H8A-MC-LZAZ(f) Clinical Protocol

Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study)

NCT02008357

Approval Date: 9-Aug-2022

Title Page

Protocol Title: Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study)

Protocol Number: H8A-MC-LZAZ

Amendment Number: f

Compound: Solanezumab (LY2062430)

Study Phase: 3

Acronym: A4 Study

Sponsor Name: Eli Lilly and Company

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1. Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment e	16-Oct-2018
Amendment d	04-Jul-2017
Amendment c	14-Dec-2015
Amendment b	02-Sep-2014
Amendment a	18-Oct-2013
Original Protocol	08-Sep-2013

Amendment [f]

Overall Rationale for the Amendment:
The rationale of this amendment is to include changes in the primary efficacy analysis and update other sections for minor changes.

Section # and Name	Description of Change	Brief Rationale
2. Synopsis	Updated the section to align with the changes in the main body of the protocol	For consistency
6.1. Primary Objective 6.2. Secondary Objectives 11.1. Determination of Sample Size 11.2.8. Analysis of Primary Outcome (Placebo-Controlled Period) 11.2.9.1. Clinical Outcomes 11.2.9.2. Sensitivity Analyses	Revised statistical analysis from "mixed model repeated-measures (MMRM)" to "constrained longitudinal data analysis (cLDA) natural cubic spline (NCS) analysis (referred to as NCS henceforth)"	The NCS analysis method was selected to accommodate disruptions to the study from the COVID-19 pandemic. MMRM analyses will be conducted as sensitivity analyses as described in the SAP
6.2. Secondary Objectives	Changed "tau peptides phosphorylated at the threonine 181 position (p-tau$_{181}$)" to "phosphorylated tau peptides (P-tau)"	For flexibility to include other isoforms
	Added "and plasma" with CSF	Correction
	Removed "at the time of database lock for the placebo-controlled period using data available up to 2 years in the open-label period" from the first bullet point of secondary objectives of the open-label period	Correction
7.1.5. Open-Label Extension Period	Added "If the open-label period is extended beyond Visit 117, participants who complete Visit 117 before implementation of the protocol amendment that includes additional visits will be allowed to resume study visits once available at their site."	For clarification

Section # and Name	Description of Change	Brief Rationale
10.1.3.1. Cerebrospinal fluid (CSF) 11.2.9.3. Biomarker Outcomes	Removed "181" from "p-tau$_{181}$"	For flexibility to include other isoforms
10.1.4. Secondary Efficacy Clinical Outcome Measures, Open-Label Period	Added "at Visit 66 and" and removed "subjective cognitive decline,"	Correction
10.2.3. Electrocardiograms	Added "ECG will be collected in the placebo-controlled period per schedule of events and in the open-label period as unscheduled ECG per investigator discretion."	For clarification
10.3. Appropriateness of Measurements	Added "and plasma" with CSF in Paragraph 5	Correction
11.2.9.2. Sensitivity Analyses	Added "as noted in the SAP"	For clarification
11.2.9.3. Biomarker Outcomes	Removed "Aβ" and added "and P-tau, GFAP, and Neurofilament light chain" and "and P-tau" in Paragraph 1; added "GFAP Neurofilament light chain" in Paragraph 4	Correction
11.2.10. Open-Label Period	Removed "This noninferiority interim analysis will be conducted at the time of the database lock of the placebo-controlled period." from Paragraph 5	For clarification
11.2.13.2. Adverse Events	Replaced "randomization" with "the first infusion"	For clarification
Attachment 1. A4 Study Schedule: Study Schedule, A4 Protocol, Visits 6 through 66 (Placebo-Controlled Period)[a]	Changed the superscript footnote symbol from "j" to "i" in column heading "Early Term"	Correction
	Added "Clinician Diagnostic Impression (CDI)" row	Correction. The CDI was inadvertently left off the schedule in protocol amendment (e) but was added to the study database, and sites were trained to collect the CDI. The addition of this row in the Placebo-Controlled Period study schedule reflects conduct of the study at Visit 66
Attachment 1. A4 Study Schedule: Study Schedule, A4 Protocol, Visits 6 through 66 (Laboratory Specimens, Placebo-Controlled Period)[a] (completed)	Changed Visit "40" to "50" in Footnote "a"	Correction

Section # and Name	Description of Change	Brief Rationale
Attachment 4. Amendment Summary for Protocol H8A-MC-LZAZ(e)/ADC-040-A4: Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study) Revised Protocol Sections	Removed these sections	Updated according to internal Lilly guidance

2. Synopsis

Study 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 with fatal complications. The amyloid hypothesis of AD postulates that the accumulation of amyloid-β peptide (Aβ) is an early and necessary event in the pathogenesis of AD. This hypothesis suggests that treatments that slow the accumulation of Aβ in the brain or increase clearance of Aβ may be able to slow the progression of the AD clinical syndrome.

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 by the stage of mild cognitive impairment (MCI)/prodromal AD. Recent clinical trial results in mild-to-moderate AD dementia, as well as evidence from transgenic animal experiments, suggest that earlier intervention may be most beneficial to fully impact the clinical progression of the disease, particularly with therapies targeted at Aβ 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 have evidence of amyloid pathology. Clinically "normal" older individuals with biomarker evidence of elevated amyloid pathology demonstrate AD-like abnormalities on functional and structural imaging, perform less well on cognitive tests compared to amyloid-negative older individuals, are more likely to report subjective memory concerns, and are at increased risk for cognitive decline and progression to MCI and AD. Recent academic consensus workgroups focused on developing guidelines for earlier diagnosis of AD and research diagnostic criteria have defined a stage of "preclinical AD," based on biomarker evidence of AD pathology before the stage of clinically evident symptoms of cognitive impairment.

The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease "A4" study is a Phase 3, double-blind, placebo-controlled study in subjects with preclinical AD. The A4 trial preclinical AD study population will be defined as subjects with evidence of brain amyloid pathology on PET amyloid imaging who are still clinically normal but at high risk for cognitive decline. The A4 study is designed to test the hypothesis that solanezumab, a monoclonal antibody that binds Aβ, will slow decline on a cognitive composite measure designed to be sensitive to early decline in the preclinical stages of AD. This study will collect additional data on the long-term safety and efficacy of solanezumab, including computerized cognitive outcomes, as well as self and study partner reports of daily-life cognitive function outcomes, a brief resource utilization inventory, and biomarker and imaging measures.

Clinical Protocol Synopsis: Study H8A-MC-LZAZ (A4 Study)

Name of Investigational Product: Solanezumab (LY2062430)

Title of Study: Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study

Phase of Development: 3

Study Design: This is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study comparing solanezumab with placebo given as infusions once every 4 weeks over 4.5 years in approximately 1150 subjects with preclinical AD, defined as having evidence of elevated brain amyloid pathology before the stage of clinically evident cognitive impairment, with an optional open-label extension period.

Objectives: The primary objective of this study is to test the hypothesis that solanezumab, administered as an intravenous (IV) infusion every 4 weeks for 4.5 years, will slow cognitive decline as compared with placebo in subjects with preclinical AD. The primary objective will be assessed using a natural cubic spline (NCS) analysis of the primary outcome measure, the Preclinical Alzheimer Cognitive Composite (PACC), a composite that is primarily weighted on episodic memory and executive function tests, in which the specific hypothesis is that the cognitive decline at Week 240 will be significantly less for solanezumab than for placebo.

The secondary objectives of the placebo-controlled period of the study are:

- To test the hypothesis that solanezumab will slow the decline of perceived cognitive function and performance of everyday activities, as compared with placebo, using an NCS analysis of the Cognitive Function Index (CFI).
- To assess whether decline in activities of daily living begins by the end of the treatment period, and if so, whether an effect of solanezumab, compared with placebo, can be detected using an NCS analysis of the ADCS-Activities of Daily Living (ADCS-ADL) Prevention Questionnaire.
- To assess the relationship between treatment effect and time using the PACC.
- To test the hypothesis that solanezumab reduces brain amyloid burden, as compared with placebo, as assessed using florbetapir PET imaging.
- To assess effects of solanezumab on CSF concentrations of total tau and phosphorylated tau.
- To assess effects of solanezumab on CSF concentrations of Aβ
- To investigate the effect of treatment with solanezumab on volumetric magnetic resonance imaging (MRI).
- To assess the safety of solanezumab versus placebo treatment including adverse events (AEs) and immunogenicity.

The secondary objectives of the open-label period of the study are:

- To assess the persistence of effect of solanezumab treatment in participants with preclinical AD. That is, to test the hypothesis that patients originally randomized to receive placebo and later switched to solanezumab at the start of the open-label period do not "catch up" to patients originally randomized to receive solanezumab in the placebo-controlled period, using a randomized/delayed-start analysis. The main efficacy objective of the open-label period will be an interim randomized/delayed-start analysis of the PACC.

- To test the hypothesis that solanezumab will continue to slow the decline associated with preclinical AD during open-label treatment, comparing participants initially randomized to solanezumab with participants initially randomized to placebo in the double-blind treatment period, using randomized/delayed-start analysis of the Mini-Mental State Examination (MMSE), Clinical Dementia Rating-Sum of Boxes (CDR-SB), Computerized Cognitive Composite (C3), CFI, and the ADCS-ADL Prevention Questionnaire.

The exploratory objectives of the study are:

- To assess the effect of treatment with solanezumab as demonstrated using the MMSE.
- To assess the utility of a novel computerized battery, the C3, in predicting and tracking clinical decline and response to solanezumab.
- To assess the effects of treatment on healthcare resource utilization.
- To determine the best predictors of clinical decline based on the PACC.
- To develop novel sensitive outcome measures to improve the efficiency of future secondary prevention trials, including exploratory measures of self-reported assessment of cognitive and interpersonal functioning
- To assess the effect of treatment with solanezumab as demonstrated using the CDR scale.
- To assess the effect of treatment with solanezumab as demonstrated using the C-Path Consortium's Participant-Reported Outcome Questionnaire (C-Path PRO).
- To investigate the impact of solanezumab on markers of synaptic dysfunction on functional connectivity MRI.
- To assess solanezumab-associated changes in levels of plasma Aβ species and CSF Aβ species. The hypothesis that solanezumab, unlike placebo, alters amyloid-plaque associated forms of Aβ will be assessed by 1) demonstrating presence of plaque-associated Aβ species in the plasma, and 2) confirming that concentrations of CSF-free (unbound to antibody) $A\beta_{1-42}$ are increased or unchanged and CSF-free $A\beta_{1-40}$ levels are decreased with solanezumab treatment.
- To explore whether baseline markers of neurodegeneration (volumetric MRI or CSF tau or P-tau or plasma P-tau) are related to cognitive decline and response to treatment with solanezumab.
- To explore the impact of disclosure of amyloid status on questionnaires probing perception of amyloid imaging and concern about developing AD.
- To explore biomarker assessments collected at baseline and at the end of the placebo-controlled period as potential predictors of treatment effect during the open-label period.
- To assess preclinical AD during open-label treatment by comparing participants initially randomized to solanezumab in the placebo-controlled period with participants initially randomized to placebo in the double-blind treatment period, using randomized/delayed-start analysis of the Resource Use Inventory, Brief version (RUI-B).

