

Protocol 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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of Efficacy and Safety of Solanezumab versus Placebo in
Prodromal Alzheimer's Disease**

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Solanezumab (LY2062430)

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 patients with prodromal Alzheimer's disease (AD).

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Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 28-Mar-2016 GMT

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1. Protocol Synopsis

Title of Study:

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

Rationale:

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive decline in cognitive function and the ability to perform activities of daily living, ultimately resulting in dementia, typically with fatal complications. The amyloid hypothesis of AD postulates that the accumulation of amyloid- β peptide ($A\beta$) is an early and necessary event in the pathogenesis of AD. This hypothesis suggests that treatments that slow the accumulation of $A\beta$ in the brain or increase clearance of $A\beta$ may be able to slow the progression of the AD clinical syndrome. The other hallmark neuropathological lesion of AD, intraneuronal neurofibrillary tangles consisting of tau proteins, is thought to be a marker for disease progression. The relationship between these 2 pathologies is still unclear, although the presence of both is necessary for the diagnosis of definite AD.

Like many disorders, AD occurs on a continuum from asymptomatic to prodromal AD (or mild cognitive impairment), then to dementia in mild, moderate, and severe stages. Recent clinical trial results in mild-to-moderate AD dementia, as well as evidence from transgenic animal experiments, suggest that treating AD during the earlier stages would have the greatest potential benefit on the disease and its progression, particularly when considering therapies targeted at $A\beta$ reduction.

Study H8A-MC-LZBE (LZBE) is a Phase 3, placebo-controlled study in patients with prodromal AD. Study LZBE is designed to collect data on the safety and efficacy of solanezumab, including assessment of changes in amyloid and tau pathology, cognitive outcomes, functional outcomes, quality of life, and resource utilization.

Objective(s)/Endpoints:

| Objectives | Endpoints |
|--|--|
| <p>Primary To assess the hypothesis that solanezumab 400 mg Q4W will slow the clinical progression of prodromal AD over 24 months compared to placebo</p> | Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog ₁₄): change from baseline over 24 months |
| <p>Secondary To assess the effect of solanezumab vs. placebo on the clinical progression of prodromal AD over 24 months</p> | Change from baseline to 24 months on Alzheimer's Disease Cooperative Study-Activities of Daily Living scale for Mild Cognitive Impairment (ADCS-MCI-ADL), Mini Mental Status Examination (MMSE), Montreal Cognitive Assessment (MoCA), Functional Activities Questionnaire (FAQ), Neuropsychiatric Inventory (NPI), Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Free and Cued Selective Reminding Test (FCSRT) |
| <p>To assess the effect of solanezumab vs. placebo on quality of life and health outcomes in prodromal AD over 24 months</p> | Change from baseline to 24 months on Resource Utilization in Dementia–Lite (RUD-Lite), EuroQol 5-Dimensional Health-Related Quality of Life Scale (EQ-5D), Quality of Life in Alzheimer's Disease (scale) (QoL-AD) |

| Objectives | Endpoints |
|---|---|
| To assess the effect of solanezumab vs. placebo on biomarkers in prodromal AD over 24 months | Florbetapir PET or CSF A β / tau, vMRI, plasma A β , 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 | Change from baseline in neocortical tau deposits (collected in a subset of patients 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 patients 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 patients 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 |

Abbreviations: A β = amyloid- β peptide; AD = Alzheimer's disease; ADAS-Cog₁₄ = Alzheimer's Disease Assessment Scale–Cognitive subscale; ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living scale for Mild Cognitive Impairment; CDR-SB = Clinical Dementia Rating Scale–Sum of Boxes; CSF = cerebrospinal fluid; EQ-5D = EuroQol 5-Dimensional Health-Related Quality of Life Scale (EQ-5D); FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini Mental Status Examination; MoCA = Montreal Cognitive Assessment; 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; vMRI = volumetric magnetic resonance imaging.

Summary of Study Design:

Study LZBE is a multicenter, randomized, double-blind, parallel, placebo-controlled Phase 3 trial comparing solanezumab with placebo for 24 months in approximately 2450 patients with prodromal AD. Patients who meet entry criteria will be randomized in a 1:1 ratio to solanezumab 400 mg once every 4 weeks or placebo. The primary hypothesis being tested in Study LZBE is that solanezumab will slow the clinical progression of AD as compared with placebo, in patients with prodromal AD.

In addition, participants in the ¹⁸F-AV-1451 tau imaging addendum will be included in an interim analysis designed to assess the relationship between ¹⁸F-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), patients will come to a follow-up visit for biomarker and safety assessments.

Treatment Arms and Duration:

Solanezumab 400 mg once every 4 weeks by intravenous infusion or placebo once every 4 weeks by intravenous infusion up to 2 years in duration

Number of [Patients/Subjects]:

Randomized: approximately 2450

Completed: approximately 1838

Statistical Analysis:

General Considerations. All analyses will follow the intent-to-treat principle unless otherwise specified. When change from baseline is assessed, patients will be included in the analysis only if both a baseline and a postbaseline measure are available. For analyses using last observation carried forward, the last nonmissing postbaseline observation (scheduled or unscheduled) will be used to calculate change from baseline. Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05; 2-sided confidence intervals will be displayed with a 95% confidence level. All tests of interactions between treatment and other factors will be conducted at an alpha level of 0.05.

Primary Analysis. The primary objective of this study is to test the hypothesis that intravenous infusion of solanezumab will slow cognitive decline as compared with placebo in patients with prodromal AD. This will be assessed using an mixed-effect model repeated measure (MMRM) analysis of the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog₁₄) in patients with prodromal AD at baseline (Visit 1 Montreal Cognitive Assessment [MoCA] score of 17 to 28), in which the specific hypothesis is that the cognitive decline from baseline at the end of the treatment period (104 weeks) for solanezumab will be significantly less than that for placebo. The change from baseline score on the ADAS-Cog₁₄ each scheduled postbaseline visit (according to the Study Schedule) during the treatment period will be the dependent variable. The model for the fixed effects will include terms for 7 effects: baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, concomitant acetylcholinesterase inhibitor (AChEI) and/or memantine use at baseline (yes/no), and age at baseline. Visit will be considered a categorical variable with values equal to the visit numbers at which the scales were assessed. The null hypothesis is that the contrast between the solanezumab-treated patients versus placebo-treated patients at the last visit equals zero.

Interim Analysis. A single efficacy interim analysis will be assessed by the data monitoring committee after 550 randomized ¹⁸F-AV-1451 tau addendum participants have completed a baseline and 1-year ¹⁸F-AV-1451 positron emissions tomography (PET) scan, unless this interim is determined to be unnecessary by results of studies that are ongoing at the time of initial protocol development. The purpose of this interim analysis is to demonstrate that solanezumab-treated patients have less tau accumulation relative to placebo-treated patients at 12 months. In addition to comparison of tau changes across treatments, the interim analysis would also examine the relationship between changes in ¹⁸F-AV-1451 PET and changes in cognition based on the ADAS-Cog₁₄. It is anticipated that a positive correlation between these 2 measures exists – that is, patients that show increases in tau accumulation will show corresponding increases (more cognitive decline) in the ADAS-Cog₁₄. The results of the ¹⁸F-AV-1451 tau PET interim analysis will not affect the conduct of the overall study. As there is no possibility of terminating the study early for either efficacy or futility based on this analysis, no alpha-spending adjustment will be used for the final analysis and all results from the tau addendum patients will be included in the final efficacy analysis.

Analysis of Biomarkers: Biomarker change from baseline to double-blind period endpoint will be analyzed to provide biomarker-based evidence that solanezumab affects the underlying disease pathology.

Secondary Endpoints: Change from baseline will be assessed using MMRM or analysis of covariance analyses for Alzheimer's Disease Cooperative Study-Activities of Daily Living scale for Mild Cognitive Impairment (ADCS-MCI-ADL), Mini Mental Status Examination (MMSE), MoCA, Functional Activities Questionnaire (FAQ), Neuropsychiatric Inventory (NPI), Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Free and Cued Selective Reminding Test (FCSRT),

Resource Utilization in Dementia–Lite (RUD-Lite), EuroQol 5-Dimensional Health-Related Quality of Life Scale (EQ-5D), and Quality of Life in Alzheimer’s Disease (scale) (QoL-AD). A sequential gatekeeping strategy will be used for hypothesis testing involving a subset of efficacy endpoints to maintain the nominal type I error rate.

Additional subgroup analyses will be performed.

Analysis of Safety Data: Safety will be assessed by summarizing adverse events, laboratory analytes, vital signs, weight, electrocardiograms, magnetic resonance imaging, and Columbia Suicide Severity Rating Scale (C-SSRS) results. Comparisons will be made between the treatment groups.

2. Schedule of Activities

| Study Period | I | II | | | | | | | |
|--|-----------|-----------------|----|----|----|----|----|----|----|
| | Screening | Double Blind | | | | | | | |
| Suggested Interval | 6 weeks | 4 weeks | | | | | | | |
| Interval Allowed (days) | -0 to -56 | 21 – 35 | | | | | | | |
| Visit | V1 | V2 ^a | V3 | V4 | V5 | V6 | V7 | V8 | V9 |
| End of Week Relative to Study Medication Start ^b | -4 | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 |
| Entry/Administrative Procedures | | | | | | | | | |
| Informed consent | X | | | | | | | | |
| Patient number assigned via IWRS | X | | | | | | | | |
| Inclusion/exclusion review | X | X | | | | | | | |
| Modified Hachinski Ischemia Scale | X | | | | | | | | |
| Physical/neurological exam | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Demographics, height, and habits | X | | | | | | | | |
| Florbetapir PET scan or lumbar puncture for study entry ^c | X | | | | | | | | |
| Randomization | | X | | | | | | | |
| Previous/concomitant medications | X | X | X | X | X | X | X | X | X |
| Preexisting conditions/adverse events | X | X | X | X | X | X | X | X | X |
| Study drug administered ^b | | X | X | X | X | X | X | X | X |
| Efficacy and Health Outcomes Assessments | | | | | | | | | |
| FCSRT | X | | | | | | | | |
| MoCA | X | | | | | | | | |
| FAQ | X | | | | | | | X | |
| ADAS-Cog ₁₄ | | X | | | X | | | X | |
| ADCS-MCI-ADL | | X | | | X | | | X | |
| CDR-SB | | X | | | | | | | |
| RBANS | | X | | | | | | | |
| MMSE | | X | | | | | | X | |
| NPI | | X | | | | | | X | |
| RUD-Lite | | X | | | | | | X | |
| EQ-5D | | X | | | | | | X | |
| QoL-AD | | X | | | | | | X | |

