ADL) are missing or unknown, every effort will be made to obtain the score for the missing item or items.

For ADAS-Cog_{14}, if <30% (4 or fewer of a total of 14) of the items are missing, the total score (maximum = 90) will be imputed as follows: The total from remaining items will be multiplied by a factor that includes the maximum score for the missing items. For example, if the first item, "Word-Recall Task," which ranges from a score of 0 through 10 (maximum = 10), is missing,

and the second item "Commands," which ranges from a score of 0 to 5 (maximum = 5), is missing, then the multiplication factor = 90/(90 - [10 + 5]) = 90/75 = 1.2. Thus, the total score for this example will be the sum of the remaining 12 items multiplied by 1.2. The imputed number will be rounded up to the nearest integer. If more than 4 items are missing, the total score for ADAS-Cog_{14} at that visit will be considered missing.

For the ADCS-MCI-ADL, if <30% of the items are missing, the total score will be imputed. The sum of the nonmissing items will be prorated to the sum of total items. The imputed number will be rounded up to the nearest integer. If the nearest integer is greater than the maximum possible score, the imputed score will be equal to the maximum score. If >30% of the items are missing, the total score for ADCS-MCI-ADL at that visit will be considered missing.

The same imputation technique will be applied to the Clinical Dementia Rating-Sum of Boxes (CDR-SB). If only 1 box (of 6) of the CDR is missing, the sum of the boxes will be imputed by prorating the sum from the other 5 boxes. If the score from more than 1 box is not available, the CDR-SB at that visit will be considered missing.

For all other scales, if any item is missing, any total or sum involving that item will be considered missing.

6.3. Analysis Populations

Table LZBE.6.1 below defines each of the analysis populations used in this study. Table LZBE.6.2 lists the study measures that will be summarized and/or analyzed in each population.

Table LZBE.6.1. Analysis Populations for Study H8A-MC-LZBE

Population Name	Description of Population
All Subjects Entered	All subjects who signed informed consent.
ITT Population	All randomized subjects.
Safety Population	All randomized subjects with at least 1 complete or partial infusion of study medication.

Abbreviation: ITT = intent-to treat.

Table LZBE.6.2. Study Measures Summarized for Each Analysis Population

Population Name	Variables Assessed
ITT Population	Tables and Listings of the following: subject disposition, subject characteristics, and concomitant medications
Safety Population	Tables and Listings of the following: adverse events, laboratory results, vital signs, MRI safety data, and suicidal ideation or behavior

Abbreviations: ITT = intent-to treat; MRI = magnetic resonance imaging.

6.4. Subject Disposition

The reason for discontinuation will be collected at the early discontinuation visit and at the follow-up visit that should occur 4 months after last dose. A listing of subject disposition will be generated for all randomized subjects.

6.5. Subject Characteristics

Baseline characteristics will be summarized for the ITT population by treatment group and overall. Summaries will include descriptive statistics for continuous and categorical measures. Subject characteristics to be presented include the following:

- age (calculated as [date of informed consent – (year of birth, July 1)]/365.25)
- gender
- race
- ethnicity
- country
- height
- body weight
- body mass index (weight [kg] / [height (m)]^2)
- tobacco use
- alcohol use
- caffeine use
- years of education
- work status
- time since onset of first prodromal AD symptoms
- time since diagnosis
- Montreal Cognitive Assessment, Functional Activities Questionnaire, and Free and Cued Selective Reminding Test at screening (Visit 1)
- Baseline severity of impairment as measured by ADAS-Cog$_{14}$, ADCS-MCI-ADL, Mini-Mental State Examination, CDR-SB, CDR global score, Neuropsychiatric Inventory, Resource Utilization in Dementia, EuroQol 5-Dimensional Health-Related Quality of Life Scale Proxy, Quality of Life in Alzheimer's Disease (scale) patient and proxy, and Repeatable Battery for the Assessment of Neuropsychological Status at Visit 2
- Apolipoprotein E (ApoE) genotype (ε2/ε4, ε3/ε4, ε4/ε4, no ε4)
- ApoE4 carrier status (carrier [ε2/ε4, ε3/ε4, ε4/ε4], noncarrier [ε3/ε3, ε2/ε2, ε3/ε2])
- having 1 or more first degree relatives with AD
- acetylcholinesterase inhibitors and/or memantine use at baseline

6.6. Concomitant Therapy

Concomitant medications are defined as those being taken on or after first infusion. A summary of concomitant medications will be presented as frequencies and percentages for each treatment group.

If the start or stop dates of therapies are missing or partial to the degree that determination cannot be made of whether the therapy is prior or concomitant, the therapy will be deemed concomitant.