Diagnosis and Main Criteria for Inclusion and Exclusions: Subjects will be males and females 65 to 85 years old with preclinical AD, defined as having an MMSE score between 25 and 30, a Logical Memory test, part IIa score between 6 and 18, and a global CDR of 0; and having screening florbetapir PET scan indicating brain amyloid pathology. Subjects will be excluded if they have a screening MRI with results that show >4 ARIA-H or any ARIA-E, have any major or unstable illness, including unstable ischemic cardiovascular disease, or require use of excluded medications.

Number of Planned Subjects: Approximately 1150 (575 solanezumab, 575 placebo).

Dose and Mode of Administration: The study was initiated with solanezumab 400 mg or placebo, administered as an IV infusion once every 4 weeks. Partway through the study, the dose was increased to 1600 mg every 4 weeks. Subjects will receive 400 mg solanezumab or placebo via IV infusion every 4 weeks for at least 2 doses, followed by 800 mg every 4 weeks for at least 2 doses, and then 1600 mg every 4 weeks until the conclusion of the study.

Planned Duration of Treatment:
Screening period: Up to 90 days
Placebo-controlled treatment period: 240 weeks
Open-label treatment period: Up to 204 weeks

Criteria for Evaluation:

Efficacy: PACC, MMSE, ADCS-ADL Prevention Questionnaire, CDR-SB, CFI, C3 (including the C-Path PRO and the Memory Complaint Questionnaire), and the RUI-B.

Disclosure of Amyloid Status**:** Perception of amyloid imaging as well as impact of disclosure will be assessed using the Views and Perceptions of Amyloid Imaging Questionnaire, the Concerns about Alzheimer's Disease Questionnaire, the Impact of Events Scale, and the Future Time Perspective Scale.

Biomarkers and Imaging: Plasma solanezumab and Aβ isoforms concentrations and serum anti-solanezumab antibodies (immunogenicity) will be measured from processed blood samples using validated immunoassay and/or mass spectrometry methods. Solanezumab treatment effects will be determined by measuring CSF Aβ isoforms and tau proteins in those subjects who undergo lumbar puncture and by analyzing amyloid burden on PET scans, as well as volumetric and functional MRI metrics.

Pharmacokinetics**:** Observed concentrations will be graphically compared to model predicted concentrations. The impact of immunogenicity on pharmacokinetics (PK) will be investigated graphically. Population PK and association with efficacy, biomarkers, and safety parameters may be reported.

Safety**:** Safety assessments will include routine physical and neurological examinations, AEs, vital signs (including temperature and weight), 12-lead electrocardiogram (ECG), and laboratory evaluations, including immunogenicity directed towards solanezumab. In addition, the Assessment of Psychological Well Being will be used to monitor for anxiety and depression. Suicide-related thoughts and behaviors will be evaluated using the Columbia Suicide Severity Rating Scale (C-SSRS). Two types of amyloid-related imaging abnormalities (ARIA)—hemosiderin deposition (ARIA-H, also known as microhemorrhage) and edema/effusions (ARIA-E, also known as vasogenic edema) will also be assessed through scheduled MRIs.

Statistical Methods:

General Considerations**:** All analyses will follow the intent-to-treat (ITT) principle unless otherwise specified. When change from baseline is assessed, subjects will be included in the analysis only if both a baseline and a postbaseline measure are available (referred to as a modified ITT approach). 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 endpoint of this study, PACC, will be analyzed using an NCS analysis.

The original modified intent-to-treat (mITT) analysis (that is, all participants as randomized to treatment who have a baseline and at least 1 postbaseline measure) for the primary outcome will be retained and conducted at the end of the treatment period, although the dose will be increased during the study; in other words, the primary analysis will include all data for the solanezumab group as the treatment group versus placebo. As with the original analysis plan, the hypothesis for this analysis will be tested against an alpha level of .05.

The change from baseline score at each visit when the composite score is assessed will be the dependent variable. Visit will be considered a categorical variable with values equal to the visit numbers at which the measure was scheduled. The null hypothesis is that the treatment difference between the solanezumab group versus placebo at Week 240 equals zero.

Secondary and Exploratory Endpoints: Change from baseline will be assessed using NCS analyses for the MMSE, CFI, ADCS-ADL Prevention Questionnaire, CDR-SB, and C3. Analysis will also be done on the RUI-B which will be used to assess health care resource utilization over the course of the study. If a gatekeeping strategy is used for hypothesis testing involving a subset of efficacy endpoints, this strategy will be prespecified in the statistical analysis plan prior to database lock. Additional subgroup analyses will be performed. Imaging variables including PET amyloid imaging and volumetric and functional MRI will be analyzed using both region of interest methods and whole brain analyses. Analyses of plasma Aβ and CSF biomarkers will be performed. Additional sensitivity analyses will be performed to explore the effect of increasing the dose from 400 mg to 1600 mg partway through the study. These sensitivity analyses will include analyses conducted on the PACC and other clinical measures after censoring all observations after the study-wide dose increase, and analyses to estimate the potential differences in the treatment effect for the original dose and the higher dose by modeling the effects of a time-varying dose indicator variable.

Randomized/Delayed-Start Analysis: The PACC, MMSE, CDR-SB, C3, CFI, and the ADCS-ADL Prevention Questionnaire will be analyzed to investigate the long-term effect of anti-amyloid treatment on cognitive decline in preclinical AD. If the primary A4 results in the placebo-controlled period are positive, disease-modifying effects will be assessed using a noninferiority hypothesis in an MMRM model, in which the specific hypothesis is that the advantage of solanezumab treatment demonstrated in the placebo-controlled period is sufficiently maintained in the open-label period. This randomized/delayed-start analysis will assess whether solanezumab has a persistent effect on disease course.

Safety: Safety will be assessed by summarizing AEs, laboratory analytes, vital signs (including temperature and weight), ECGs, MRIs, C-SSRS, immunogenicity, and Assessment of Psychological Well Being results. Comparisons will be made between the treatment groups. Safety analyses of the open-label extension will span across both the placebo-controlled study period and the open-label study period in order to be able to compare early-start safety risks to early-start efficacy benefits.

3. Table of Contents

Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study)

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List of Tables, Figures, and Attachments

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4. Abbreviations and Definitions

Term	Definition
A4	Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (study title)
Aβ	amyloid-β peptide
AchEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADCS	Alzheimer's Disease Cooperative Study
ADCS-ADL	Alzheimer's Disease Cooperative Study—Activities of Daily Living
ADCS-PI	Alzheimer's Disease Cooperative Study—Prevention Instruments trial
ADL	activities of daily living
ADNI	Alzheimer's Disease Neuroimaging Initiative
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.
AIBL	Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing
ALT	alanine aminotransferase
APOE	apolipoprotein E gene
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities—edema/effusions, also known as vasogenic edema
ARIA-H	amyloid-related imaging abnormalities—hemosiderin deposition, also known as microhemorrhage
AST	aspartate aminotransferase
ATRI	Alzheimer's Therapeutic Research Institute
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A double-blind study is one in which neither the subject 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.

C3	Computerized Cognitive Composite
CDI	Clinician Diagnostic Impression
CDR	Clinical Dementia Rating
CDR-G	Clinical Dementia Rating—Global score
CDR-SB	Clinical Dementia Rating—Sum of Boxes score
CFI	Cognitive Function Index
CI	confidence interval
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.
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
Confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
C-Path PRO	C-Path Consortium's Participant-Reported Outcome Questionnaire
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result under controlled conditions.
EOS	End of trial (study): End of study is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last subject.

Enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
Enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical study are protected.
FCSRT	Free and Cued Selective Reminding Test
FDA	United States Food and Drug Administration
GCP	good clinical practice
HABS	Harvard Aging Brain Study
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IES	Impact of Events Scale
IgG	immunoglobulin G-1
IND	Investigational New Drug application
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
Interim analysis	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
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.

ITT	intent 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 subject (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects 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.
IWRS	interactive web response system
LMIIa	Logical Memory test, part IIa
LP	lumbar puncture
LS	least squares
MAC-Q	Memory Complaint Questionnaire
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NCS	natural cubic spline
PACC	Preclinical Alzheimer's Cognitive Composite
PET	positron emission tomography
PHI	protected health information
PK/PD	pharmacokinetics/pharmacodynamics
P-tau	phosphorylated tau
QTcB	QT interval corrected using Bazett's formula
randomize	The process of assigning subjects to an experimental group on a random basis.
Re-screen	To screen a subject who was previously declared a screen failure for the same study.
RUI	Resource Use Inventory
RUI-B	Resource Use Inventory, Brief version
SAE	serious adverse event

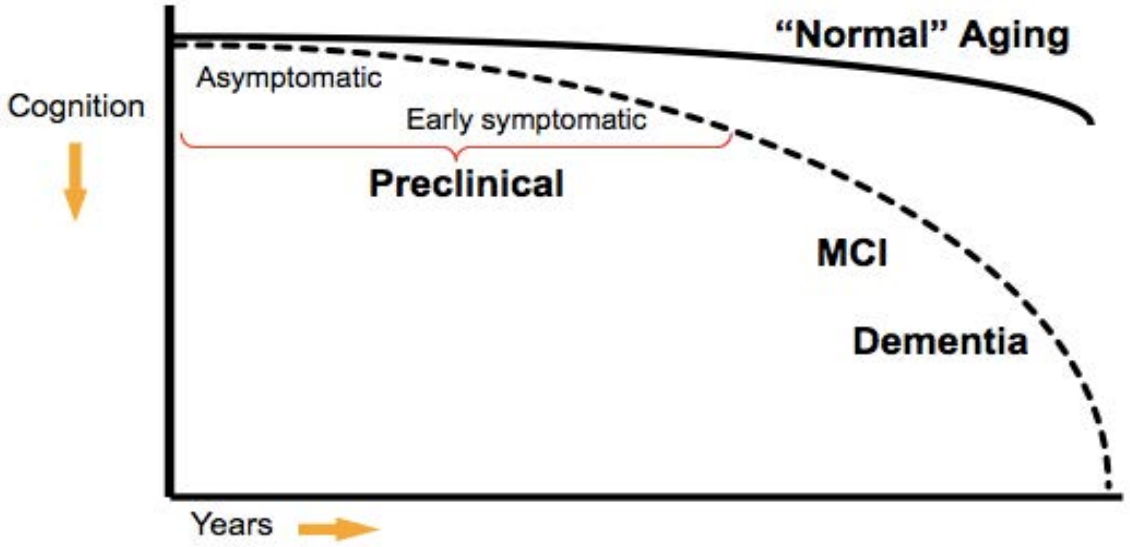
SAP	statistical analysis plan
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves diagnostic psychological tests, urine and blood sampling, MRI, PET amyloid imaging, ECG, and an optional lumbar puncture.
SSR	sample size re-estimation
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
SUSARs	suspected unexpected serious adverse reactions
SUVr	standardized uptake value ratio
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.
ULN	upper limit of normal
vMRI	volumetric magnetic resonance imaging
WAIS-R	Wechsler Adult Intelligence Scale-Revised

Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study)

5. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by a progressive decline in cognitive function and the ability to perform activities of daily living. Converging evidence suggests that the pathophysiological process of AD begins more than a decade before the clinical stage now recognized as AD dementia (Sperling et al. 2011a; Bateman et al. 2012; Villemagne et al. 2013). Even by the stage of mild cognitive impairment (MCI)/prodromal AD, the neurodegeneration of AD is thought to be well established (Gómez-Isla et al. 1996; Jack et al. 2010). Clinical trial results in mild-to-moderate AD dementia, as well as evidence from transgenic animal experiments, suggest that earlier intervention may be needed to slow the progression of the clinical course of AD, particularly with therapies designed to decrease amyloid-β (Aβ) (Sperling et al. 2011b). Academic consensus workgroups focused on developing guidelines for earlier diagnosis of AD and research diagnostic criteria have defined a stage of preclinical AD, based on biomarker evidence of AD pathology, before the stage of clinically evident cognitive impairment (Dubois et al. 2010; Sperling et al. 2011a). Recent evidence suggests that older individuals with biomarker evidence of brain amyloid accumulation demonstrate structural and functional imaging abnormalities consistent with those seen in AD dementia (Hedden et al. 2009; Sperling et al. 2009; Schott et al. 2010; Chételat et al. 2012; Andrews et al. 2013). Individuals with evidence of elevated brain amyloid (amyloid-positive) perform less well on cognitive tests compared to those without evidence of brain amyloid accumulation (amyloid-negative) and are at increased risk for cognitive decline and progression to MCI and AD (Morris et al. 2009; Rentz et al. 2010; Knopman et al. 2012; Lim et al. 2012a, 2012b, 2013; Ellis et al. 2013; Sperling et al. 2013; Vos et al. 2013; Petersen et al. 2016; Donohue et al. 2017; Mormino et al. 2017).

Alzheimer's disease has evolved to become conceptualized as a continuum of disease (Figure A4.1). The preclinical stage of AD is postulated to begin with an asymptomatic stage of accumulating brain pathology followed by very subtle cognitive decline, which can be detected with sensitive neuropsychological tests and cognitive complaint measures (Sperling et al. 2011a).



Abbreviation: MCI = mild cognitive impairment.

Figure A4.1. The continuum of Alzheimer's disease versus normal aging.

Individuals in the preclinical stage of AD have evidence of amyloid pathology and often early signs of neurodegeneration (elevated cerebrospinal fluid [CSF] tau, mild cortical thinning) but do not yet have widespread, irreversible neuronal loss. This preclinical stage of AD may precede MCI by several years and represents an important stage for potential early intervention aimed at slowing the pathophysiological process and delaying the appearance of readily appreciated clinical manifestations of AD.

In this context, a study in preclinical AD titled Anti-Amyloid Treatment in Asymptomatic AD (the "A4" study) was designed and initiated by a collaboration between the Alzheimer Disease Cooperative Study (ADCS) and Lilly. This large, multicenter, placebo-controlled study with an approximately 4.5-year treatment duration is now enrolling older individuals with evidence of brain amyloid pathology who are still clinically normal but performing in the lower end of the clinically normal range on memory measures and are at particularly high risk for cognitive decline. Partway through the study, the study management activities of the ADCS were shifted to the Alzheimer's Therapeutic Research Institute (ATRI), which serves as the Coordinating Center. Some aspects of the study will involve continued collaboration between the ADCS, ATRI, and Lilly.

Before initiation of the A4 study, the ADCS independently evaluated several investigational anti-Aβ antibodies as candidates for the study, and ultimately chose solanezumab based on its safety profile and cognitive effects in mild AD observed in the Phase 3 studies. The A4 study is funded by Lilly, the National Institutes of Health, and multiple philanthropic organizations. The A4 study is being conducted under Lilly's IND 11,631 for solanezumab (FDA correspondence, 19 March 2013); thus Lilly is the regulatory sponsor. The overall goal of the study is to test the

hypothesis that targeting Aβ in the preclinical stage of AD will slow the pathophysiological process and cognitive decline in the preclinical stages of AD, thus affecting the clinical course of the disease.

Solanezumab is a humanized anti-Aβ peptide immunoglobulin G-1 (IgG) monoclonal antibody. The murine anti-Aβ monoclonal antibody from which solanezumab was derived is known as m266.2. These antibodies recognize a mid-domain epitope of the Aβ peptide (amino acid residues 16-25). Solanezumab was designed with the intent to increase central nervous system clearance of Aβ, slow or reverse Aβ deposition in brain parenchyma, and with chronic treatment, potentially slow the progression of AD.

The clinical development program for solanezumab includes the completed Phase 3 Studies H8A-MC-LZAM (LZAM) and H8A-MC-LZAN (LZAN), also known as EXPEDITION and EXPEDITION2, respectively, which compared 400 mg of solanezumab intravenously every 4 weeks (400 mg Q4W) and placebo treatments for 18 months in subjects with mild-to-moderate AD, as well as the concluded Phase 3 open-label extension Study H8A-MC-LZAO (LZAO) in which all subjects are treated with solanezumab. Although primary objectives were not met in either Study LZAM or LZAN, prespecified secondary analyses strongly suggested cognitive effects in the mild AD population using pooled data from the 2 studies.

Based on these Phase 3 results and discussions with FDA, an additional Phase 3 study of solanezumab 400 mg Q4W in patients with mild AD and evidence of amyloid pathology, Study H8A-MC-LZAX (LZAX), was conducted. The primary endpoint was not met in the concluded placebo-controlled period of Study LZAX. Subjects treated with solanezumab 400 mg Q4W did not experience a statistically significant slowing in cognitive decline compared with subjects treated with placebo (p=.095), as measured by the 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale ($ADAS\text{-}Cog_{14}$). The study results directionally favored solanezumab, but the magnitude of the treatment difference was small. Several secondary analyses, including the Clinical Dementia Rating—Sum of Boxes score (CDR-SB), ADCS-iADL, and Mini-Mental State Examination (MMSE), showed small, nominally statistically significant benefits of solanezumab.

To date, no safety issues have been identified that would create an unfavorable benefit-risk balance for solanezumab. Few differences in the incidence of deaths, serious adverse events (SAEs), discontinuations due to adverse events (AEs), treatment-emergent adverse events (TEAEs), laboratory values, electrocardiograms (ECGs), treatment-emergent immunogenicity, treatment-emergent changes in amyloid-related imaging abnormalities (ARIA), and infusion reactions were observed between placebo- and solanezumab-treated subjects in the Phase 3 studies. In Studies LZAM and LZAN, a potential safety signal was identified for a heterogeneous set of cardiac-related events that included atrial fibrillation, bradycardia, and angina pectoris, reported in more than 1% but less than 2% of patients. The cardiac safety signal was not confirmed in Study LZAX and therefore is no longer considered a potential risk with solanezumab treatment. As measured by the Columbia Suicide Severity Rating Scale (C-SSRS), suicidal ideation and behaviors were infrequent, but a greater prevalence was observed among solanezumab- compared with placebo-treated mild AD dementia patients in Study LZAX. This

safety signal has not been observed in other solanezumab studies. At this time, it cannot be determined whether the imbalance observed in Study LZAX is causally related to solanezumab treatment. This safety signal will continue to be assessed in the ongoing A4 study. More details are available in the Investigator's Brochure (IB).

As described in the IB, 2 types of ARIA—hemosiderin deposition (ARIA-H, also known as cerebral microhemorrhage) and edema/effusions (ARIA-E, also known as vasogenic edema) and serious hypersensitivity reactions (immediate and nonimmediate) including anaphylaxis and infusion-related reactions—have been identified as potential risks for Aβ-based AD therapies. Magnetic resonance imaging (MRI) scans and AEs will be obtained in this study to assess these potential risks.

Study H8A-MC-LZAZ (LZAZ), or the A4 study ("Anti-Amyloid Treatment in Asymptomatic AD"), will test the hypothesis that treatment with solanezumab administered as an intravenous (IV) infusion every 4 weeks will slow cognitive decline in preclinical AD as compared with placebo. This study will include the use of biomarkers to assess the impact of treatment with solanezumab on biomarkers of AD pathology. The A4 Study was initially designed with a dose of 400 mg solanezumab given by IV infusion every 4 weeks over a period of approximately 3 years. Based on the new efficacy and safety results from Study LZAX described above, as well as safety and biomarker results with higher doses of solanezumab in Phase 1 and 2 studies, the solanezumab dose in the A4 Study was escalated to 1600 mg Q4W (Section 9.4). In addition, the duration of treatment was increased to approximately 4.5 years, based on new information regarding the rate of amyloid-related decline among clinically normal older individuals over time from ongoing observational studies (Section 7.2).

More information about the known and expected benefits, risks, and reasonably anticipated AEs of solanezumab may be found in the IB. Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB. Information on SAEs expected in the study population independent of drug exposure will be assessed in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to test the hypothesis that solanezumab, administered as an IV infusion every 4 weeks for 4.5 years, will slow cognitive decline as compared with placebo in subjects with preclinical AD. The primary objective will be assessed using a constrained longitudinal data analysis (cLDA) natural cubic spline (NCS) analysis (referred to as NCS henceforth) of the primary outcome measure, the Preclinical Alzheimer Cognitive Composite (PACC), a composite that is primarily weighted on episodic memory and executive function tests, in which the specific hypothesis is that the cognitive decline at Week 240 will be significantly less for solanezumab than for placebo.

6.2. Secondary Objectives

The secondary objectives of the placebo-controlled period of the study are as follows:

- To test the hypothesis that solanezumab will slow the decline of perceived cognitive function and performance of everyday activities, as compared with placebo, using an NCS analysis of the Cognitive Function Index (CFI).
- To assess whether decline in activities of daily living begins by the end of the treatment period, and if so, whether an effect of solanezumab, compared with placebo, can be detected using an NCS analysis of the ADCS-Activities of Daily Living (ADL) Prevention Questionnaire.
- To assess the relationship between treatment effect and time using the PACC.
- To test the hypothesis that solanezumab reduces brain amyloid burden, as compared with placebo, as assessed using florbetapir positron emission tomography (PET) imaging.
- To assess effects of solanezumab on CSF and plasma concentrations of total tau peptides and phosphorylated tau peptides (P-tau).
- To assess effects of solanezumab on CSF concentrations of Aβ.
- To investigate the effect of treatment with solanezumab on volumetric MRI.
- To assess the safety of solanezumab versus placebo treatment, including AEs and immunogenicity.

The secondary objectives of the open-label period of the study are as follows:

- To assess the persistence of effect of solanezumab treatment in participants with preclinical AD. That is, to test the hypothesis that patients originally randomized to receive placebo and later switched to solanezumab at the start of the open-label period do not “catch up” to patients originally randomized to receive solanezumab in the placebo-controlled period, using a randomized/delayed-start analysis. The main efficacy objective of the

open-label period will be an interim randomized/delayed-start analysis of the PACC.