| Study Period | I | II | | | | | | | |
|--|--------------------|-----------------|----|----|----|----|----|----|----|
| | Screening | Double Blind | | | | | | | |
| | Suggested Interval | 4 weeks | | | | | | | |
| Interval Allowed (days) | -0 to -56 | 21 – 35 | | | | | | | |
| Visit | V1 | V2 ^a | V3 | V4 | V5 | V6 | V7 | V8 | V9 |
| End of Week Relative to Study Medication Start ^b | -4 | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 |
| Blood Sampling | | | | | | | | | |
| Clinical chemistry, hematology | X | | | | | | | X | |
| Serum HCG (if applicable) | X | | | | | | | | |
| Plasma solanezumab ^d | | X | X | X | X | | | X | |
| Plasma Aβ | | X | X | | X | | | X | |
| Serum anti-solanezumab | | X | X | | X | | | X | |
| Plasma and serum for biomarker storage | | X | X | | X | | | X | |
| Blood for assessment of APOE genotype | | X | | | | | | | |
| Blood for pharmacogenomics | | X | | | | | | | |
| Other Safety Assessments | | | | | | | | | |
| Urine HCG (if applicable, on day of PET) | X | | | | | | | | |
| Vital signs and weight | X | X | | | X | | | X | |
| ECG | X | X | | | | | | X | |
| MRI | X | | | | | | | | |
| C-SSRS/Self-Harm Supplement Form | X | X | X | X | X | X | X | X | X |
| Second lumbar puncture time points (if applicable) ^c | | | X | X | X | | | X | |

| | II | | | | | | | | | |
|---|---------------------|------------|------------|------------|------------|------------------------|------------|------------|------------|------------|
| Study Period | Double Blind | | | | | | | | | |
| Suggested Interval | 4 weeks | | | | | | | | | |
| Interval Allowed (days) | 21 – 35 | | | | | | | | | |
| Visit | V10 | V11 | V12 | V13 | V14 | V15^a | V16 | V17 | V18 | V19 |
| End of Week Relative to Study Medication Start^b | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 |
| Administrative Procedures | | | | | | | | | | |
| Study drug administered ^b | X | X | X | X | X | X | X | X | X | X |
| Efficacy and Health Outcome Measures | | | | | | | | | | |
| FCSRT | | | | | | X | | | | |
| MoCA | | | | | | X | | | | |
| FAQ | | | | | | X | | | | |
| ADAS-Cog ₁₄ | | X | | | | X | | | X | |
| ADCS-MCI-ADL | | X | | | | X | | | X | |
| CDR-SB | | | | | | X | | | | |
| RBANS | | | | | | X | | | | |
| MMSE | | | | | | X | | | | |
| NPI | | | | | | X | | | | |
| RUD-Lite | | | | | | X | | | | |
| EQ-5D | | | | | | X | | | | |
| QoL-AD | | | | | | X | | | | |

| Study Period Suggested Interval Interval Allowed (days) Visit | II Double Blind | | | | | | | | | |
|--|--------------------|-----|-----|-----|-----|------------------|-----|-----|-----|-----|
| | 4 weeks | | | | | | | | | |
| | 21 – 35 | | | | | | | | | |
| | V10 | V11 | V12 | V13 | V14 | V15 ^a | V16 | V17 | V18 | V19 |
| End of Week Relative to Study Medication Start ^b | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 |
| Blood Sampling | | | | | | | | | | |
| Clinical chemistry, hematology | | | | | | X | | | | |
| Plasma solanezumab ^d | | | | | | X | | | | |
| Plasma Aβ | | | | | | X | | | | |
| Serum anti-solanezumab | | | | | | X | | | | |
| Plasma and serum for biomarker storage | | | | | | X | | | | |
| Other Safety Assessments | | | | | | | | | | |
| Physical/neurological exam | | | | | | X | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X |
| Urine HCG (if applicable, on day of PET) | | | | | | X | | | | |
| Vital signs and weight | | X | | | | | | | X | |
| ECG | | | | | | X | | | | |
| MRI | | | | | | X | | | | |
| C-SSRS/Self-Harm Supplement Form | X | X | X | X | X | X | X | X | X | X |
| Second lumbar puncture time points (if applicable)^b | | | | | | X | | | | |

| Study Period | II | | | | | | | | | | III |
|---|--------------|-----|-----|-----|-----|-----|-----|-----|------------------|-----------------|--------------------|
| | Double Blind | | | | | | | | | | Follow-Up |
| Suggested Interval | 4 weeks | | | | | | | | | | 12 weeks |
| Interval Allowed (days) | 21 – 35 | | | | | | | | | | |
| Visit | V20 | V21 | V22 | V23 | V24 | V25 | V26 | V27 | V28 ^a | ED ^a | V 301 ^c |
| End of Week Relative to Study Medication Start ^b | 72 | 76 | 80 | 84 | 88 | 92 | 96 | 100 | 104 | | 116 |
| Administrative Procedures | | | | | | | | | | | |
| Study drug administered ^b | X | X | X | X | X | X | X | X | | | |
| Disposition Event: Study Discontinuation or Completion | | | | | | | | | X | X | |
| Efficacy and Health Outcome Measures | | | | | | | | | | | |
| FCSRT | | | | | | | | | X | X | |
| MoCA | | | | | | | | | X | X | |
| FAQ | | X | | | | | | | X | X | |
| ADAS-Cog ₁₄ | | X | | | X | | | | X | X | |
| ADCS-MCI-ADL | | X | | | X | | | | X | X | |
| CDR-SB | | | | | | | | | X | X | |
| RBANS | | | | | | | | | X | X | |
| MMSE | | X | | | | | | | X | X | |
| NPI | | X | | | | | | | X | X | |
| RUD-Lite | | X | | | | | | | X | X | |
| EQ-5D | | X | | | | | | | X | X | |
| QoL-AD | | X | | | | | | | X | X | |

| Study Period | II Double Blind | | | | | | | | | | III Follow-Up |
|---|--------------------|-----|-----|-----|-----|-----|-----|-----|------------------|-----------------|-------------------|
| | 4 weeks | | | | | | | | | | 12 weeks |
| Suggested Interval | 21 – 35 | | | | | | | | | | |
| Interval Allowed (days) | | | | | | | | | | | |
| Visit | V20 | V21 | V22 | V23 | V24 | V25 | V26 | V27 | V28 ^a | ED ^a | V301 ^c |
| End of Week Relative to Study Medication Start ^b | 72 | 76 | 80 | 84 | 88 | 92 | 96 | 100 | 104 | | 116 |
| Blood Sampling | | | | | | | | | | | |
| Clinical chemistry, hematology | | X | | | | | | | X | X | |
| Plasma solanezumab ^d | | X | | | | | | | X | X | |
| Plasma A β | | X | | | | | | | X | X | |
| Serum anti-solanezumab | | X | | | | | | | X | X | |
| Plasma and serum for biomarker storage | | X | | | | | | | X | X | X |
| Other Safety Assessments | | | | | | | | | | | |
| Physical/neurological exam | | | | | | | | | X | X | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X |
| Urine HCG (if applicable, on day of PET) | | | | | | | | | X | X | |
| Vital signs and weight | | X | | | X | | | | X | X | X |
| ECG | | X | | | | | | | X | X | |
| MRI | | | | | | | | | X | X | |
| C-SSRS/Self-Harm Supplement Form | X | X | X | X | X | X | X | X | X | X | X |
| Second lumbar puncture time points (if applicable)^c | | X | | | | | | | X | X | |
| Second florbetapir PET scan (if applicable)^c | | | | | | | | | X | X | |

Schedule of Activities (concluded)

Abbreviations: A β = amyloid- β peptides; ADAS-COG₁₄ = 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; APOE = apolipoprotein E; CDR-SB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; EQ-5D = EuroQol 5-Dimensional Health-Related Quality of Life Scale; FAQ = Functional Activities Questionnaire; FCSRT = Free and Cued Selective Reminding Test; HCG = human chorionic gonadotropin; hr = Hour; INR = International Normalized Ratio; IWRS = interactive web response system; LP = lumbar puncture; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; PT = prothrombin time; PTT = partial thromboplastin time; 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; V = visit.

- a If desired, the following visits may take place over 2 consecutive days: Visit 2 (randomization visit), Visit 15 (Week 52), Visit 28 (Week 104), and ED. If done over 2 days, it is recommended that the following procedures be performed on Day 2: CDR-SB, RBANS, NPI, and FCSRT, as applicable. Dosing should occur at the end of the second day.
- b Visits should be scheduled as close as possible to the intended week in relation to baseline. Furthermore, visits must be scheduled such that study drug administration never occurs at intervals of less than 21 days.
- c All patients will have either a florbetapir PET scan or lumbar puncture at screening to determine eligibility. If florbetapir PET scan is used, this procedure will be repeated at the 24-month endpoint (or early discontinuation). If LP is used, then a second LP will be administered at 1 later time point, with LP patients being assigned by the IWRS to have the second LP at Week 4, 8, 12, 24, 52, 76, or 104 (or ED). Opting out of the 2nd LP will not be considered a protocol deviation. Any CSF collected via LP as part of the main study or the optional LP addendum will be analyzed for A β s, tau proteins, solanezumab, and biomarker storage. LPs are to be performed before study drug administration. It will not be considered a protocol deviation if the LP is not performed or if CSF is not collected for storage and future analysis in countries prohibiting sample storage. Patients undergoing LP will have PT/INR, PTT, and platelet count tested prior to each LP.
- d Pharmacokinetic samples should be obtained immediately before dosing at all designated visits. In addition, postdose samples should be taken at Visits 2 and 5.
- e Visit 301 should be scheduled to occur 4 months after last dose (that is, 3 months after Visit 28 or in case of ED, 4 months after last dose).

3. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive decline in cognitive function and the ability to perform activities of daily living, ultimately resulting in dementia, typically with fatal complications. The amyloid hypothesis of AD postulates that the accumulation of amyloid- β peptide ($A\beta$) is an early and necessary event in the pathogenesis of AD. This hypothesis suggests that treatments that slow the accumulation of $A\beta$ in the brain or increase clearance of $A\beta$ may be able to slow the progression of the AD clinical syndrome. The other hallmark neuropathological lesion of AD, intraneuronal neurofibrillary tangles consisting of tau proteins, is thought to be a marker for disease progression. The relationship between these 2 pathologies is still unclear, although the presence of both is necessary for the diagnosis of definite AD.

Converging evidence from both genetic at-risk and age at-risk cohorts suggests that the pathophysiological process of AD begins well more than a decade before the clinical stage now recognized as AD dementia, and that neurodegeneration is already apparent on magnetic resonance imaging (MRI) by the stage of prodromal AD. Like many disorders, AD occurs on a continuum from asymptomatic to prodromal AD (or mild cognitive impairment), then to dementia in mild, moderate, and severe stages. Recent clinical trial results in mild-to-moderate AD dementia, as well as evidence from transgenic animal experiments, suggest that treating AD during the earlier stages would have the greatest potential benefit on the disease and its progression, particularly when considering therapies targeted at $A\beta$ reduction.