Medications will be coded using the World Health Organization drug dictionary.

6.7. Safety Analyses

6.7.1. Extent of Exposure

The exposure to study drug will be summarized for each treatment group. Overall duration of exposure will be calculated as date of last study visit during the treatment period – date of first infusion + 1 day. Exposure will be provided in a listing.

6.7.2. Adverse Events

Adverse events will be coded according to established Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events (TEAEs) will be defined as events that first occurred or worsened on or after first infusion date until the follow-up visit (Visit 301). Should there be insufficient data for adverse event start date, stop date, and time to make this comparison, the adverse event will be considered treatment emergent. Treatment-emergent adverse events will be determined based on MedDRA lowest level term.

An overview of adverse events, including the number and percentage of subjects who died, experienced serious adverse events, discontinued due to adverse events, and who experienced TEAEs, will be provided. In addition, a listing of the adverse events will be provided.

6.7.3. Clinical Laboratory Evaluation

Laboratory measurements for clinical chemistry and hematology panels will be summarized using continuous data (change from baseline) and categorical or ordinal data (proportion of treatment-emergent abnormalities).

Summaries and analyses of continuous lab data (change from baseline) will be performed using International System of Units (SI units). If there are multiple records of laboratory measurements at baseline or postbaseline visit, the last record for each time period will be used.

The proportion of subjects with treatment-emergent high or treatment-emergent low, or treatment-emergent abnormal laboratory values at any postbaseline visit will be summarized by treatment and overall. Treatment-emergent high or low laboratory abnormality will be based on SI unit. Planned and unplanned measurements will be included. A treatment-emergent high value is defined as a change from a low value or normal value at all baseline visits to a value greater than the high limit at any time after baseline. A treatment-emergent low value is defined as a change from a high value or normal value at all baseline visits to a value less than the low limit at any time after baseline. A treatment-emergent abnormal value (only applies to categorical results) is defined as a change from normal at all baseline visits to abnormal at any time after baseline.

For each laboratory analyte, only subjects who were low or normal at baseline and have at least one postbaseline will be included in the denominator when computing the proportion of subjects with treatment-emergent high values. Similarly, only subjects who were high or normal at baseline and have at least one postbaseline will be included in the denominator when computing the proportion of subjects with treatment-emergent low values.

6.7.4. Vital Signs and Other Physical Findings

Summary statistics will be presented for observed values at baseline and for change from baseline results at each scheduled postbaseline visit. Systolic and diastolic blood pressure and pulse (collected in sitting position), temperature, and weight by treatment group for all subjects in the safety population will be summarized.

6.7.5. Magnetic Resonance Imaging Data

Magnetic resonance imaging (MRI) is scheduled to be obtained at screening (Visit 1), 52 weeks (Visit 15), 104 weeks (Visit 28), and early discontinuation visit (ED). Due to early discontinuation of the study, MRI data will only be available at screening and ED. Frequencies and percentages of the following parameters of amyloid-related imaging abnormality (ARIA) edema (ARIA-E, also known as vasogenic edema) and hemorrhage (ARIA-H, also known as microhemorrhage), will be summarized.

- ARIA-H
    - Number of ARIA-H (1, 2 to 4, 5 to 10, >10, no presence, or nonevaluable) at screening and ED
    - Shift from screening to early discontinuation
- ARIA-E
    - Severity (mild, moderate, severe, questionable, nonevaluable, or no presence) at screening and ED.
    - Change (unchanged in size, increased in size, decreased in size or complete resolution) from screening to ED.

6.7.6. Suicidal Ideation or Behavior

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent, based on the Columbia-Suicide Severity Rating Scale (C-SSRS), will be collected. A listing by subject and visit will be provided and only includes subjects who show suicidal ideation/behavior or self-injurious behavior without suicidal intent (ie, if a subjectanswers all “no” for the C-SSRS, then that subject will not be displayed). However, if a subject reported any suicidal ideation/behavior or self-injurious behavior without suicidal intent at any time point, then all ideation and behavior will be displayed, even if not positive.

6.8. Interim Analyses and Data Monitoring

Due to early discontinuation of the study, there will be no planned data monitoring committee meeting or interim analysis.

7. References

Doraiswamy PM, Sperling RA, Johnson K, Reiman EM, Wong TZ, Sabbagh MN, Sadowsky CH, Fleisher AS, Carpenter A, Joshi AD, Lu M, Grundman M, Mintun MA, Skovronsky DM, Pontecorvo MJ; AV45-A11 Study Group. Florbetapir F 18 amyloid PET and 36-month cognitive decline: a prospective multicenter study. *Mol Psychiatry*. 2014;19:1044-1051.

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