- To test the hypothesis that solanezumab will continue to slow the decline associated with preclinical AD during open-label treatment, comparing participants initially randomized to solanezumab with participants initially randomized to placebo in the double-blind treatment period, using randomized/delayed-start analysis of the MMSE, CDR-SB, C3, CFI, and the ADCS-ADL Prevention Questionnaire.

6.3. Exploratory Objectives

The exploratory objectives of the study are follows:

- To assess the effect of treatment with solanezumab as demonstrated using the MMSE.
- To assess the utility of a novel computerized battery, the Computerized Cognitive Composite (C3), in predicting and tracking clinical decline and response to solanezumab.
- To assess the effects of treatment on healthcare resource utilization.
- To determine the best predictors of clinical decline based on the PACC.
- To develop novel sensitive outcome measures to improve the efficiency of future secondary prevention trials, including exploratory measures of self-reported assessment of cognitive and interpersonal functioning.
- To assess the effect of treatment with solanezumab as demonstrated using the Clinical Dementia Rating (CDR) scale.
- To assess the effect of treatment with solanezumab as demonstrated using the C-Path Consortium's Participant-Reported Outcome Questionnaire (C-Path PRO).
- To investigate the impact of solanezumab on markers of synaptic dysfunction on functional connectivity MRI.
- To assess solanezumab-associated changes in levels of plasma Aβ species and CSF Aβ species. The hypothesis that solanezumab, unlike placebo, alters amyloid-plaque associated forms of Aβ will be assessed by 1) demonstrating presence of plaque-associated Aβ species in the plasma, and 2) confirming that concentrations of CSF free (unbound to antibody) $A\beta_{1-42}$ are increased or unchanged and CSF free $A\beta_{1-40}$ levels are decreased with solanezumab treatment.
- To explore whether baseline markers of neurodegeneration (volumetric MRI or CSF tau or p-tau) are related to cognitive decline and response to treatment with solanezumab.
- To explore the impact of disclosure of amyloid status on questionnaires probing perception of amyloid imaging and concern about developing AD.

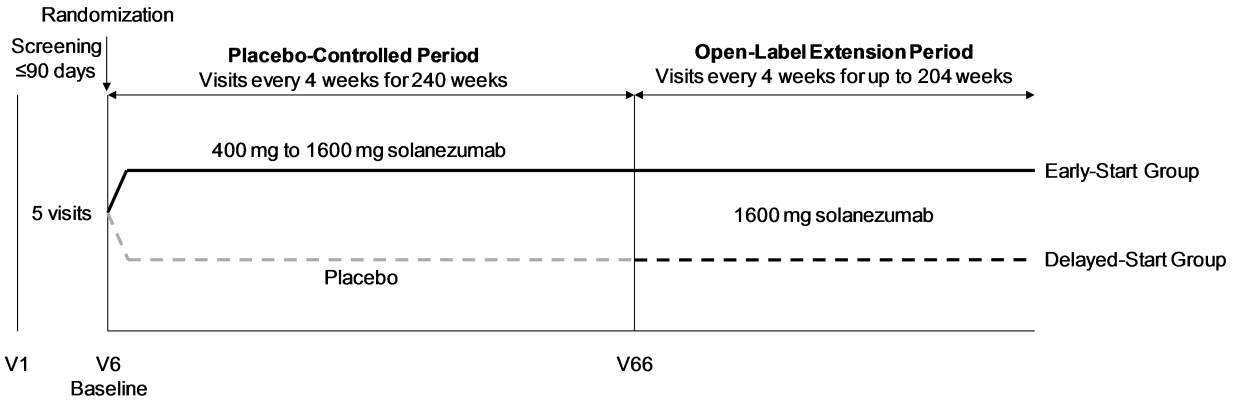
- To explore biomarker assessments collected at baseline and at the end of the placebo-controlled period as potential predictors of treatment effect during the open-label period.
- To assess preclinical AD during open-label treatment by comparing participants initially randomized to solanezumab in the placebo-controlled period with participants initially randomized to placebo in the double-blind treatment period, using randomized/delayed-start analysis of the RUI-B.

7. Investigational Plan

7.1. Summary of Study Design

The A4 Study is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study comparing solanezumab with placebo for 240 weeks in approximately 1150 subjects ages 65 to 85 years old with preclinical AD, defined as having evidence of brain amyloid pathology without clinically evident cognitive impairment at screening. Subjects who meet entry criteria will be randomized in a 1:1 ratio (approximately 575 per treatment arm) to solanezumab or placebo once every 4 weeks. Subjects will be randomized at the site by education – high (13 or more years) or low (12 or less years) and the presence of one or more apolipoprotein E gene (APOE) ε4 alleles (yes, no). The primary hypothesis being tested is that the cognitive decline at the end of the treatment phase will be significantly less for solanezumab than for placebo. Subjects completing the placebo-controlled period of the study can opt to participate in the open-label period of the study that will last for up to 204 weeks or until the primary analyses of the placebo-controlled period of the study are completed and reviewed.

Figure A4.2 illustrates the study design. The Study Schedule (Attachment 1) details procedures and tests occurring at specific times during the study.



Abbreviation: V=visit.

Figure A4.2. A4 study design.

7.1.1. Prescreening

During the prescreen phase, potential subjects will be identified and assessed to determine if they may potentially qualify for the A4 study following the site's standard practice.

7.1.2. Screening Phase (Visits 1 to 5)

The entire screening period spans the time from Visit 1 to Visit 5. Study assessments are shown in the Study Schedule (Attachment 1).

Up to 90 days are permitted to allow for completion of all screening procedures, assessments, Aβ status disclosure, and evaluation of results from laboratory tests, ECGs, PET imaging, MRI, and optional lumbar puncture (LP). A central read of the MRI should be completed before an LP is performed.

The subject can only proceed to baseline (Visit 6) once all screening procedures as described in the Study Schedule (Attachment 1) are completed and the investigator or qualified designee and clinical monitor have confirmed that the subject is eligible to be randomized.

Current or planned use of concomitant medications, the effects of vacations or absences on protocol compliance, and general compliance with the protocol will be discussed during the screening phase. Subjects who do not meet all inclusion criteria or who meet any exclusion criteria will not be allowed to participate in the study.

7.1.2.1. Initial Screening Visit (Visit 1)

At or before the first screening visit (Visit 1), the full A4 study will be explained to the subject and study partner. Informed consent and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization must be obtained from the subject before any study procedures are conducted.

All subjects will be educated about amyloid imaging as part of the recruitment and informed consent process. The Columbia Suicide Severity Rating Scale (C-SSRS) and psychological well-being questionnaires will be administered. This information will be used to help the clinician determine whether or not a subject is psychologically able to participate further in the study and to provide a pretest baseline for predisclosure comparison on these measures. Additionally, questionnaires to explore subjects' views and perceptions of amyloid imaging, concerns about AD, and perception of time will be administered.

During the initial screening visit (Visit 1), the MMSE, Logical Memory test part IIa (LMIIa), and CDR will be administered in order to determine the subject's general eligibility for the study. Safety measures will be collected to further ensure the subject meets eligibility criteria: medical history/concurrent medications are reviewed, and physical/neurological exam, ECGs, and vital signs will be collected. A blood draw and urinalysis for screening labs, genotyping, and biomarker samples will be performed. Screening labs results must be reviewed by the investigator or qualified designee for assessment of the subject's eligibility.

For a complete list of all Visit 1 procedures, please refer to the Study Schedule (Attachment 1). Procedures for Visit 1 may be completed over multiple days but all Visit 1 procedures must be completed before the subject can proceed to the screening florbetapir PET scan (Visit 2).

7.1.2.2. Screening Florbetapir PET Scan (Visit 2)

A florbetapir PET scan will be performed for eligibility purposes during the screening phase. In order to best identify a population that is at risk of decline, a centralized PET lab will be used to determine eligibility for the study based on both visual and quantitative metrics for elevated amyloid burden.

Information regarding study eligibility for each subject will be conveyed to the site principal investigator. All subjects will be scheduled for an in-clinic visit to disclose the florbetapir PET scan results (Section 7.1.2.3).

Specific instructions for the florbetapir PET scan will be provided in the Technical Operations Manual.

7.1.2.3. Amyloid Status Disclosure (Visit 3)

The C3 and C-Path PRO will be administered at this visit prior to disclosure. The C3 will be optional in Japan.

All subjects that undergo a florbetapir PET scan will have their results disclosed during an in-clinic visit with a clinical investigator approved for this role by the Coordinating Center. Study partner attendance is not required, but may be permitted if the subject desires. Each subject's concern about developing AD and his/her views and perceptions of amyloid imaging, as well as perception of time, will be assessed via questionnaires after the disclosure.

Lastly, the Impact of Events Scale (IES) will be administered over the phone within 3 business days following the amyloid status disclosure visit.

For a complete list of all Visit 3 procedures, please refer to the Study Schedule (Attachment 1).

Subjects who meet florbetapir PET entry criteria will proceed to the next visit per the study schedule.

7.1.2.4. Screening MRI Scan (Visit 4)

All subjects who have elevated amyloid as determined by the screening florbetapir PET scan and wish to, and are eligible to continue in the study after the amyloid eligibility disclosure visit will proceed to the MRI visit.

There are core magnetic resonance sequences required for all subjects to determine eligibility for the study and to acquire baseline volumetric and functional data for subsequent comparison. There are additional magnetic resonance sequences that will be acquired depending on scanner type.

Sites must submit the MRI scan without patient identifiable information to the Coordinating Center in a timely fashion (preferably within 24 hours) after acquisition to facilitate central read.

A central read will be conducted to assist in determining eligibility for the study on the basis of MRI findings, particularly the presence of microhemorrhages. In instances where more than 4 microhemorrhages or any ARIA-E are identified, the scan will be flagged for review and the subject will be deemed ineligible for the study. Other findings that are flagged during the central read will be reviewed by the Project Director and Medical Monitors or designees to determine if the subject is eligible to continue. For patients with mild to moderate AD, the presence of ARIA-E at baseline is extremely uncommon (<0.5%, Carlson et al. 2011); thus, in subjects with preclinical AD, the rate of ARIA-E at baseline is likely to be even less prevalent.

Eligible subjects will proceed to Visit 5 if they consented to the optional LP, otherwise they will proceed to baseline (Visit 6).

For a complete list of all Visit 4 procedures, please refer to the Study Schedule (Attachment 1).

Specific instructions for the screening MRI scan will be provided in the relevant procedures manual.

7.1.2.5. Optional Lumbar Puncture (Visit 5)

The optional LP study is available only in the US, Canada, and Japan. Subjects who consent to the optional LP will have an LP performed at Visit 5. Magnetic resonance imaging, and central read of the MRI, should occur prior to LP.

Failure to perform an LP or obtain CSF will not constitute a protocol violation.

Specific instructions for the LP will be provided in the relevant procedures manual.

7.1.3. Placebo-Controlled Period (Visits 6 to 66)

The placebo-controlled period is a double-blind treatment phase beginning at baseline (Visit 6). Subjects who meet entry criteria will be enrolled and randomized to receive either solanezumab or placebo once every 4 weeks administered on site as an IV infusion. Subjects should be observed for approximately 1 hour following the first infusion of study drug. Infusions will be administered and assessments will be performed according to the Study Schedule (Attachment 1). Procedures for some visits may take more than 1 day. At the following visits (known as "infusion-only" visits), the only scheduled procedures are administration of the infusion and collection of AEs and concomitant medications: Visits 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43, 44, 46, 47, 49, 40, 52, 53, 55, 56, 58, 59, 61, 62, 64, and 65.