Data from autopsy cohorts and cerebrospinal fluid (CSF) and positron emission tomography (PET) scan amyloid imaging studies demonstrate that approximately 30% of individuals over the age of 65 years have evidence of amyloid pathology. More recently, PET studies have demonstrated a close relationship between development of amyloid and subsequent development of cortical tau deposition. And, focal tau deposition on tau PET is more closely related to the focal neurodegenerative process than is amyloid. Clinically "normal" older individuals with evidence of amyloid pathology on imaging perform less well on cognitive tests compared to amyloid-negative age- and education-matched older individuals, are more likely to report subjective memory or other cognitive concerns, and are at increased risk for cognitive decline and progression to prodromal AD and AD dementia (Doraiswamy et al. 2014).

Solanezumab is a monoclonal antibody being developed as a therapy for AD. It binds selectively to soluble forms of $A\beta$ monomers, and is thought to reduce levels of free $A\beta$ in the central nervous system (CNS) by changing the equilibrium of $A\beta$ between periphery and CNS, thus drawing $A\beta$ from the CNS into the bloodstream. $A\beta$ is bound by solanezumab largely in the periphery with approximately 0.1% crossing the blood brain barrier, creating an equilibrium shift out of the CNS (the "peripheral sink" hypothesis). Solanezumab has demonstrated reasonable safety in prior Phase 3 studies, with the most relevant treatment-emergent adverse event (TEAE) being amyloid-related imaging abnormalities (ARIA) in approximately 1% of solanezumab-treated patients, which have typically been asymptomatic and non-serious (refer to current Investigator Brochure [IB] for details).

This study of the efficacy and safety of solanezumab is a Phase 3, double-blind, placebo-controlled study in patients with prodromal AD. Patients appropriate for the study have cognitive impairment and biomarker evidence consistent with AD pathological changes, but no significant impairments in instrumental activities of daily living (iADLs) nor deficits meeting a diagnosis of AD dementia. These disease characteristics are consistent with the term *prodromal AD* as defined by the International Working Group (IWG) for New Research Criteria for the Diagnosis of Alzheimer's Disease (Dubois et al. 2007, 2010, 2014) and with the term *mild cognitive impairment (MCI) due to AD* as defined by the National Institute on Aging in conjunction with the Alzheimer's Association (NIA-AA; Albert et al. 2011). Lilly has chosen to use the term *prodromal AD* for this study because it is unique to AD, whereas there are multiple causes of MCI, making prodromal AD the more straightforward designation.

4. Objectives and Endpoints

Table LZBE.1 shows the objectives and endpoints of the study.

Table LZBE.1. Objectives and Endpoints

| Objectives | Endpoints |
|--|---|
| <p>Primary To assess the hypothesis that solanezumab 400 mg Q4W will slow the clinical progression of prodromal AD over 24 months compared to placebo</p> | Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog ₁₄): change from baseline over 24 months |
| <p>Secondary To assess the effect of solanezumab vs. placebo on the clinical progression of prodromal AD over 24 months</p> | Changes from baseline to 24 months on Alzheimer's Disease Cooperative Study-Activities of Daily Living scale for Mild Cognitive Impairment (ADCS-MCI-ADL), Mini Mental Status Examination (MMSE), Montreal Cognitive Assessment (MoCA), Functional Activities Questionnaire (FAQ), Neuropsychiatric Inventory (NPI), Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Free and Cued Selective Reminding Test (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 Resource Utilization in Dementia–Lite (RUD-Lite), EuroQol 5-Dimensional Health-Related Quality of Life Scale (EQ-5D), Quality of Life in Alzheimer's Disease (scale) (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 A β / tau, vMRI, plasma A β , 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 patients 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 patients 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 patients 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 | Endpoints |
|---|--|
| <p>Exploratory To generate additional data for validation of the Preclinical Alzheimer's Cognitive Composite score (PACC), a composite endpoint being used in another Lilly study To compare MMSE and MoCA scales To assess time to significant progression</p> | <p>Changes from baseline in components of the MMSE, RBANS, and FCSRT over 24 months Changes from baseline in MMSE and MoCA over 24 months Time to progression to CDR-SB score of 1.0, and significant change on other cognitive, and functional measures</p> |

Abbreviations: Aβ = amyloid-β peptide; AD = Alzheimer's disease; ADAS-COG₁₄ = 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; 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. Overview 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 patients with prodromal AD. Patients 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. Patients will be randomized by site and by use of florbetapir PET scanning or CSF for study eligibility (Section 6.1). The primary hypothesis being tested in Study LZBE is that solanezumab will slow the clinical progression of AD as compared with placebo in patients with prodromal AD.

In addition, participants in the ^{18}F -AV-1451 tau imaging addendum will be included in an interim analysis (Section 10.8) 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), patients will come to a follow-up visit for biomarker and safety assessments.

5.2. End of Double-Blind Treatment Period and End of Trial

The analysis of the primary and secondary objectives will use data collected through the end of the double-blind treatment period, defined as Visit 28 (Week 104) for the last patient. The resulting dataset will be used to produce the initial clinical study report (CSR) for the study.

“End of the trial” refers to the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient (including the follow-up visit). The end of the trial will therefore occur after the end of the double-blind treatment period, after the last patient has completed the follow-up visit.

5.3. Scientific Rationale for Study Design

The amyloid hypothesis, as yet unproven, postulates that amyloid-laden neuritic plaques are the first and likely inciting pathological cause of AD-related neurodegeneration (Hardy 1996; Selkoe 1997; Price et al. 1998; Naslund et al. 2000). Therefore, as in most progressive diseases, the earlier the inciting pathology can be removed, the more likely long-term pathological impact will be curtailed. Moving anti-amyloid treatments earlier in the stage of AD is hypothesized to impact cortical neurodegeneration earlier in the disease process and thereby reduce long-term clinical deficits. By addressing AD pathology in the prodromal AD stage, it is theoretically possible to prevent or delay the onset of AD dementia, the stage of AD where patients can no longer perform iADLs independently. The prodromal stage of AD represents a critical stage during which treatment has the potential to slow the progression of disease before sufficient damage is done to the brain to cause dementia.

It should be noted that the stage of AD under study may be referred to as prodromal AD or as MCI due to AD. Prodromal AD, as defined by the IWG (Dubois et al. 2007, 2010, 2014), refers

to the early symptomatic, pre-dementia stage of AD in which clinical symptoms including episodic memory loss of the hippocampal type (characterized by a free recall deficit on testing not normalized with cueing) are present, but not sufficiently severe to affect iADLs and do not warrant a diagnosis of dementia; and in which biomarker evidence from CSF or amyloid PET imaging is supportive of the presence of AD pathological changes. These diagnostic criteria are consistent with those established by the NIA-AA (Albert et al. 2011) for MCI due to AD, which likewise require the presence of a clinical and cognitive syndrome involving cognitive impairment consistent with that associated with AD, preservation of independence in functional abilities, and lack of dementia; and provide guidance on the certainty of degree of diagnosis of MCI due to AD based on biomarker evidence of AD pathology.

5.4. Justification for Dose

A dose of solanezumab 400 mg administered intravenously every 4 weeks was selected based on current preclinical and pharmacodynamic data. This dose is expected to produce reductions in plasma unbound concentrations of A β , which may result in a net increase in the rate of transfer of A β from the CNS compartment to the plasma compartment, as well as show a slowing of cognitive and functional decline in patients diagnosed with prodromal AD.

5.5. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of solanezumab are to be found in the IB.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

Patient Characteristics and Diagnostic Criteria

- [1] Is aged 55-85 years
- [2] Has a diagnosis by the study investigator of a clinical syndrome of cognitive impairment consistent with prodromal AD per IWG diagnostic criteria or MCI due to AD per NIA-AA diagnostic criteria, confirmed by all of the following:
 - a. Subjective cognitive complaint or informant report of cognitive impairment for at least 6 months prior to Visit 1
 - b. No significant impairment of iADLs by patient and informant report and in the judgment of the investigator (that is, patients are maintaining their independence of functioning in daily life with minimal aids or assistance)
 - c. Not demented, based on IWG or NIA-AA guideline criteria
- [3] Scores 17-28 on Montreal Cognitive Assessment (MoCA) at Visit 1
- [4] Scores <27 on free recall cutoff score from the Free and Cued Selective Reminding Test (FCSRT) (Picture version) at Visit 1
- [5] Scores ≤ 4 on Modified Hachinski Ischemia Scale
- [6] Scores >0 on the Functional Activities Questionnaire (FAQ)
- [7] Has a reliable study partner who is in frequent contact with the patient (defined as at least 10 hours per week), will accompany the patient to the study visits, and will be available by telephone at designated times

Note: Study partners must be able to communicate with site personnel and be willing to comply with protocol requirements, and in the investigator's opinion must have adequate literacy to complete the protocol-specified questionnaires. Study partners must come in person to all visits with assessments that require their input.

- [8] Has a florbetapir PET scan or CSF result at screening consistent with the presence of amyloid pathology (see also Exclusion Criterion [34]). (Note: Previously acquired amyloid PET scans unrelated to Study LZBE may be permitted for use in meeting this criterion. Refer to specific guidance in the manual of operations.)

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Diagnostic Assessments

- [9] Has had MRI or computed tomography (CT) of brain within previous 2 years showing pathology that would be inconsistent with a diagnosis of AD

Medical Conditions

- [10] If female and of childbearing potential, tests positive for pregnancy at Visit 1 on a serum pregnancy test; or does not agree to use 1 highly effective method of contraception or a combination of 2 effective methods of contraception for the entirety of the study
- [11] Lacks adequate venous access for intravenous infusions and blood samples at monthly visits
- [12] Has history of serious infectious disease affecting CNS within previous 5 years
- [13] Has history within previous 5 years of head trauma resulting in protracted loss of consciousness
- [14] Has a current diagnosis of major depressive disorder as per the current Diagnostic and Statistical Manual of Mental Disorders (DSM) or any current primary psychiatric diagnosis other than AD (as per DSM) if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the patient's ability to complete the study. Patients with history of schizophrenia or other chronic psychosis are excluded.
- [15] Has history of primary or recurrent malignant disease within previous 5 years, with the exception of successfully treated cutaneous squamous cell carcinoma of the skin, basal cell carcinoma, cervical carcinoma in situ, or in situ prostate cancer with normal prostate-specific antigen post-treatment
- [16] Has any current unstable and/or clinically significant medical condition at Visit 1 that in the investigator's opinion could interfere with participation in the study
- [17] Has known allergy to humanized monoclonal antibodies
- [18] Has history of human immunodeficiency virus (HIV), clinically significant multiple or severe drug allergies, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)
- [19] Has history of chronic alcohol or drug abuse or dependence within the previous 5 years

- [20] Is clinically judged by the investigator to be at serious risk for suicide
- [21] Has electrocardiogram (ECG) abnormalities obtained at Visit 1 that, in the opinion of the investigator, are clinically significant with regard to the patient's participation in the study
- [22] Has alanine aminotransaminase (ALT/SGPT) values ≥ 2 times the upper limit of normal (ULN) of the performing laboratory, aspartate aminotransaminase (AST/SGOT) values ≥ 3 times the ULN, or total bilirubin values ≥ 2 times the ULN, at Visit 1
- [23] Has an ongoing clinically significant laboratory abnormality, as determined by the investigator
- [24] Has Visit 1 MRI with results showing >4 ARIA-H microhemorrhages or presence of ARIA-E (Section 9.3.6)
- [25] Has any contraindications for MRI studies, including claustrophobia, the presence of metal (ferromagnetic) implants, or a cardiac pacemaker that is not compatible with MRI

Prior/Concomitant Therapy

- [26] Has received treatment with a stable dose of an acetylcholinesterase inhibitor (AChEI) or memantine for less than 2 months before randomization. (If a patient has recently stopped an AChEI and/or memantine, he or she must have discontinued treatment at least 2 months before randomization.)
- [27] Has received medications that affect the CNS for less than 4 weeks; note that doses of chronic medications that affect the CNS must be stable for at least 4 weeks before randomization.

Prior/Concurrent Clinical Trial Experience

- [28] Has previously completed or withdrawn from this study or other solanezumab studies, or previous participation in any other study investigating active immunization against A β . Has previously completed or withdrawn from a study of passive immunization against A β with another antibody within the last 120 days.
- [29] Is currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the investigational product used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. Participation in observational studies may be permitted upon review of the observational study protocol and approval by the sponsor.
- [30] Has participated within the last 30 days (for Japan, 4 months) in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

Other Exclusions

- [31] Lacks, in the investigator's opinion, adequate premorbid literacy, adequate vision, or adequate hearing to complete the required psychometric tests
- [32] Are investigator site personnel directly affiliated with this study and/or their immediate families, or have study partners who are investigator site personnel directly affiliated with this study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
- [33] Are Lilly employees or employees of third-party organizations (TPOs) involved in study who require exclusion of their employees, or have study partners who are Lilly employees or are employees of TPOs involved in study who require exclusion of their employees

Exclusion Criteria for Patients Using Lumbar Puncture to Meet Inclusion Criterion [8]

- [34] If using lumbar puncture (LP) to meet Inclusion Criterion [8], a patient will be excluded from having an LP if he or she meets any of the following criteria: has allergy to all local anesthetics (such as lidocaine); has any medical condition requiring treatment with an anticoagulant such as heparin, vitamin K regeneration blockers, or new oral anticoagulants; or has any other contraindication in the opinion of the investigator (for example, suspected increased intracranial pressure or MRI abnormality that would contraindicate LP).

6.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) for reasons other than not meeting amyloid burden criteria may be re-screened. Individuals may be re-screened once. The interval between an initial screen and a re-screen should be at least 8 weeks. When rescreening is performed the participants must sign a new informed consent form (ICF) and will be assigned a new identification number. Approval from the sponsor must be obtained in advance for all re-screens.

6.4. Lifestyle and/or Dietary Requirements

Study participants should be instructed not to donate blood or blood products during the study or for 8 weeks following the study.

Males who undergo PET scans during the study must be instructed not to donate sperm for 24 hours after each scan, and if they have female partners of child-bearing potential, to abstain from sex for 24 hours after each scan.

7. Treatment

7.1. Treatments Administered

This study involves a comparison of solanezumab 400 mg versus placebo administered intravenously every 4 weeks. The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent to site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.2. Method of Treatment Assignment

Patients 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 patient. Site personnel will confirm that they have located the correct vial 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.

7.2.1. Selection and Timing of Doses

Infusion should occur over the course of at least 30 minutes. Premedication for dosing is not planned; however, if a patient demonstrates an infusion reaction to the study drug suggestive of allergy or hypersensitivity, the patient may be premedicated at the discretion of the investigator with appropriate medications (for example, diphenhydramine hydrochloride and/or acetaminophen), and the infusion time may be extended for the remaining infusions. An attempt should be made to complete the infusion within 2 hours of when first started. Patients should be observed for approximately 1 hour following the first infusion of study drug at Visit 2. Any premedications given are to be documented as concomitant therapy. The actual time of all dose administrations will be recorded in the patient's case report form (CRF).

Note that all cognitive and functional scales are to be administered before infusions.

7.3. Blinding

This is a double-blind study. To preserve the blinding of the study, a minimal number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

7.4. Packaging and Labeling

Clinical trial materials will be labeled according to the country's regulatory requirements.

7.5. Preparation/Handling/Storage

The site will be provided vials containing 400 mg/20 mL of solanezumab (or 20 mL placebo). The vials should be stored at 2°C to 8°C (36°F to 46°F).

For each dose, the content of 1 vial will be diluted with sterile sodium chloride intravenous infusion (0.9%) to a total volume of approximately 70 mL. Before infusion, the diluted solution should be inspected visually for particulate matter or discoloration. If particulate matter or discoloration is present, the solution should be discarded and a new solution made. After each intravenous bag is prepared, it will be identified as a dose of study drug without identification of the drug or dose. Once prepared, the infusion solution should be stored at room temperature (~25°C) for a total of no more than 6 hours.

7.6. Dose Modification

Not applicable.

7.7. Treatment Compliance

Because dosing occurs at study visits, patients who attend all visits and successfully receive infusions are automatically compliant with treatment. Any infusions at which 75% (approximately 52.5 mL when mixed in a 70-mL bag of normal saline) or more of the infusate is given will be considered a complete infusion.

If a patient attends a visit but does not receive a complete infusion (for example, due to technical complications), every effort should be made to complete the infusion within 24 hours if possible. If less than 75% of the infusion solution is given, this must be recorded as an incomplete infusion in the CRF.

Missed infusions should be recorded on the CRF. A patient will be considered significantly noncompliant if he or she misses 2 consecutive infusions, or 4 or more infusions at any time, and may be discontinued from the study. Patients who miss 2 consecutive infusions or 4 or more infusions for medical reasons (for example, MRI findings) can continue the study with approval of the sponsor.

7.8. Concomitant Therapy

For patients who are taking medications that may have an acute effect on cognition (and therefore on cognitive testing) and who must change doses or stop or start such medications, the sponsor or designee must be contacted beforehand to determine whether the patient should continue in the study and whether the clinical outcome measures should be performed. Starting on antimentia treatment is allowed during the trial for patients who worsen clinically during the study; however, the sponsor or designee must be contacted before initiation of therapy, and dosing should remain stable once a target dose is achieved. Sponsor approval must also be obtained for any subsequent dosing changes. A list of medications requiring sponsor consultation is provided in a separate manual of operations.

All concomitant medication taken during the study must be recorded on the Concomitant Medication CRF. Patients and their study partners will be instructed to consult the investigator or other appropriate study personnel at the site before initiation of any new medications or supplements and before changing dose of any current concomitant medications or supplements.

Patients who are receiving AChEIs and/or memantine are permitted to enter the study if stable on these medications prior to randomization.

Use of sedatives or hypnotics (including medications with sedating side effects such as antihistamines) should be avoided for 8 hours before administration of the cognitive and functional tests unless they are given chronically.

7.9. Treatment after Study Completion

The availability of an extension study will be determined before the first patient completes Visit 28. If an extension study is available, patients who complete Study LZBE may be eligible to participate if enrollment criteria for the extension study are met. Patients participating in such a study would receive study medication for the extension study only after all assessments for Study LZBE are completed. Patients not participating would not receive any study medication after the last infusion visit for Study LZBE (Week 100).

8. Discontinuation Criteria

8.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

8.2. Discontinuation from the Study

Patients will be discontinued from the study drug and from the study in the following circumstances, and will undergo early discontinuation procedures as shown in the Schedule of Activities (Section 2):

- Prolonged acute infusion reaction suggestive of allergic/hypersensitivity reaction (that is, not rapidly responsive to medication such as antihistamines, nonsteroidal anti-inflammatory drugs, and/or narcotics and/or brief interruption of infusion)

Note: Acute allergic/hypersensitivity reactions may occur with any agent that causes cytokine release (for example, monoclonal antibodies or other biological agents). Cytokine release may or may not be related to the mechanism of the infused biologic agent. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of infusion. Signs/symptoms may include: drug fever, arthralgia, bronchospasm, cough, dizziness, dyspnea, fatigue, headache, hypertension, hypotension, myalgia, nausea, pruritus, rash, rigors/chills, sweating (diaphoresis), tachycardia, urticaria, and vomiting.

- Requirement for a ferromagnetic implant or insertion of a cardiac pacemaker that is not MRI-compatible
- An investigator, site personnel performing assessments, or a patient is unblinded to a specific patient's treatment assignment.
- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- Investigator decision: The investigator decides that the patient should be discontinued from the study. If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

- Patient decision: The patient or the patient's designee requests to be withdrawn from the study.
- Adverse event: If the investigator decides that the patient should be withdrawn from the study because of an SAE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately (Section 8.2).

In addition, patients *may* be discontinued from the study drug and from the study in the following circumstances, and if discontinued, will undergo early discontinuation procedures as shown in the Schedule of Activities (Section 2):

- Appearance of clinically significant new cerebral ischemic or hemorrhagic events or ARIA-E (amyloid-related imaging abnormality—edema/effusions, also known as cerebral vasogenic edema) by MRI (Section 9.3.6); patients with new MRI findings can continue to participate in the study depending on clinical significance as determined by the investigator.

Note: While most cases of ARIA-E are asymptomatic, when symptoms do occur they are reported to be most commonly headache, worsening of cognitive function, alteration of consciousness, seizures, unsteadiness, and vomiting. Even when symptomatic ARIA-E is present, in most cases treatment is not required beyond discontinuation of the study medication until the imaging abnormalities are resolved. If a patient simultaneously develops more than one of the symptoms suggestive of ARIA-E; that is, headache, worsening of cognitive function, alteration of consciousness, seizures, unsteadiness, or vomiting, then an unscheduled MRI may be obtained. A single symptom suggestive of ARIA-E of sufficient severity may also warrant an MRI. The unscheduled MRI should be performed in the same manner as the currently scheduled MRIs in the protocol, which includes sending the images for central review.

- Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor:
 - ALT or AST >8X ULN
 - ALT or AST >5X ULN for more than 2 weeks
 - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or prothrombin time >1.5X ULN
 - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
 - alkaline phosphatase (ALP) >3X ULN
 - ALP >2.5X ULN and TBL >2X ULN
 - ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Mean Bazett-corrected QT interval (QTcB) >500 msec and an absolute change >60 msec (or equivalent JTcB changes if appropriate) when compared with baseline (the most recent measurement made at either Visit 1 or Visit 2)
- Missed infusions: If a patient misses 2 consecutive infusions, or 4 or more infusions at any time overall during the study, the patient may be discontinued from the study. Patients who miss 2 consecutive infusions or 4 or more infusions for medical reasons (for example, MRI findings) may continue the study with approval of the sponsor.