All visits (in-clinic and infusions) after randomization (Visit 6) should be scheduled to occur as close as possible to the target date, relative to baseline Day 1. A window of ±10 days will be permitted for all visits.

Final assessments in the placebo-controlled period will be performed at Visit 66 (Week 240), 4 weeks following the subject's last dose of study medication (Week 236) in the placebo-controlled period.

7.1.4. Dose Escalation

All subjects will be escalated to a dose of 1600 mg Q4W according to amendment (d). After at least 2 infusions of 400 mg Q4W, subjects will be escalated to 800 mg Q4W for at least 2 infusions, and then 1600 mg Q4W until the conclusion of the treatment (Section 9.1).

At a minimum, the first 200 subjects (approximately 100 each in the solanezumab and placebo treatment groups) who receive the increased dose will be included in a dose escalation safety cohort to receive additional safety assessments and monitoring (described in Section 10.2.11) during dose escalation to monitor the safety of the higher doses.

Subjects who escalate dose after entry in the dose escalation safety cohort has been closed will receive safety monitoring as described in the main Study Schedule.

All subjects who are active in the study should be escalated to a dose of 1600 mg Q4W as described above. Subjects may be permitted to delay dose escalation at the investigator's discretion; this will not be considered a protocol deviation.

Additional site training will be provided to ensure appropriate implementation of the protocol modifications.

7.1.5. Open-Label Extension Period

Subjects who complete the placebo-controlled period will be eligible to participate in the open-label extension period. Subjects participating in the open-label period will receive open-label solanezumab treatment for varying durations. While all subjects will receive solanezumab treatment during the open-label period, subjects, site personnel, and study teams will remain blinded to initial treatment assignment in the placebo-controlled period until the conclusion of the study.

The open-label period uses a common close design such that all subjects will complete the period at the same time: when analyses of the placebo-controlled period are completed and reviewed. Given the common close design, the overall duration of treatment for each patient will differ. If the study is positive, participants may be offered the opportunity to continue in the open-label period beyond the common close. Subjects who opt to participate in the open-label period should begin the open-label period at Visit 66 (Week 240) after completion of all Visit 66 tests and procedures. However, subjects may enter the open-label period of the study and receive their first open-label infusion of study drug up to 12 weeks following completion of the placebo-controlled period Visit 66 assessments and procedures. In extenuating circumstances, subjects may enter the open-label period after 12 weeks with the approval of a Medical Monitor and/or Project Director. See the Study Schedule (Attachment 1) for the timing of events and measures to be assessed. Procedures for some visits may take more than 1 day.

Subjects who choose not to participate in the open-label period will not receive any study medication after the last infusion visit for the placebo-controlled period (Week 236). Sites must obtain approval from the Coordinating Center before engaging in open-label activities.

If the open-label period is extended beyond Visit 117, participants who complete Visit 117 before implementation of the protocol amendment that includes additional visits will be allowed to resume study visits once available at their site.

7.2. Discussion of Design and Control

Study Population. As AD is thought to represent a continuum of disease, discrete stages of AD will of necessity need to be operationally defined. Entry criteria were chosen to maximize selection of individuals who are still considered clinically normal but who may be at high risk of subsequent cognitive decline and the eventual onset of clinical signs and symptoms diagnostic of prodromal or mild AD. Cut-points for screening memory tests will exclude individuals who are

performing >0.5 standard deviation (SD) above age- and education-adjusted normative means, as these individuals may be better able to compensate for imminent cognitive decline over the course of the study. Instead, the study will enroll people who have memory performance down to 1.0 SD below education-adjusted normative means, which overlaps the cognitive performance range of early MCI without meeting the definition for MCI (since CDR must be 0). Recent evidence suggests that people with evidence of amyloid pathology are more likely to perform in the bottom of the "normal range" on sensitive neuropsychological tests and have a higher risk of cognitive decline and progression to MCI and AD dementia (Doraiswamy et al. 2012; Knopman et al. 2012; Sperling et al. 2013; Villemagne et al. 2013). Furthermore, subjects are required to be ages 65 to 85 at the time of screening, to maximize the likelihood of identifying subjects that will meet the preclinical AD amyloid pathology inclusion criteria, as research in the field suggests that incidence/prevalence of amyloid pathology is highest in this group compared to those under age 65. Measures will be in place to ensure sufficient enrollment of individuals at the higher end of this age range and to enroll under-represented minority populations.

Selection of Primary Outcome Measure. The PACC composite measure, which comprises the Total Recall score from the Free and Cued Selective Reminding Test (FCSRT), the Delayed Paragraph Recall score on the Logical Memory IIa test from the Wechsler Memory Scale, the Digit-Symbol Substitution test from the Wechsler Adult Intelligence Scale-Revised, and the MMSE total score, was developed to be sensitive to change in preclinical AD, based on evidence that episodic memory, executive function, and orientation are domains that show change early in the course of disease. Several combinations of measures for these domains derived from well-accepted clinical outcome measures were assessed using data from longitudinal studies in clinically normal populations, comparing patients who declined from normal to MCI to those who remained normal. The combination of measures that showed the greatest power was one that included episodic memory, timed executive function, and global measures (including orientation) and this combination became the PACC (see Attachment 3 for more details).

Study Duration. Based on evidence from longitudinal studies available when Study LZAZ/A4 was initially designed, a duration of 168 weeks (approximately 3 years) was thought to be appropriate to evaluate the efficacy of solanezumab compared with placebo in slowing progression of preclinical AD. However, new data regarding the amount of decline over time in the preclinical AD population became available from observational studies during the conduct of the A4 study, suggesting that extending the treatment duration may increase the likelihood of observing a treatment effect. For example, data from ongoing observational studies, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Australian Imaging, Biomarker and Lifestyle (AIBL) study, and the Harvard Aging Brain Study (HABS) suggest that amyloid-related decline among clinically normal older individuals accelerates between 3 and 6 years of observation (Lim et al. 2016; Donohue et al. 2017; Mormino et al. 2017; Papp et al. 2017). Differences in decline, as measured by the PACC, the primary outcome measure in the A4 study, between Aβ-negative and Aβ-positive clinically normal individuals increase over time, with the greatest increases at the 4- and 5-year time points (Section 11.1). Therefore, the A4 study duration was increased to 240 weeks (approximately 4.5 years).

Open-Label Period. An open-label period was added to the A4 study to determine whether effects of solanezumab observed at the end of the placebo-controlled period, in participants originally assigned to solanezumab (early start), are maintained over a longer period of time, in comparison to the participants originally assigned to placebo who start during the open-label extension period (delayed start). If such maintenance is observed, that will indicate a persistent effect on disease course that is not observed when starting treatment later. Specifically, it is hypothesized that the early-start group will show attenuated cognitive decline compared to delayed start, and that the delayed-start group will not "catch-up" to the early-start group that was continually treated with solanezumab, consistent with disease modification. Secondary analyses to determine long-term effects of solanezumab on clinically meaningful functional outcomes will be investigated. In addition, the influence of pathophysiologic disease stage, as assessed by biomarkers, on treatment response, will be explored in the open-label period. The open-label period will extend up to 204 weeks, until the primary efficacy analyses from the placebo-controlled period are completed.

8. Study Population

The population for this study can be characterized as at-risk clinically normal individuals with preclinical AD based on evidence of brain amyloid pathology and cognitive performance in the lower range of education-adjusted norms, which in combination puts these individuals at a high risk for decline.

Eligible subjects will be males and females with preclinical AD, as specified in the entry criteria that follow. Individuals who fail screening due to ineligible results on the amyloid PET scan may not be re-screened. One re-screen may be permitted if subject fails screening for some other reason.

Subjects who meet all of the inclusion criteria and are not excluded by any of the exclusion criteria are considered eligible. Subjects with subjective memory complaint are permitted to enter as long as they receive a global CDR score of 0.

Study participants should be instructed not to donate bodily fluids during the study or for 12 weeks after receiving the last dose of study medication.

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

8.1. Inclusion Criteria

A subject is eligible to be included in the study only if he or she meets all of the following criteria:

[1] Male or female ages 65 to 85 years old.

[2] Has an MMSE score at screening of 25 to 30.

[3] Has a global CDR score at screening of 0.

[4] Has a Logical Memory II score at screening of 6 to 18.

[5] Has a florbetapir PET scan that shows evidence of brain amyloid pathology at Visit 2.

[6] In general, permitted medications should be stable for 6 weeks prior to baseline (Visit 6). Changes to medications that, in the opinion of the investigator, are not likely to impact baseline visit assessments are permissible.

[7] Has a study partner that is willing to participate as a source of information and has at least weekly contact with the subject (contact can be in-person, via telephone or electronic communication). The study partner must have sufficient contact such that the investigator feels the study partner can provide meaningful information about the subject's daily function.

[8] In the investigator's opinion, is both willing and able to participate in all required procedures for the duration of the study (at least 240 weeks), including adequate literacy in English, Spanish, or Japanese, and adequate vision and hearing to complete the required psychometric tests.

8.2. Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

[1] Is receiving a prescription acetylcholinesterase inhibitor (AChEI) and/or memantine at screening (Visit 1) or baseline (Visit 6).

[2] Lacks good venous access, such that IV drug delivery or multiple blood draws would be precluded.

[3] Has current serious or unstable illness including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic, psychiatric, immunologic, or hematologic disease or other conditions that, in the investigator's opinion, could interfere with the analyses of safety and efficacy in this study.

[4] Has had a history within the last 5 years of a serious infectious disease affecting the brain (including neurosyphilis, meningitis, or encephalitis) or head trauma resulting in protracted loss of consciousness.

[5] Has had a history within the last 5 years of a primary or recurrent malignant disease, with the exception of any in situ cancer that was appropriately treated and is being appropriately monitored, such as resected cutaneous squamous cell carcinoma in situ or in situ prostate cancer with normal prostate-specific antigen post-treatment.

[6] Has allergies to humanized monoclonal antibodies.

[7] Has a known history of HIV, clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).

[8] Has a history within the past 5 years of chronic alcohol or drug abuse/dependence as defined by the most current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM).

[9] Has a history within the past 2 years of major depression or bipolar disorder as defined by the most current version of the DSM.

[10] Has a history of schizophrenia as defined by the most current version of the DSM.

[11] Is clinically judged by the investigator to be at serious risk for suicide.

[12] Has a current or recent (within 6 weeks prior to baseline [Visit 6]) laboratory result (if available) that indicates a clinically significant laboratory abnormality that may influence baseline assessments as determined by the investigator. Will allow thyroid or B12 insufficiency if adequately treated for 3 months prior to screening (Visit 1).

[13] Has ECG obtained during screening that, in the opinion of the investigator, is clinically significant with regard to the subject's participation in the study. Bazett's corrected QT (QTcB) interval must be evaluated and must not exceed >458 msec in males or >474 msec in females.

[14] At screen, has alanine aminotransferase (ALT/SGPT) values >2X the upper limit of normal (ULN) of the performing laboratory, aspartate aminotransferase (AST/SGOT) values >3X ULN, or total bilirubin values >2X ULN.

[15] Has a screening MRI scan (Visit 4) with results showing >4 hemosiderin deposits (definite microhemorrhages or areas of superficial siderosis); or any ARIA-E.

[16] Has any contraindications for MRI studies, including claustrophobia, the presence of metal (ferromagnetic) implants, or a cardiac pacemaker that is not compatible with MRI.

[17] Resides in a skilled nursing facility.

[18] Is receiving any medication that has significant central nervous system (CNS) effects that in the investigator's opinion would interfere with cognitive testing and protocol compliance. The procedures manual provides a list of medications that impair cognition that are permitted in the study but need to be withheld prior to cognitive testing.

[19] Has previously completed or withdrawn from this study or other solanezumab studies, or previous participation in any study investigating active immunization against Aβ.

[20] Has previously completed or withdrawn from a study of passive immunization with another antibody within the last 120 days.

[21] Pregnant, lactating or of child bearing potential (that is, women must be 2 years post-menopausal or surgically sterile to be considered not child bearing potential).

[22] Is investigator site personnel directly affiliated with this study and/or immediate family, or has a study partner who is investigator site personnel directly affiliated with this study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[23] Is an ADCS, ATRI, or Lilly employee, or has a study partner who is an ADCS, ATRI, or Lilly employee.

[24] 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 Project Director or one of the Medical Monitors.

For subjects participating in LP, all of the above, plus:

[25] Current use of anticoagulants, such as warfarin or dabigatran.

8.2.1. Rationale for Exclusion of Certain Study Candidates

Inclusion Criteria [2] through [4] eliminate subjects who already have manifest dementia in favor of subjects likely to have preclinical AD. Inclusion Criterion [5] ensures brain amyloid pathology to eliminate subjects at low risk of cognitive decline. Inclusion Criteria [7] and [8] ensure that the subject and a study partner will be available and able to comply with protocol requirements. Exclusion Criterion [1] eliminates subjects receiving common AD treatments since such subjects are likely to be at a later stage of AD. Exclusion Criterion [2] prevents incomplete dosing of study drug. Inclusion Criterion [6] and Exclusion Criteria [3] through [17], [21], and [24] protect subject safety or analysis of safety. Exclusion Criteria [18] through [20] exclude subjects whose concomitant medication dosing could confound the results of the study in the analysis of the PACC. Exclusion Criteria [22] and [23] reduce both the possibility of coercion and the potential for bias that may be introduced at the study site. Exclusion Criterion [25] protects safety for those participating in the optional LP.

8.3. Inclusion and Exclusion Criteria: Open-Label Extension Period

All participants who complete the placebo-controlled period will be allowed to continue into the open-label period, even if they no longer meet the initial inclusion criteria. Specifically, participants who have progressed to a Clinical Dementia Rating—Global score (CDR-G) of >0, started anticholinergic medications or other treatment for AD, or have accumulated ≥5 microhemorrhages will be eligible to continue into the open-label period.

8.4. Discontinuations

8.4.1. Discontinuation of Subjects

The criteria for enrollment must be followed explicitly. If the investigator site identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the Project Director must be notified. If the Monitor identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. Inadvertently enrolled subjects may be maintained in the study and on investigational product when the Project Director agrees with the investigator that it is medically appropriate for that subject. The investigator must obtain documented approval from the Project Director to allow the inadvertently enrolled subject to continue in the study.

Subjects who do not meet entry criteria or who are excluded by exclusion criteria from screening tests and procedures should be discontinued from the study before randomization.

Subjects who exhibit any of the following conditions during the study may be discontinued from the study.

- Appearance of clinically significant new cerebral ischemic or hemorrhagic events or symptomatic ARIA-E or greater than 4 new microhemorrhages detected on the central read on follow up MRI scans will be flagged for review by the central review. Subject may be able to continue to participate in the study depending on clinical significance as determined by the Project Director, Medical Monitor, and the Site 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 treatment until the symptoms are resolved. If a subject simultaneously develops more than 1 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 scan may be obtained. A single symptom suggestive of ARIA-E of sufficient severity may also warrant an MRI scan. The unscheduled MRI scan should be performed in the same manner as the currently scheduled MRI scans in the protocol, which includes sending the images for central review. For guidance, please refer to the instructions described in the relevant procedures manual.

- Prolonged acute infusion 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 infusion reactions may occur with any agent that causes cytokine release (for example, some 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. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever), arthralgia, bronchospasm, cough, dizziness, dyspnea, fatigue, headache, hypertension, hypotension, myalgia, nausea, pruritus, rash, rigors/chills, sweating (diaphoresis), tachycardia, urticaria, and vomiting.

- Discontinuation of the study drug for abnormal liver tests should be considered by the investigator when a subject meet 1 of the following conditions after consultation with the 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 >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%)

In addition, subjects may be discontinued from the study drug and from the study in the following circumstances, including but not limited to:

- Mean QTcB >500 msec and an absolute change >60 msec when compared with baseline (the most recent measurement made at either screening [Visit 1 through 5] or baseline [Visit 6]).
- 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
- Investigator Decision
  - The investigator decides that the subject should be discontinued from the study.
  - If the subject, 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.
- Subject Decision
  - The subject requests to be withdrawn from the study.
- Sponsor Decision
  - ATRI or Lilly or its designee stops the study.
- Adverse Event
  - If the investigator and/or the subject decides that the subject should be withdrawn because of an SAE or other clinically significant AE, the investigational product is to be discontinued and appropriate measures are to be taken. ATRI or Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations (Section 10.2).

Subjects who discontinue early from the investigational product and/or study early will be encouraged to have an early termination visit at the point of discontinuation, with procedures performed as shown in the Study Schedule (Attachment 1). Refer to the relevant procedures manual for further detail.

8.4.2. Discontinuation of Study Sites

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

8.4.3. Discontinuation of the Study

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

8.5. Recruitment and Retention Strategies

Recruitment will occur through a variety of mechanisms. ATRI will use a coordinated recruitment plan to ensure that enrollment occurs in a timely fashion. The overall goals of the plan are to raise awareness of AD trials among targeted populations to ensure adequate enrollment. Through relationships with the National Institute on Aging (NIA) and coordination with its Alzheimer's Disease Education and Referral Center, existing resources are being leveraged. The study recruitment and retention team will develop materials specific to the A4 study for use by the sites, provide ongoing recruitment assistance and support, and develop tracking procedures to monitor effectiveness of recruitment efforts.

9. Treatment

9.1. Treatments Administered

This study was initiated as a comparison of solanezumab 400 mg compared with placebo. The active drug group was given an IV infusion of solanezumab 400 mg once every 4 weeks. The study protocol was amended to increase the dose; subjects will be escalated to 800 mg Q4W for at least 2 infusions, and then 1600 mg Q4W until the conclusion of the treatment, as described below (Table A4.1). Dosing should be once every 4 weeks; a minimum of 14 days between infusions is required.

Table A4.1. Treatment Regimens

Regimen	Dose from Visit 6 (Week 0) through Visit 65 (Week 236), Placebo-Controlled Period
Solanezumab	• 400 mg IV infusion every 4 weeks for at least 2 doses[a], and then: • 800 mg IV infusion every 4 weeks for at least 2 doses, and • 1600 mg IV infusion every 4 weeks through Week 236
Placebo	sterile saline solution (0.9% sodium chloride) IV infusion every 4 weeks (infusion volumes to increase accordingly with dose escalation paradigm as described in the operations manual)
	Dose from Visit 66 (Week 240) through Visit 116 (Week 440), Open-Label Period
Early-start solanezumab[b]	1600 mg IV infusion every 4 weeks through Week 440[c]
Delayed-start solanezumab[b]	• 400 mg IV infusion every 4 weeks for at least 2 doses[a, c], • 800 mg IV infusion every 4 weeks for at least 2 doses[c], and • 1600 mg IV infusion every 4 weeks through Week 440[c]

Abbreviation: IV = intravenous.

[a] Subjects who initiated the study before the implementation of amendment (d) may have more than 2 doses of 400 mg Q4W.

[b] "Early-start solanezumab" refers to the treatment regimen received by subjects randomized to solanezumab in the placebo-controlled period who continue to receive solanezumab in the open-label period. "Delayed-start solanezumab" refers to the treatment regimen received by subjects randomized to placebo in the placebo-controlled period who switch to solanezumab treatment in the open-label period.

[c] Subjects who are receiving 400 mg Q4W or 800 mg Q4W when they complete the placebo-controlled period may be maintained at that dose in the open-label period.

Changes in the escalation schedule may be made at the investigator's discretion with the notification of a Medical Monitor.

The investigator or his/her designee is responsible for the following:

- Explaining the correct use of the investigational agent(s) to the site personnel
- Verifying that instructions are followed properly
- Maintaining accurate records of investigational product dispensing and collection
- Returning all unused medication to Lilly or its designee at the end of the study

Subjects 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.

9.2. Materials and Supplies

The site will be provided vials containing 400 mg/20 mL of solanezumab (or placebo). The vials should be stored at 2ºC to 8ºC (36ºF to 46ºF). Normal sterile saline solution (0.9% sodium chloride) will be used for dilution. Details regarding preparation of the infusion are provided in the procedures manual.

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 should be made. After each IV bag is prepared, it will be identified as a dose of study drug without identification of the drug or dose. Once prepared, the infusate solution should be stored at room temperature for a total of no more than 6 hours.

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

9.3. Method of Assignment to Treatment

Subjects who meet all criteria for enrollment will be randomized in a 1:1 ratio to double-blind treatment at baseline (Visit 6). For between-group comparability, subjects will be randomized within site by education – high (13 or more years) or low (12 or less years), and by the presence of one or more APOE ε4 alleles (yes, no). Assignment to treatment groups will be determined by a computer-generated random sequence.

An interactive web response system (IWRS) will be used to assign which vials are to be used for dosing for each subject. Site personnel will confirm that they have located the correct vial by entering a confirmation number found on the label into the IWRS.

9.4. Rationale for Selection of Doses in the Study

The A4 study was initiated with active drug of solanezumab 400 mg given intravenously every 4 weeks (400 mg Q4W). Selection of the 400 mg Q4W dose was based largely but not entirely upon the peripheral sink hypothesis, which held that maximizing peripheral target engagement would change Aβ equilibria, resulting in altered amyloid deposition in the central compartment, ultimately leading to a slowing of disease progression. The 400 mg Q4W dose was selected to lower free plasma Aβ concentrations by at least 90%, a level that exceeded what had been associated with slowing of amyloid plaque deposition in transgenic rodent species.

The primary endpoint was not met in the recently concluded Phase 3 Study LZAX of solanezumab 400 mg Q4W in subjects with mild dementia due to AD, defined by a baseline MMSE score of 20 to 26. Subjects treated with solanezumab did not experience a statistically significant slowing in cognitive decline compared with subjects treated with placebo (p=.095), as measured by the 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog14). The study results, including several secondary clinical endpoints, directionally favored solanezumab, but the magnitudes of treatment differences were consistently small. In general, safety findings were consistent with those observed previously in Studies LZAM and LZAN.