8.3. Patients Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients and/or study partners who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of lost-to-follow-up patients within legal and ethical boundaries for all patients randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog; Rosen et al. 1984). The ADAS is a rater-administered instrument that was designed to assess the severity of the dysfunction in the cognitive and noncognitive behaviors characteristic of persons with AD; ADAS-Cog refers to the cognitive subscale which was originally designed with 11 items (the ADAS-Cog₁₁). An expanded version that includes 3 additional items more sensitive in patients at earlier stages of AD, the ADAS-Cog₁₄ (Mohs et al. 1997), will be used as a primary efficacy measure. It consists of 14 items assessing areas of cognitive function most typically impaired in AD: orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures. The ADAS-Cog₁₄ allows better discrimination of differences among milder AD patients than the ADAS-Cog₁₁. The ADAS-Cog₁₄ scale ranges from 0 to 90, with higher scores indicating greater disease severity.

Note: The administration of the ADAS-Cog will be recorded (audio only) at each administration for quality review purposes except where prohibited by local laws and regulations. The ADAS-Cog and Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment–Activities of Daily Living Inventory (ADCS-MCI-ADL) must be performed by 2 different qualified raters.

9.1.2. Secondary Efficacy Assessments

Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory for Mildly Cognitively Impaired (ADCS-MCI-ADL; Pedrosa et al. 2010). The ADCS-MCI-ADL is a functional evaluation scale for MCI patients, based on information provided by an informant (in this case the study partner), that describes the performance of patients in several ADLs. It was adapted from the original ADCS-ADL scale, which was constructed to evaluate patients with dementia in the Alzheimer's Disease Cooperative Study, as a measure of the AD patients' performance in activities of daily living (ADLs) (Galasko et al. 1997). An 18-item ADCS-MCI-ADL was developed alongside the original ADCS-ADL, but more recently a 24-item version (Pedrosa et al. 2010) was developed to incorporate additional items considered appropriate to the MCI population, which has been shown to better distinguish between healthy subjects and people with MCI. This study will use the 24-item version. The range for this scale

is 0 to 69, with lower scores indicating greater disease severity. For each of the specific items, the informant is first asked if the patient attempted the ADL during the past 4 weeks. If the patient did attempt the ADL, the informant is asked to rate the patient's performance level based on a set of performance descriptions. Scores for each item and the overall score for the tool are calculated.

Note: The administration of the ADCS-MCI-ADL will be recorded (audio only) at each administration for quality review purposes except where prohibited by local laws and regulations. The ADAS-Cog₁₄ and ADCS-MCI-ADL must be performed by 2 different qualified raters.

Mini-Mental State Examination (MMSE; Folstein et al. 1975). The MMSE is a brief instrument used to assess cognitive function. The instrument is divided into 2 sections. The first section measures orientation, memory, and attention. The maximum score for the first section is 21. The second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures. The maximum score for the second section is 9. The range for the total MMSE score is 0 to 30.

Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005). The MoCA is a brief 30-point cognitive screening test developed with high sensitivity and specificity for detecting MCI in patients who perform in the normal range on the MMSE. Compared to the MMSE, the MoCA uses more numerous and demanding tasks to assess executive function, higher level language abilities, memory, and complex visuospatial processing.

Note: The administration of the MoCA will be recorded (audio only) at each administration for quality review purposes except where prohibited by local laws and regulations. The MMSE and MoCA should not be administered in succession (that is, at least one other scale should be administered in between) and if possible should be done by different raters.

Neuropsychiatric Inventory (NPI; Cummings et al. 1994). The NPI is a tool for assessing psychopathology in patients with dementia and other neurologic disorders. Information is obtained from an informant familiar with the patient's behavior (often a caregiver; in this study, the study partner). A screening question assays each subarea of the NPI—delusions, hallucinations, agitation, apathy, anxiety, depression, euphoria, irritability, disinhibition, and aberrant motor behavior. Two questions inquire about neurovegetative changes, including alterations in appetite and nighttime behavior disturbances. If the answer to the screening question is no, no further questions are pursued. If the answer is yes, subquestions are asked and ratings of the frequency and severity of the behavior are made by the informant through the use of scales with anchor points. The distress induced in the informant by each behavior is also rated. Scores for each subscale, the total tool, informant distress associated with each behavior, and total informant distress are computed. The NPI standard version consists of 10 items with informant distress scale and 2 neurovegetative questions. Four subscales can be defined based on a previously reported factor analysis: Mood (depression, anxiety, nighttime behavior, appetite, and irritability); Psychosis (delusions, hallucinations, and agitation); Frontal (euphoria and disinhibition); and Other (apathy and aberrant motor behavior) (Frisoni et al. 1999).

Clinical Dementia Rating Scale (CDR-SB; Berg et al. 1992). The CDR is a semi-structured interview performed with the patient and informant that provides an index of global functioning. The informant is queried about the patient’s memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The patient’s memory, orientation, judgment, and problem-solving ability are assessed. By assigning a severity score for each of the 6 domains, a total score known as sum of boxes is obtained—hence the abbreviation, CDR-SB.

Resource Utilization in Dementia—Lite questionnaire (RUD-Lite; Wimo et al. 1998). The RUD-Lite is an abbreviated version of the Resource Utilization in Dementia (RUD) scale designed to assess the healthcare resource utilization of patients and their caregivers (or in this case, study partners) and to determine the level of formal and informal care attributable to AD. The data are collected through a structured interview. Information on both study partners (caregiving time and work status) and patients (accommodation and healthcare resource utilization) is gathered from the baseline and final assessment interviews. Study partners will be asked to provide data on time spent assisting patients’ basic ADLs such as using the toilet, eating, dressing, grooming, walking, and bathing; assisting patients’ instrumental ADLs such as shopping, cooking, housekeeping, laundry, transportation, taking medication, and managing finances; and providing supervision. The resource utilization quantified by the RUD-Lite can be used for calculating cost offsets and in cost-effectiveness models.

Note that as of 2016, only the full RUD is supported by its copyright owners, such that users who wish to administer a shorter version must pull out questions from the RUD. Study LZBE is administering the short version of the RUD once formally known as the RUD-Lite and will continue to use the name “RUD-Lite” for consistency with other solanezumab protocols that have administered this scale.

EuroQoL-5D Proxy Version (EQ-5D; Kind 1996). The EQ-5D is a standardized instrument used to measure overall health status and is applicable to a wide range of health conditions and treatments. It provides both a descriptive profile and a single index value for health status. The 5D in the name refers to the 5-dimensional classification system for health states used in the instrument. Each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) has 5 levels of severity (no, slight, moderate, severe, and extreme problems). Scores on individual dimensions are recorded, as is a total score that sums the individual dimension scores. A visual analog scale also assesses the informant’s impression of the patient’s overall health state. Reliability and validity of the proxy version for use with an AD population have been demonstrated (Jönsson et al. 2006; Naglie et al. 2006). Scores can be converted into weighted health state preferences for quality-adjusted life year models.

Quality of Life in Alzheimer’s Disease (QoL-AD; Logsdon et al. 2002; Thorgrimsen et al. 2003). The QoL-AD is a disease-specific measure of quality of life for an AD population. It includes 13 items, each rated on a 4-point scale. Summing the items provides an overall score to index the patient’s quality of life. The QoL-AD is administered to the patient by a rater and asks the patient to provide ratings on mood, relationships, memory, finances, and so on. The patient’s study partner also is asked to complete the measure. Reliability and validity in samples of AD patients and their caregivers have been demonstrated.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al. 1998). The RBANS is a collection of 12 subtests representing 5 neurocognitive domains: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. The raw scores from each subtest within a domain are converted to a summary score, or Index Score that summarizes the patient's overall level of performance on this measure. Version A of the scale will be used at baseline and endpoint; Version B will be used at the 12-month visit.

Free and Cued Selective Reminding Test (FCSRT; Grober and Buschke 1987). The FCSRT is a neuropsychological test of memory under conditions that control attention and cognitive processing in order to obtain an assessment of memory unconfounded by normal age-related changes in cognition. Both a word and picture version are available; this study will use the picture version. The FCSRT has previously demonstrated sensitivity in prediction of decline from MCI to AD dementia in other studies (Amieva et al. 2008; Dubois et al. 2010), and in predicting dementia in previous cohort studies from the Baltimore Longitudinal Study of Aging (Grober et al. 2008) and the Einstein Study of Aging (Derby et al. 2013).

Note: The administration of the FCSRT will be recorded (audio only) at each administration for quality review purposes except where prohibited by local laws and regulations.

Functional Activities Questionnaire (FAQ; Pfeffer et al. 1982). The FAQ is a rater-administered instrument directed at the caregiver (in this case, the study partner) that assesses perceived ability in performing instrumental everyday activities thought to be especially cognitively complex (for example, financial management, shopping, playing games, food preparation, traveling, keeping appointments, keeping track of current events, and understanding media). Each of the 10 items offers 6 response alternatives, varying in level of dependence and familiarity of the task, which are recorded so that each item receives a score ranging from 1 (*complete independence*) to 4 (*complete dependence*). The sum of 10 items provides an overall assessment of perceived functional ability. A growing literature supports the FAQ as a measure sensitive to changes in AD patients at the earlier end of the disease spectrum (Tabert et al. 2002; Teng et al. 2010).

Note: The administration of the FAQ will be recorded (audio only) at each administration for quality review purposes except where prohibited by local laws and regulations.

Florbetapir PET scan. Change in amyloid burden (as assessed by florbetapir binding) will be compared in solanezumab- and placebo-treated patients. See [Appendix 4](#) for information about radiation dose.

¹⁸F AV-1451 PET scan. Changes in tau (as assessed by ¹⁸F AV-1451 binding) will be collected as part of an addendum.

9.1.3. Appropriateness of Assessments

Efficacy. The ADAS-Cog is a well-accepted measure of cognitive functioning in patients with mild to moderate AD; the 14-item version is considered more sensitive in milder AD. The ADCS-MCI-ADL is also well recognized as a measure of functional abilities in patients with

prodromal AD/MCI. A growing literature supports the FAQ as a measure sensitive to changes in milder AD populations. Additional descriptions and references supporting use of these and other scales are provided in Sections 9.1.1 and 9.1.2.

Safety. Safety measures used in this study are all well established.

9.2. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

9.2.1. Adverse Events

A clinical study AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to a drug or drug delivery system.

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, study site personnel will record via CRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to investigational product and/or protocol procedure via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, PET tracers, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A “reasonable possibility” means that there is a cause and effect relationship between the investigational product, PET tracers, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient’s investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying if possible, the circumstances leading to any dosage modifications or discontinuations of treatment.

9.2.2. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment

Although all AEs after signing the ICF are recorded in the CRF, SAE reporting begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product or PET imaging, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2.2. Adverse Events of Special Interest

Adverse events associated with specific TEAE clusters will be monitored. The TEAE clusters of interest include:

- Infusion-related reactions
- TEAEs associated with anti-solanezumab antibodies (immunogenicity)
- ARIA-H (amyloid-related imaging abnormality—hemorrhage/hemosiderin deposition, also known as cerebral microhemorrhage)
- ARIA-E
- Hemorrhagic stroke and microhemorrhage
- Cardiac ischemia-related events
- Cardiac arrhythmia-related events

Data on cerebro-cardiovascular events (for example, death, myocardial infarction, stroke, etc.) will be adjudicated by an external Clinical Endpoint Committee (CEC). The role of the CEC is to adjudicate defined clinical events, in a blinded, consistent, and unbiased manner throughout the course of a study. Complete details will be available in the CEC charter.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Other Safety Assessments

9.3.1. Physical Examinations and Neurologic Examination

Physical and neurological examinations will be conducted as specified in the Schedule of Activities (Section 2) and as clinically indicated.