Safety analyses from Studies LZAM and LZAN individually and the pooled LZAM and LZAN data indicated a potential safety signal for a heterogeneous set of cardiac events, but this signal was not confirmed based on data from Study LZAX. As measured by the Columbia Suicide Severity Rating Scale (C-SSRS), suicidal ideation and behaviors were infrequent, but greater frequency was observed among solanezumab- compared with placebo-treated patients in Study LZAX. This safety signal has not been observed in other solanezumab studies. At this time, it cannot be determined whether the imbalance observed in Study LZAX is causally related to solanezumab treatment. Lilly will continue to assess this safety signal in the A4 study. The negative efficacy outcome of Study LZAX suggests that an approach to dose selection based on peripheral target engagement may not predict clinical efficacy in Phase 3 trials. Thus, central target engagement based on biomarkers may provide better predictive value for Phase 3 dose selection.

Phase 2 solanezumab data suggest greater central target engagement may be achieved with dosing greater than 400 mg Q4W. A dose of 400 mg every week (400 mg QW), which is equivalent to 1600 mg over a 4-week period, was given in Phase 2 Studies LZAJ and LZAK, and showed an increased CSF Aβ signal and an acceptable safety profile.

Exposure–response analyses were conducted following the completion of Studies LZAM, LZAN, and LZAX, but given that only a single dose level was administered in these studies, no compelling relationship between exposure and change in various cognitive endpoints could be discerned.

Biomarker data from patients receiving LPs in Studies LZAM, LZAN, and LZAX suggest that the effect of solanezumab on $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ species in the CNS (central target engagement) was present but relatively modest in those studies. Total Aβ concentrations tended to increase with increasing solanezumab concentrations in the CSF, without reaching an apparent plateau, suggesting that higher solanezumab exposures in the CNS would lead to higher levels of target engagement. Indeed, total $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ concentrations were observed to be substantially higher, with a dose of 400 mg QW examined after 12 weeks of dosing in the Phase 2 Study LZAJ, as compared with the Q4W dosing regimen.

To date, the pharmacokinetics (PK) of solanezumab have been explored in single doses up to 10 mg/kg (approximately 700 mg), or multiple doses of up to 400 mg QW. The PK of solanezumab have been linear with respect to dose, and stationary with respect to time. Accordingly, the average plasma solanezumab concentration over 4 weeks at a dosing regimen of 1600 mg Q4W would be anticipated to be equivalent to the exposure over 4 weeks at the previously tested 400 mg QW dosing regimen. This projected exposure is less than the no-observed-adverse-effect level (NOAEL) exposure determined in monkeys as part of a 12-month chronic toxicology study. Assuming linear PK, the projected C_{max} at 1600 mg Q4W is anticipated to provide an exposure multiple that is similar to that calculated for the projected average concentration.

Solanezumab was well tolerated in monkeys, with no adverse effects observed at the maximum dose studied, 100 mg/kg. Solanezumab exposures at 1600 mg Q4W were projected using

clinical data collected at 400 mg Q4W. These exposure estimates provide a 5.8X multiple to the exposures in monkeys at the 100 mg/kg dose.

The safety of higher doses than 400 mg Q4W has also been studied during the solanezumab development program. Single ascending-dose Studies H8A-LC-LZAH (LZAH) and H8A-JE-LZAI (LZAI) investigated the safety and tolerability of solanezumab in AD patients at doses up to 10 mg/kg, which is approximately equivalent to 700 mg. The safety findings from these studies (described below) suggested an acceptable safety profile for continued development of solanezumab. Phase 2 Studies LZAJ (12-week treatment duration) and LZAK (8-week treatment duration) included doses of 400 mg QW, the equivalent of 1600 mg of solanezumab in each 4-week period; these studies (described below) also demonstrated an acceptable safety profile for solanezumab.

In Studies LZAH and LZAI, a total of 8 patients received single doses of solanezumab 10 mg/kg. Three patients reported AEs that were related to solanezumab in the opinion of the investigator. Two of these patients experienced AEs, including feeling cold, mild tremor, chest pressure, and mild dizziness, that were judged by the investigator to be most likely due to infusion reactions, similar to the infusion-type reactions described with other intravenously administered proteins. For these 2 patients, the symptoms were mild and resolved without specific treatment (for example, antihistamines). A third report considered related to study drug, muscle spasms, occurred 0.1 hour after infusion and lasted 0.5 hours.

In Studies LZAJ and LZAK, a total of 22 patients received solanezumab 400 mg QW for 8 to 12 weeks. The most commonly reported AEs were back pain, confusional state, cough, hyperhidrosis, and nausea, reported in 2 patients each.

Studies LZAH, LZAI, and LZAJ were completed before ARIA-H and ARIA-E were understood as potential risks for anti-amyloid therapies, and thus ARIA-H and ARIA-E were not specifically assessed on MRI. However, subjects underwent baseline and follow-up MRI scans, and no changes in MRI were reported as AEs or SAEs. Study LZAK was the first study of solanezumab that specifically assessed for ARIA-H and ARIA-E on MRI. Magnetic resonance imaging scans were obtained at Week 4 and Week 8 (after the final infusion). No ARIA-E, ARIA-H, or infusion reactions were reported in this study. There were no changes in MRI reported as AEs or SAEs.

Taken together, these data suggest that increasing the dose to 1600 mg Q4W is appropriate to increase the probability of observing a treatment effect in the study while maintaining subject safety.

9.5. Administration and Timing of Doses

Details about infusion preparation and timing of administration are provided in the procedures manual. If a subject demonstrates an infusion reaction to the study drug, the subject may be premedicated with antihistamine (such as diphenhydramine hydrochloride, 50 mg orally or intravenously), 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. Subjects should be

observed for approximately 1 hour following the first infusion of 400 mg in the placebo-controlled period. Subjects on dose escalation safety cohorts will be monitored post infusion as mentioned in Section 10.2.11.1.

Note: All clinical scales and specimen collections are to be performed before infusions.

9.6. Blinding

The placebo-controlled period is a double-blind study phase in which subjects and site personnel will be blinded to therapy. In order to preserve blinding, a minimal number of study personnel that support interim analyses and safety review will see the randomization table and treatment assignments before the study is complete. In the open-label period, treatment will remain blinded for up to the first 4 infusions to allow participants to dose escalate as described in Section 9.1 without unblinding subjects and site personnel to the original treatment assignment in the placebo-controlled period. After the 4-visit dose escalation period, all subjects will receive open-label solanezumab treatment and will remain blinded to the subject's original treatment assignment. In essence, all subjects are randomized at Visit 6 to early-start or delayed-start solanezumab treatment. To maintain blinding, dose reductions are not allowed during the dose escalation visits in the open-label period. If a dose reduction is desired, the dose at that visit should be withheld; when dosing is reinstated, the participant should begin unblinded dose escalation at 400 mg Q4W.

Emergency unblinding for AEs may be performed through an IWRS. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. Any unblinding event performed via the IWRS will be recorded and reported by the IWRS.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject 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 Project Director prior to unblinding a subject's treatment assignment. If a subject's treatment assignment is unblinded, ATRI and Lilly must be notified immediately.

If an investigator, site personnel performing assessments, or subject is unblinded, the subject must be discontinued from the study. In cases where there is ethical reason to have the subject remain in the study, the investigator must obtain specific approval from the Project Director for the subject to continue in the study.

9.7. Concomitant Therapy

All concomitant medication taken during the study must be recorded. Subjects 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.

Prescription acetylcholinesterase inhibitors (AChEIs) and/or memantine are exclusionary during initial screening. Starting prescription AChEIs and/or memantine during the course of the study

will not be permitted without explicit permission for an exemption for medical necessity. Before a subject starts an AChEI and/or memantine or other treatments for cognitive impairment, a Medical Monitor must be contacted to determine whether or not the subject should continue in the study and whether or not clinical outcome measures should be performed. Participants who begin treatment with AChEIs and/or memantine during the placebo-controlled period will be eligible to continue in the open-label extension period.

Use of benzodiazepines for treatment on an as-needed basis for insomnia or daily dosing as anxiolytics is permitted. If they are being given chronically, use of sedatives or hypnotics should be avoided for 8 hours before administration of cognitive tests. If sedating medication is given for MRI at any visit or for any short-term use, then all cognitive assessments must be administered at least 24 hours after administration of the sedative.

Stable use of pain medications will be permitted. Short-term use of narcotics is allowable if not administered within 24 hours prior to cognitive assessments.

Other concomitant medications that affect CNS function may be given if the dose remains unchanged throughout the study. Doses of these compounds should remain constant from 6 weeks before randomization (Visit 6).

To avoid effects on cognitive measures:

- subjects should not stop receiving any medications that affect CNS function during the study,
- subjects should not add any medications that affect CNS function to the treatment regimen, and
- subjects should not change doses of medications that affect CNS function.

If unforeseen starting, stopping, or changing of stable doses of drugs that affect CNS function occurs during the study, a Medical Monitor must be contacted to determine whether or not the subject should continue in the study and whether or not outcome measures should be performed.

Anticoagulants, such as warfarin (Coumadin) and dabigatran (Pradaxa) are not permitted for subjects who undergo a LP. Starting anticoagulants during the course of the study, if deemed medically necessary, will be permitted; however, subsequent LP will not be conducted.

9.8. Treatment Compliance

Because dosing occurs at study visits, subjects who attend all visits and successfully receive infusions are automatically compliant with treatment. Any infusions at which 75% or more of the infusate is given will be considered a complete infusion.

If a subject 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 infusate is given, this must be recorded as an incomplete infusion on the case report form (CRF).

Missed infusions should be recorded on the CRF. Subjects who miss 3 consecutive infusions or 10 or more cumulative infusions at any time during the course of the study may be discontinued from the study. Subjects who miss 3 consecutive infusions or 10 or more cumulative infusions for medical reasons (for example, MRI findings) or other extenuating circumstances can continue in the study with the approval of a Medical Monitor and/or Project Director.

10. Outcome Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

10.1. Clinical Measures

Cognitive testing should always be performed before medical procedures that could be stressful for the subjects (for example, blood draws). Additionally, cognitive testing for each subject should be performed at approximately the same time on each day that testing occurs and should be administered by the same rater to reduce potential variability. More details are provided in the relevant procedures manual. If a clinical measure cannot be collected at the scheduled visit, that assessment may be collected at a subsequent visit, if that visit occurs within 8 weeks of the scheduled visit window.