Physical examinations will include assessment of general appearance, skin, head and neck, lymph nodes, thyroid, abdomen (bowel sounds and liver and spleen palpation), back (costovertebral angle tenderness), and musculoskeletal, cardiovascular, and respiratory systems. Neurological examinations will include assessment of cranial nerves, motor and sensory systems, muscle stretch reflexes, balance and coordination, and gait. The physical and neurological

examination will be performed by a physician, nurse practitioner, or physician's assistant (for Japan, physician only).

Body weight and height will be recorded according to the Schedule of Activities (Section 2).

If a clinically meaningful change in an MRI is noted during the study, an additional full neurological exam will be performed as soon as possible, along with any other medical follow-up deemed necessary by the investigator.

Any clinically significant change from baseline on follow-up physical and neurological examinations should be reported to Lilly or its designee as an AE via CRF.

9.3.2. *Electrocardiograms*

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study-specific recommendations included in the manual of operations for the study.

Electrocardiograms will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the subject meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

All ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full overread. A report based on data from this overread will be issued to the investigative site. When there are differences in ECG interpretation between the local and central readings, the locally read interpretation will be used for study entry and immediate patient management, and the centrally read interpretation will be used for data analysis and report writing purposes.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via CRF.

9.3.3. *Vital Signs*

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2) and following the study-specific recommendations included in the manual of operations for the study.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via CRF.

9.3.4. *Body Weight and Height*

Body weight and height will be recorded according to the Schedule of Activities (Section 2).

9.3.5. Laboratory Tests

For each patient, laboratory tests detailed in (Appendix 2) should be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via CRF.

9.3.6. Magnetic Resonance Imaging

Magnetic resonance imaging of the brain will be performed according to the Schedule of Activities (Section 2) and as clinically indicated. This technology will be used to check for evidence of hemorrhage/hemosiderin deposition (ARIA-H, also known as cerebral microhemorrhage) and edema/effusions (ARIA-E, also known as cerebral vasogenic edema). (The volumetric MRI data will also be used to calculate brain volumes.) The MRI scans will be sent for analysis to a centralized MRI vendor designated by Lilly. The scans will be reviewed by the investigator or qualified designee for immediate patient management or assessment of patient's study eligibility as appropriate. Any clinically significant findings noted at baseline that result in a diagnosis should be recorded as a preexisting condition or AE. Specific analyses of the scans, including assessments of ARIA-H and ARIA-E and calculations of brain volumes, will subsequently be interpreted by the centralized MRI vendor for data analysis and report-writing purposes. Results of centrally read MRIs regarding patient care/safety will be reported back to sites even though there was a local read.

9.3.7. Columbia Suicide Severity Rating Scale (Adult Version)

Consistent with Food and Drug Administration (FDA) regulatory guidance (FDA 2012), any occurrence of suicide-related thoughts and behaviors will be assessed as indicated in the Schedule of Activities (Section 2) using the Columbia Suicide Severity Rating Scale (C-SSRS), a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The scale includes suggested questions to elicit the type of information needed to determine if a suicide-related thought or behavior occurred.

Terms captured by the use of the C-SSRS can be mapped to Columbia Classification Algorithm for Suicide Assessment (Posner et al. 2007) to facilitate future pooling of data.

The first time the scale is administered in this study, the C-SSRS "Baseline" version will be used, and the findings will constitute the baseline assessment. The C-SSRS "Since Last Visit" scale will be used for all subsequent assessments. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided. The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

9.3.8. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. In addition, unblinded data on safety-related measures and SAEs will be periodically reviewed by a Data Monitoring Committee (DMC; Section 10.8) until database lock of the double-blind period. Complete details will be available in the DMC charter.

If a study patient experiences elevated ALT $\geq 3X$ ULN, ALP $\geq 2X$ ULN, or elevated TBL $\geq 2X$ ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See [Appendix 3](#).

In the event that blinded safety monitoring identifies an issue that may need to be addressed by unblinding at the group level, those blinded individuals may recommend to members of the DMC that they should conduct additional analyses of the safety data.

9.4. Sample Collection and Testing

The Schedule of Activities (Section 2) lists the schedule for sample collections in this study.

[Appendix 2](#) lists the clinical laboratory tests that will be performed for this study.

9.4.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health.

Cerebrospinal fluid will be collected in some patients to determine whether patients meet the inclusion criteria, and in other patients as part of the optional LP addendum.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.4.2. CSF A β and Tau Proteins and Solanezumab

Screening LPs may be performed as part of the study eligibility criteria for patients opting to use CSF A β levels to determine patient eligibility for study participation (Section 0). For these patients, a second LP will be administered at 1 later time point. These patients will be assigned to have the second LP at Week 4, 8, 12, 24, 52, 76, or 104 (or early discontinuation). Specific instructions for the LP procedure itself will be provided in the manual of operations.

The collected CSF will be assayed for measurement of solanezumab, A β species, tau proteins, and storage of CSF for use in future research. The results of CSF analyses will be used to determine whether patients meet inclusion/exclusion criteria and to compare solanezumab and placebo treatment effects. A portion of the collected CSF will be used for central laboratory testing of CSF solanezumab, A β species, and tau proteins. The remainder will be aliquotted and stored for future research where allowed. In countries prohibiting sample storage, it will not be considered a protocol deviation if CSF is not collected for storage and future analysis.

9.4.2.1. Timing of CSF Sampling

Visits when CSF is sampled are shown in the body and footnotes of the Schedule of Activities (Section 2).

9.4.2.2. CSF Collection Procedures

Cerebrospinal fluid will be collected according to the procedure described in [Appendix 3](#). It is critical that for each CSF sample, the date of sample acquisition is accurately recorded.

Sample handling and shipment to the central laboratory will occur per instructions given to the investigative study site.

Samples collected from placebo-treated patients during the double-blind period will not be assayed for solanezumab. Bioanalytical CSF samples collected to measure investigational product concentration will be retained for a maximum of 2 years following last patient visit for the study.

Cerebrospinal fluid samples collected to assess A β species and tau proteins and allow for future research may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor (Section 9.4.6.2).

Results from analysis of screening samples of CSF in regards to patient inclusion eligibility will be reported to investigative sites (that is, eligible or not eligible for inclusion).

Results from analyses of CSF for solanezumab, A β species, and tau proteins to assess treatment effects will not be reported to investigative sites or other blinded personnel at a subject level.

9.4.3. Plasma Samples for Assessment of A β s and Solanezumab

9.4.3.1. Timing of Plasma Sampling

Visits when plasma is sampled and the time of sampling relative to study drug dosing are shown in the body and footnotes of the Schedule of Activities (Section 2). Samples from placebo-treated patients will not be assayed for solanezumab. Amyloid- β peptide or solanezumab concentration results in plasma that could unblind the study will not be reported to investigative sites or other blinded personnel.

9.4.3.2. Plasma Collection Procedures

Venous blood samples will be drawn into sodium ethylenediaminetetraacetic acid tubes for the determination of plasma concentrations of solanezumab and A β peptides at the times indicated in

the Schedule of Activities (Section 2). A saline well or heparin lock may be used to facilitate blood collection.

On the dosing day, the blood will be collected from the arm that did not receive the infusion of study drug.

It is critical that for each blood sample, date and time of sample acquisition and date and time of administration of study drug are accurately recorded. Only plasma samples collected from patients dosed with solanezumab will be assayed for solanezumab.

Sample handling and shipment to the central laboratory will occur per instructions given to the investigative study site.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 2 years following last patient visit for the study.

The remainder of the plasma not used for the assessment of A β species may be stored for a maximum of 15 years following last patient visit for the study at a facility selected by the sponsor (Section 9.4.6.2).

Results of plasma solanezumab and A β analyses that could unblind the study will not be reported to investigative sites or other blinded personnel at a subject level.

9.4.4. Serum Samples for Anti-Solanezumab Immunogenicity

9.4.4.1. Timing of Blood Sampling

Where local regulations and ethical review boards (ERBs) allow, serum for immunogenicity testing will be prepared from blood drawn at the designated visits and times relative to study drug dosing as indicated in the body and footnotes of the Schedule of Activities (Section 2). Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of solanezumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of solanezumab. Serum immunogenicity results and any associated plasma A β peptide and solanezumab drug results used to interpret immunogenicity test results that could unblind the study will not be reported to investigative sites or other blinded personnel.

9.4.4.2. Blood Collection Procedures

It is critical that for each serum sample, date and time of sample acquisition and date and time of administration of study drug are accurately recorded.

Sample handling and shipment to the central laboratory will occur per instructions given to the investigative study site.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to solanezumab.

9.4.5. Apolipoprotein E Genotyping

Apolipoprotein E (APOE) genotyping is a mandatory part of this study, unless country-specific laws and regulations prohibit this type of testing. Blood sampling for APOE genotyping will be performed as shown in the Schedule of Activities (Section 2). Neither patients nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results. Failure to collect samples for APOE will not be considered a protocol deviation if country-specific regulations prohibit the testing of genetic material or transportation of such material outside of the country.

9.4.6. Samples for Biomarker Research

9.4.6.1. Pharmacogenetic Samples

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to solanezumab and to investigate genetic variants thought to play a role in AD. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, candidate gene studies, and epigenetic analyses. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

9.4.6.2. Biomarker Storage Samples

As discussed above, serum, plasma, and CSF samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to solanezumab, pathways associated with AD, mechanism of action of solanezumab, and/or research method or in validating diagnostic tools or assay(s) related to AD.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

9.5. Health Economics

Refer to Section [9.1.2](#) for description of health economics outcomes.

10. Statistical Considerations and Data Analysis

10.1. 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, we used an expected decline in ADAS-Cog₁₄ at 2 years of 4.41 points for placebo-treated patients and 3.21 points for solanezumab-treated patients, 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 patients per arm (919 completers per arm) or 2450 total randomized patients will have approximately 89% power to detect a significant treatment difference at 2 years using a 2-sided significance level of 0.05.

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

10.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

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 patients are assigned by random allocation, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. When change from baseline is assessed, patients 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.

For mixed-effect model repeated measure (MMRM) models, observations collected at nonscheduled visits will not be included in the analyses. For analyses using last observation carried forward, the last non-missing postbaseline observation (scheduled or unscheduled) will be used to calculate change from baseline.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05; 2-sided confidence intervals (CIs) will be displayed with a 95% confidence level. All tests of interactions between treatment and other factors will be conducted at an alpha level of 0.05.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Complete details of the statistical methods to be used in this study are contained in the statistical analysis plan (SAP).

10.2.1. Analysis Populations

The primary and secondary efficacy measures will be analyzed using the ITT population. In addition, each of these measures will be analyzed using the per-protocol population and the completer population to verify the robustness of the results. Summaries and analyses for safety measures will be based on the safety population. Tabulation of the number and percentage of patients included in each population will be provided. The SAP contains detailed descriptions for each of these patient populations.

10.2.2. Handling of Missing Items for Scales

If any of the individual items for the ADAS-Cog or ADCS-MCI-ADL are missing or unknown, every effort will be made to obtain the score for the missing item or items.

For ADAS-Cog₁₄, 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-Cog₁₄ 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-iADL at that visit will be considered missing.

The same imputation technique will be applied to the 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.

10.2.3. Pooling of Investigators

This study will be conducted by multiple investigators at multiple sites internationally. In the event that a site has an inadequate number of patients (defined as 0 or 1 randomized patient per treatment group) for the planned analyses, the following strategy will be implemented. Data from all such sites within a country will be pooled. If the resulting pool within a country is still inadequate, no further pooling will be performed.

10.3. Treatment Group Comparability

10.3.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study. The percentage of patients discontinuing from each treatment group will be compared by reason for discontinuation using Fisher's exact test.

10.3.2. Protocol Deviations

Listings of patients with significant protocol deviations will be provided for the ITT population. The following list of significant protocol deviations will be determined from the clinical database and from the Lilly clinical/medical group:

- Informed consent deviation
- Did not have an assessment of the ADAS-Cog at any of the visits at which the scale was scheduled to be assessed
- Did not have an assessment of the ADCS-MCI-ADL at any of the visits at which the scale was scheduled to be assessed
- Protocol deviations of inclusion/exclusion criteria
- Had a study dosing algorithm deviation (such as if patients randomized to Treatment A were given Treatment B or patients randomized to Treatment A never received the assigned study drug)
- Had unqualified rater or raters with substantial scoring errors for the ADAS-Cog at any time
- Had unqualified rater or raters with substantial scoring errors for the ADCS-MCI-ADL at any time
- Did not have the same study partner(s) throughout the trial
- Greater than or equal to 20% of infusions are incomplete
- Had change in doses of AChEI medication(s) and/or memantine or have started/stopped AChEI medication(s) and/or memantine anytime during the study without consulting the sponsor
- Deviated from the protocol in any other way

10.3.3. Patient Characteristics

The patient's age, gender, race, 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 AD symptoms, time since diagnosis, MMSE at Visit 1, APOE4 carrier status (carrier [$\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$], noncarrier [$\epsilon 3/\epsilon 3$, $\epsilon 2/\epsilon 2$]), APOE4 genotype ($\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$, no $\epsilon 4$), having 1 or more first degree relatives with AD, and AChEI and/or memantine use at baseline will be recorded.

Baseline characteristics will be summarized for the ITT and per-protocol populations by treatment group and overall. Summaries will include descriptive statistics for continuous and categorical measures. Fisher's exact test or Pearson's chi-square test will be used for treatment-group comparisons of categorical data. For continuous data, analysis of variance with independent factors for treatment will be used.

10.3.4. Concomitant Therapy

Approved AD medications will be permitted in this study as described in Section 7.8. Patients who begin such treatments during the study will be analyzed as part of the ITT population. Analyses stratified by use of these medications at baseline will be conducted.

10.3.5. Treatment Compliance

The proportion of patients who are significantly noncompliant as noted in Section 7.7 will be summarized and compared among all treatment groups using Fisher's exact test.

10.4. Primary and Secondary Analyses

10.4.1. Primary Analyses

The primary objective of this study is to test the hypothesis that intravenous infusion of solanezumab will slow cognitive decline as compared with placebo in patients with prodromal AD. This will be assessed using an MMRM analysis of the ADAS-Cog₁₄ in patients with prodromal AD at baseline (Visit 1 MoCA score of 17 to 28), in which the specific hypothesis is that the cognitive decline from baseline at the end of the treatment period (104 weeks) for solanezumab will be significantly less than that for placebo.

The change from baseline score on the ADAS-Cog₁₄ at each scheduled postbaseline visit (according to the Study Schedule) during the treatment period will be the dependent variable. The model for the fixed effects will include terms for 7 effects: baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. Visit will be considered a categorical variable with values equal to the visit numbers at which the scales were assessed. The null hypothesis is that the contrast between the solanezumab-treated patients versus placebo-treated patients at the last visit equals zero. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

10.4.2. Secondary Analyses

10.4.2.1. Clinical Outcomes

Similar to the primary analysis, each of the secondary efficacy outcomes will be assessed using an MMRM analysis. These secondary efficacy outcomes include ADCS-MCI-ADL, MMSE, MoCA, CDR-SB, NPI, RUD-Lite, EQ-5D Proxy, QoL-AD patient and proxy, RBANS, and FAQ. For each secondary efficacy measure, the change from baseline score at each scheduled postbaseline visit (according to the Study Schedule) during the treatment period will be analyzed using the same MMRM model described for the primary analysis.

An additional MMRM analysis, termed a slopes analysis, will be conducted examining the change from baseline score on the ADAS-Cog₁₄, ADCS-MCI-ADL, CDR-SB, FAQ, MMSE, and MoCA at each scheduled postbaseline visit. In contrast to the primary analyses, which considered visit (time) as a categorical variable, time from randomization will be treated as a continuous variable. The model for the fixed effects will include baseline score, pooled investigator, treatment, time, treatment-by-time interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. The treatment-by-time interaction term will be examined to assess whether solanezumab and placebo have differing slopes in terms of cognitive or functional progression. The effect of a quadratic term for time (and its associated interaction with treatment) on the model will also be examined.

Categorical analyses of slowing cognitive and functional decline will be conducted comparing proportions of patients reaching certain levels of decline between solanezumab and placebo. The precise definitions of cognitive and functional decline and analysis methods will be detailed in the SAP prior to database lock.

Any additional analyses of secondary efficacy outcomes will be specified in the SAP prior to database lock.

10.4.2.2. Biomarker Outcomes

10.4.2.2.1. Analysis of Plasma A β

To evaluate the change in plasma A β (assayed plasma A β ₁₋₄₀ and A β ₁₋₄₂) after treatment, an MMRM will be used to compare change from baseline to 4, 12, 24, 52, 76, and 104 weeks after randomization. This analysis will be done separately for each plasma A β parameter. The model for the fixed effects will include terms for the following independent effects: baseline plasma A β , treatment, visit, treatment-by-visit interaction, and age at baseline. Visit will be considered a categorical variable with values equal to the visit numbers at which plasma A β is assessed. The null hypothesis is that the difference in least squares (LS) mean between the solanezumab group and placebo equals zero.

10.4.2.2.2. Analysis of Volumetric MRI Data

To evaluate the changes in volumetric MRI (vMRI) data after treatment, an MMRM will be used to compare change from baseline to 52 and 104 weeks after randomization. The model will include terms for the following independent effects: baseline vMRI value, treatment, visit, treatment-by-visit interaction, and age at baseline. Visit will be considered a categorical variable

with values equal to the visit numbers at which vMRI is assessed. The null hypothesis is that the difference in LS mean between the solanezumab group and placebo equals zero.

10.4.2.2.3. Analysis of Amyloid PET Imaging

To provide further supporting evidence that solanezumab attenuates the underlying pathologic process in AD, the change in brain amyloid burden obtained using florbetapir PET imaging will be assessed. Parameters from various brain regions of interest as well as a composite brain measure will be assessed. Each patient participating in amyloid PET imaging should provide a baseline and postbaseline assessment. Change in standard uptake value ratio (SUV_r) normalized to the appropriate reference region will be examined using an analysis of covariance (ANCOVA) model containing terms for baseline SUV_r, treatment, and age at baseline. The null hypothesis is that the difference in LS mean between the solanezumab group and placebo equals zero.

10.4.2.2.4. Analysis of Cerebrospinal Fluid

To provide further supporting evidence that solanezumab attenuates the underlying pathologic process in AD, changes in CSF parameters, including total and free A β ₁₋₄₀ and A β ₁₋₄₂ species and total tau and P-tau₁₈₁ peptides, will be assessed. For each patient who undergoes an LP at the beginning of the study (screening or baseline visit) and a second LP (whether as part of the main protocol or the LP addendum), change from baseline in measured CSF A β and tau proteins will be assessed. Changes in these CSF parameters at each postbaseline collection point will be examined using an ANCOVA model containing terms for baseline, treatment, and age at baseline. The null hypotheses are that the difference in LS means between the solanezumab group and placebo equals zero at each of the scheduled time points.

10.5. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, weight/height measurements, MRI scans, ECGs, and immunogenicity measures during the treatment period.

Safety analyses for the treatment period will include comparisons between solanezumab and placebo. All hypotheses will be tested at a 2-sided 0.05 significance level. No adjustments for multiple comparisons will be made.

For analysis comparing proportion of treatment-emergent abnormalities between treatment groups for laboratory analytes, vital signs, weight, MRI scans, and ECGs, only patients who have both a baseline observation and a postbaseline observation will be included in the analysis for each analyte or parameter, respectively.

Suicide-related thoughts and behaviors, based on the C-SSRS, will be listed by patient and visit. Only patients that show suicidal ideation/behavior will be displayed (that is, if a patient answers are all “no” for the C-SSRS, then that patient will not be displayed). However, if a patient reported any ideation or behavior at any time point, then all their ideation and behavior will be displayed, even if not positive.

10.6. Pharmacokinetic/Pharmacodynamic Analyses

The distribution of observed plasma solanezumab concentrations will be graphically compared to simulated solanezumab concentrations generated by a population pharmacokinetic (PK) model developed with data from previous Phase 3 trials. If warranted, the population PK model parameters may be updated by combining data from this study with that from previous Phase 3 studies and re-fitting the final model. The population PK model may be used to estimate exposure parameters (for example, plasma solanezumab area under the curve), if appropriate. As warranted, the relationship between exposure estimates and safety, biomarker, or efficacy outcomes may be investigated through graphical or other analyses.

To evaluate the potential impact of immunogenicity on solanezumab PK, plasma solanezumab concentrations from patients with treatment-emergent immunogenicity will be plotted as a function of time, along with mean plasma solanezumab concentrations in all patients. The anti-solanezumab titer associated with each plasma solanezumab concentration will be indicated on the graph (for example, by assigning a different symbol to each titer level). A region representing the middle 90% of observed plasma solanezumab concentrations in all patients will also be presented on the graph. If this graphical analysis demonstrates a trend in plasma solanezumab concentrations in patients with treatment-emergent immunogenicity relative to the overall trial population, additional work may be performed to characterize this trend.

10.7. Other Analyses

10.7.1. Health Economics

Health economics analyses are addressed in Section [10.4.2](#).

10.7.2. Subgroup Analyses

To assess the effects of various demographic and baseline characteristics, subgroup analyses of the primary endpoint, ADAS-Cog₁₄, will be performed based on the following variables: gender, age, race, APOE4 carrier status, country, concomitant AD therapy, and compliance with study drug. The specific groupings of patients based on these variables will be outlined in the SAP. All subgroup analyses will be considered secondary analyses. Additional subgroup analyses may be performed as suggested by the data.

10.7.3. Gatekeeping Strategy

A gatekeeping strategy will be used in Study LZBE for testing a prespecified set of secondary outcomes to ensure family-wise protection against type I error of falsely rejecting any of the null hypotheses. Secondary outcomes will only be tested at the completion of the double-blind treatment phase (not at the interim analysis) and will be based on the nominal alpha level as specified in the interim analysis description below.

Details of the gatekeeping strategy will be contained in the SAP.

10.8. Interim Analyses and Data Monitoring Committee

10.8.1. Data Monitoring Committee

Periodic study monitoring will be conducted under the auspices of an independent, external DMC assigned to the study. Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients. The DMC will meet periodically as outlined in the DMC Charter.

Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the completed study has been unblinded. Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document.

10.8.2. Interim Analysis

A single efficacy interim analysis will be assessed by the DMC after 550 randomized ¹⁸F-AV-1451 tau addendum participants have completed a baseline and 1-year ¹⁸F-AV-1451 PET scan, unless this interim is determined to be unnecessary by results of studies that are ongoing at the time of initial protocol development. The purpose of this interim analysis is to assess the relationship between ¹⁸F-AV-1451 tau PET and solanezumab treatment at 12 months.

Based on unpublished preliminary ¹⁸F-AV-1451 PET data from untreated patients with MCI at 9 months, a mean increase in SUV_r of 0.071 units and a standard deviation of 0.105 units was observed. Conservatively using these same estimates at the 1-year time point and assuming a reduction in tau accumulation of 40% (increase of 0.043 SUV_r units) in solanezumab-treated patients as compared to placebo-treated patients and the same standard deviation, the effect size is 0.267 units SUV_r. Given 275 randomized patients per arm (550 total patients included in the interim analysis), this analysis will have approximately 87% power to detect a significant treatment difference at 1 year using a 2-sided significance level of 0.05.

In addition to comparison of tau changes across treatments, the interim analysis would also examine the relationship between changes in ¹⁸F-AV-1451 PET and changes in cognition based on the ADAS-Cog₁₄. It is anticipated that a positive correlation between these 2 measures exists – that is, it is anticipated that patients who show increases in tau accumulation will show corresponding increases (more cognitive decline) on the ADAS-Cog₁₄.

The results of the ¹⁸F-AV-1451 tau PET interim analysis will not affect the conduct of the overall study. As there is no possibility of terminating the study early for either efficacy or futility based on this analysis, no alpha-spending adjustment will be used for the final analysis and all results from the tau addendum patients will be included in the final efficacy analysis. Furthermore, should there be occasion for unblinded interim analysis results to be shared beyond the DMC, any such sharing would be limited to personnel who are not part of the LZBE study team, in order to protect its integrity as a double-blind study.

If any additional unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

11. Study Governance Considerations

11.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

11.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

11.1.2. Ethical Review

The investigator or an appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

11.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party.

11.1.4. Investigator Information

Physicians with a specialty in neurology, geriatrics, or psychiatry who have documented experience in AD trials will participate as investigators in this clinical trial. In addition, licensed clinicians who have clearly documented extensive experience in AD trials may participate as investigators in the clinical trial upon approval by the sponsor.

11.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

11.1.6. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most qualified enrolled patients will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The regulatory sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of their knowledge, the report accurately describes the conduct and results of the study.

11.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its

representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data collected by a third-party (for example, imaging) will be encoded by the third-party and stored electronically in the third-party's database system. Validated data will subsequently be transferred to Lilly's data warehouse, using standard Lilly file transfer processes.

Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

11.3. Study and Site Closure

11.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

11.3.2. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

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Appendix 1. Abbreviations and Definitions

| Term | Definition |
|------------------------------|---|
| Aβ | amyloid- β peptide |
| AChEI | acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-Cog₁₄ | Alzheimer's Disease Assessment Scale–Cognitive subscale |
| ADCS-MCI-ADL | Alzheimer's Disease Cooperative Study-Activities of Daily Living scale for Mild Cognitive Impairment |
| ADLs | activities of daily living |
| AE | adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| APOE | apolipoprotein E |
| ARIA | amyloid-related imaging abnormality |
| ARIA-E | amyloid-related imaging abnormality—edema/effusions, also known as cerebral vasogenic edema |
| ARIA-H | amyloid-related imaging abnormality—hemorrhage/hemosiderin deposition, also known as cerebral microhemorrhage |
| AST | aspartate aminotransferase |
| blinding/masking | <p>A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not.</p> <p>A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.</p> |
| CDR-SB | Clinical Dementia Rating Scale–Sum of Boxes |

| | |
|------------------|---|
| CEC | Clinical Endpoint Committee |
| CIOMS | Council for International Organizations of Medical Sciences |
| CNS | central nervous system |
| complaint | A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system. |
| CRF | case report form |
| CRP | clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer. |
| CSF | cerebrospinal fluid |
| CSR | clinical study report |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| DMC | data monitoring committee |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| ECG | electrocardiogram |
| enroll | The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment. |
| enter | Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives. |
| EQ-5D | EuroQol 5-Dimensional Health-Related Quality of Life Scale |
| ERB | ethical review board |
| FAQ | Functional Activities Questionnaire |
| FCSRT | Free and Cued Selective Reminding Test |
| FDA | (United States) Food and Drug Administration |
| GCP | good clinical practice |
| iADL | instrumental activities of daily living |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |

| | |
|--------------------------------|---|
| interim analysis | An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked. |
| investigational product | A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. |
| ITT | intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment. |
| IWG | International Working Group for New Research Criteria for the Diagnosis of Alzheimer's Disease |
| IWRS | interactive web-response system |
| LP | lumbar puncture |
| LS | least squares |
| MCI | mild cognitive impairment |
| MMRM | mixed-effect model repeated measure |
| MMSE | Mini Mental Status Examination |
| MoCA | Montreal Cognitive Assessment |
| MRI | magnetic resonance imaging |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| NPI | Neuropsychiatric Inventory |
| PET | positron emissions tomography |
| PK | pharmacokinetics |
| QoL-AD | Quality of Life in Alzheimer's Disease (scale) |
| QTcB | Bazett-corrected QT interval |
| RBANS | Repeatable Battery for the Assessment of Neuropsychological Status |
| RUD | Resource Utilization in Dementia |
| RUD-Lite | Resource Utilization in Dementia-Lite |
| SAE | serious adverse event |

| | |
|---------------|--|
| SAP | statistical analysis plan |
| screen | The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. |
| SUSARs | suspected unexpected serious adverse reactions |
| SUVr | standard uptake value ratio |
| TBL | total bilirubin level |
| TEAE | treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment. |
| TPO | third-party organization |
| ULN | upper limit of normal |
| vMRI | volumetric magnetic resonance imaging |

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology^a

Hemoglobin
 Hematocrit
 Erythrocyte count (RBC)
 Mean cell volume
 Mean cell hemoglobin concentration
 Leukocytes (WBC)
 Neutrophils, segmented
 Lymphocytes
 Monocytes
 Eosinophils
 Basophils
 Platelets

Clinical Chemistry^a

Serum Concentrations of:

Sodium
 Potassium
 Total bilirubin
 Direct bilirubin
 Alkaline phosphatase
 Alanine aminotransferase (ALT)
 Aspartate aminotransferase (AST)
 Blood urea nitrogen (BUN)
 Creatinine
 Uric acid
 Calcium
 Glucose, nonfasting
 Albumin
 Cholesterol
 Creatine kinase (CK)

Pregnancy Test (females only)^{b,c}

Lumbar Puncture (screening or optional)^{a, d}

Solanezumab
 A β proteins
 Tau proteins

Abbreviations: A β = amyloid- β peptide; LP = lumbar puncture; PET = positron emissions tomography; RBC = red blood cells; WBC = white blood cells.

^a Assayed by Lilly-designated (central) laboratory.

^b Assayed by local or investigator-designated laboratory.

^c Female patients of childbearing potential must test negative on a serum pregnancy test at screening and must test negative on a urine pregnancy test on the day of any PET scan, prior to the administration of radiopharmaceutical agent.

^d Patients who undergo LP will have coagulation panel (prothrombin time [PT]/International Normalized Ratio [INR] and partial thromboplastin time [PTT]) and platelet count) obtained from a local laboratory up to 4 weeks before each LP.

Appendix 3. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology^a

Hemoglobin
Hematocrit
RBC
WBC
Neutrophils, segmented
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Hepatic Chemistry^a

Total bilirubin
Direct bilirubin
Alkaline phosphatase
ALT
AST
GGT
CPK

Haptoglobin^a

Hepatic Coagulation^a

Prothrombin Time
Prothrombin Time, INR

Hepatic Serologies^{a,b}

Hepatitis A antibody, total
Hepatitis A antibody, IgM
Hepatitis B surface antigen
Hepatitis B surface antibody
Hepatitis B Core antibody
Hepatitis C antibody
Hepatitis E antibody, IgG
Hepatitis E antibody, IgM

Anti-nuclear antibody^a

Alkaline Phosphatase Isoenzymes^a

Anti-smooth muscle antibody (or anti-actin antibody)^a

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

^a Assayed by Lilly-designated or local laboratory.

^b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 4. Summary of Radiation Dose

Patients who undergo florbetapir PET scans to determine eligibility for the study will be exposed to radiation during the PET scan. Details on the amount of exposure estimated to occur on each PET imaging occasion, in each year of the study, and cumulatively, are provided in [Table LZBE.2](#) below.

Table LZBE.2. Effective Radiation Dose (mSv) from Florbetapir PET Scans

| | Effective Dose (mSv) per Scan ^a | Number of Scans in First Year | Effective Dose (mSv) for Scans in First Year | Number of Scans in Second Year ^b | Effective Dose (mSv) for Scans in Second Year ^b | Total Effective Dose (mSv) |
|---|--|-------------------------------|--|---|--|----------------------------|
| Florbetapir F 18 (amyloid) Scan (10 mCi iv) | 7.43 | 1 | 7.43 | 1 | 7.43 | 14.86 |

Abbreviations: CT = computed tomography; iv = intravenous infusion; PET = positron emission tomography.

^a Dose shown includes radiation exposure from the radiotracer and also assumes a non-clinical CT scan is obtained (estimated at 0.4 mSv) as part of the PET scan attenuation correction process when the scan is done on a PET/CT scanner. A clinical CT scan is not needed during the PET scan session and because it would add additional radiation exposure is not recommended.

^b Second florbetapir scan done at end of second year or in the event of early discontinuation.

Source: Florbetapir F18 Injection (Amyvid™) Package Insert, 2016.

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