10.1.1. Primary Efficacy Outcome Measure, Placebo-Controlled Period: ADCS Preclinical Alzheimer Cognitive Composite

The primary outcome measure, the PACC, will be collected at the times shown in the Study Schedule (Attachment 1; Mormino et al. 2017). The PACC is a cognitive composite that is weighted towards episodic memory but also includes timed executive function tests and a global test. Its development is described in Attachment 3. The components include:

- ***Total Recall Score from the Free and Cued Selective Reminding Test (FCSRT).*** The FCSRT (Grober et al. 1988, 2008; Ferris et al. 2006) is a 16-item word list with visual and auditory presentation that uses semantic cuing to facilitate encoding and retrieval. The test can be scored 3 ways: a free recall score ranging from 0 to 48 assesses number of words recalled freely (without cuing), a free and cued score ranging from 0 to 48 assesses the number of words recalled freely as well as those recalled with cuing, and a third score ranging from 0 to 96 adds the previous 2 scores together.
- ***Delayed Paragraph Recall score on the Logical Memory IIa test from the Wechsler Memory Scale.*** Logical Memory Test I and II (Delayed Paragraph Recall) is a modification of the episodic memory measure from the Wechsler Memory Scale-Revised (Wechsler 1987). In this modified version, free recall of 1 short story that consists of 25 bits of information will be elicited immediately after it is read aloud to the subject and again after approximately 30-minute delay. The total bits of information from the story that are recalled immediately (maximum score = 25) and after the delay interval (maximum score = 25) are recorded. The delay score (0-25 story units) will be used in the composite.

- ***Digit-Symbol Substitution Test from the Wechsler Adult Intelligence Scale-Revised (WAIS-R).*** The Digit Symbol Substitution test (Wechsler 1981) is a subset from the WAIS-R. The test consists of small blank squares presented in rows with one of 9 numbers (1-9) randomly printed directly above each blank square. A "key" is printed above the rows of blank squares. The "key" pairs numbers 1 through 9 with an unfamiliar symbol. Following a short series of practice trials, the subject must use the key to fill in the blank squares in order (working from left to right across the rows) with the symbol that is paired with the number over the blank square. The subject must work as fast as possible for 90 seconds. The measure of interest is number of squares filled in correctly within the time limit (maximum raw score = 91). This test engages multiple cognitive abilities including attention, psychomotor speed, complex scanning, visual tracking, and immediate memory.
- ***MMSE Total Score.*** The MMSE (Folstein et al. 1975) is a brief, frequently used screening instrument for Alzheimer's disease drug studies. The MMSE scale evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy 2 overlapping pentagons. The MMSE is scored as the number of correctly completed items with a lower score indicative of poorer performance and greater cognitive impairment. The total score ranges from 0 (worse) to 30 (perfect performance).

Each component score is divided by the baseline SD of that component, to form standardized Z-scores. These Z-scores are summed to form the composite, so that a 4-point change on the composite is approximately equivalent to a change of 1 baseline SD on each component.

The administration of the PACC should be recorded (audio only) for quality review purposes according to locally applicable laws and regulations.

10.1.2. Secondary Efficacy Clinical Outcome Measures, Placebo-Controlled Period

Secondary clinical outcome measures will be collected at the times shown in the Study Schedule (Attachment 1).

10.1.2.1. ADCS Activities of Daily Living – Prevention Questionnaire

The ADCS-ADL Prevention Questionnaire was developed in the ADCS-Prevention Instruments trial (ADCS-PI) and includes 18 questions related to activities of daily living (Galasko et al. 2006). Study subjects and their study partners independently rate the study subject's level of ability. Partners are additionally asked to evaluate whether activities were completed less often, required more time to complete, and if errors were made performing the task.

10.1.2.2. Clinical Dementia Rating Scale

The CDR (Morris 1993) is a clinical scale that rates the severity of dementia as absent, questionable, mild, moderate, or severe (CDR score of 0, 0.5, 1, 2, or 3, respectively). The score is based on interviews with the subject and study partner, using a structured interview that

assesses 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The ratings of degree of impairment obtained on each of the 6 categories of function are synthesized into 1 global rating of dementia (ranging from 0 to 3), with more refined measure of change available by use of the Sum of Boxes (CDR-SB). Reliability and validity has been established, as has high inter-rater reliability.

10.1.2.3. Cognitive Function Index

The CFI is a modified version of the Mail-in Cognitive Function Screening Instrument (Walsh et al. 2006; Amariglio et al. 2015), a subject- and study partner-reported outcome (patient-reported outcome) measure developed by the ADCS. This assessment includes 15 questions that assess the subject's perceived ability to perform high level functional tasks in daily-life and their sense of overall cognitive functional ability. Study subjects and their study partners independently rate the subject's abilities.

10.1.2.4. Computerized Cognitive Composite

The C3 will include tasks from the CogState battery (Darby et al. 2011; Lim et al. 2012a) aimed at measuring processing speed, working memory, visual navigation, and executive function. The C3 will also include 2 investigator-developed sensitive episodic memory probes of hippocampal function (Sperling et al. 2003; Rentz et al. 2010; Stark et al. 2010). A composite score will be generated and secondary measures will include reaction time and measure subscores.

The tablet computer iPad test session also incorporates questions about the subject's assessments of their cognitive function based on the Memory Complaint Questionnaire (MAC-Q), the C-Path PRO, and a selection of self-report questions that may be helpful in developing novel tools for assessing subjective change over time in this population. The MAC-Q (Reid et al. 2012) is a brief measure of subjective memory complaint in people with normal cognitive function. The C-Path PRO Questionnaire is an exploratory instrument being developed by the Critical Path Institute for use in early AD trials. It consists of 26 questions asking for the participant's self-assessment of current ability to perform cognitive activities and interpersonal interaction. Subjects report the frequency that they experience difficulty performing these activities.

The C3 will be optional in Japan.

10.1.2.5. Resource Use Inventory—Brief Version

The Resource Use Inventory (RUI) is an instrument designed to assess changes associated with the transition from normal aging to dementia in (1) health-related resource use (medical care, nonmedical care, and informal care) and (2) elders' participation in volunteer and paid work. Medical care includes questions on hospitalization, outpatient treatment and procedures, assistive devices, and medications. Nonmedical care includes questions on home health aides, respite care, and adult day care. Informal caregiving time participants received with instrumental and basic ADL. Both participants and their study partners contribute to the reporting of the RUI to maximize information obtained. The RUI has been used in trials of normal aging (Sano et al. 2006), MCI (Zhu et al. 2013), and dementia (Zhu et al. 2006), and items are included that are relevant to the specific stage of cognitive impairment and dementia. For this trial, a brief version of the inventory will be used (the RUI-B, where B stands for brief), including only those items

that are relevant to this stage with a focus on volunteer and paid work and items for medical and nonmedical resources.

10.1.2.6. Views and Perceptions about Amyloid Imaging

Views and Perceptions about Amyloid Imaging is an instrument that assesses perceptions about amyloid imaging and reasons for obtaining an amyloid scan. It is adapted from Roberts and Connell 2000.

10.1.2.7. Concerns about Alzheimer's Disease

Concerns about Alzheimer's Disease is a short self-report instrument about one's concern about developing Alzheimer's disease dementia. It is adapted from Roberts and Connell 2000.

10.1.2.8. Impact of Events Scale

The IES (Horowitz et al. 1979) is a 15-item self-report measure that assesses two common responses related to a specific stressful life event: intrusion and avoidance. It is a reliable scale that can be anchored to any specific life event and permits the assessment of subjects over time, comparison of the degree of distress among subgroups, and comparison of the impact of various events. The IES has been anchored to test-related distress in previous genetic testing studies and has been adapted for amyloid imaging related distress.

10.1.2.9. Future Time Perspective Scale

The Future Time Perspective scale (Roberts 2000; Lang and Carstensen 2002) measures a person's perception of his or her remaining time which in turn has been shown to explain the priority of specific goals.

10.1.2.10. Research Satisfaction Survey

A Research Satisfaction Survey will be administered to the subject in order to evaluate satisfaction with the current study. The survey will also reveal specific aspects of the study that subjects may dislike, so that improvements can be made in the design of future studies. Past studies in multiple fields have also shown that consumer input and feedback is an important element in increasing retention (for example, in psychotherapy; Miller et al. 2005; Duncan et al. 2010).

10.1.3. Biomarker Outcome Measures, Placebo-Controlled Period

Biomarker measures will be assessed as specified in the Study Schedule (Attachment 1).

10.1.3.1. Cerebrospinal Fluid (CSF)

Subjects who consent to the optional LP will have a baseline and endpoint LP performed in order to collect CSF. Analyses include but are not limited to glucose, protein, cell count, Aβ species, and tau proteins. CSF samples will also be stored for future use in research.

CSF collection, sample handling, and sample shipment will occur according to the procedures described in the relevant procedures manual. All LPs should be performed under fasting conditions (minimum 8-hour fast), preferably during the morning. The postbaseline LP should

be performed at the same time of the day as the baseline LP, and fasting status must be recorded for all LPs.

Approximately 2 mL (or more per local laboratory requirements) will be sent to a local laboratory for testing of glucose, protein, and cell count.

Solanezumab- and placebo-treated associated effects on CSF AD biomarkers will be assessed and compared. These AD biomarkers include, but are not limited to, total and free $A\beta_{1-40}$ and $A\beta_{1-42}$, total tau, and P-tau. CSF concentrations of biomarkers and solanezumab will be determined from processed CSF samples using validated immunoassay and/or mass spectrometry methods. Solanezumab- and placebo-treatment effects on CSF tau concentrations will be assessed and compared in this study. CSF total tau and P-tau are both reported to be increased in individuals with AD. Additional analyses are intended to confirm previously observed treatment effects on CSF Aβ species, which suggested that solanezumab mobilizes Aβ species from AD plaque. Results from analysis of CSF for solanezumab and biomarkers to assess treatment effects will not be reported to investigative sites or other blinded personnel at a subject level.

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

Each subject will be contacted by phone 24 hours after the LP to confirm the subject's well-being and to query about any new AEs.

10.1.3.2. Plasma Solanezumab

Plasma will be collected from all subjects for determination of plasma solanezumab concentration. Not all of these samples will be assayed for solanezumab concentration. It is intended that plasma solanezumab concentrations will be determined for approximately the first 200 subjects to complete the study. In addition, plasma solanezumab concentrations will be determined for any subject who also has positive anti-solanezumab titers. Plasma concentrations from other subjects may be determined as warranted.

Plasma concentrations of solanezumab and Aβ species for pharmacodynamic analysis may be determined from processed blood samples using validated immunoassay and/or mass spectrometry methods. Analysis of Aβ species is intended to confirm the solanezumab pharmacodynamic effect (the "peripheral sink" effect) hypothesized to enhance Aβ clearance from the CNS to the peripheral circulation. Other plasma Aβ species thought to be associated with amyloid plaque may also be analyzed.

Samples from placebo-treated subjects will not be assayed for solanezumab. Results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Sample collection, handling, and shipment will occur according to the procedures described in the relevant procedures manual.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year after all subjects complete the study (that is, the last subject's visit).

10.1.3.3. Genomic Samples

There is growing evidence that genomic characteristics may impact a subject's response to therapy. Variable response to therapy may be due to genomic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, blood samples will be collected for several types of genomic analysis.

Apolipoprotein E (APOE) genotyping is a mandatory part of this study. Neither subjects nor investigators will receive the genotyping results unless there is a country-specific law or regulation that requires notification of the results.

In the event of an unexpected AE or the observation of unusual response, the genomic samples may be tested and analysis may be performed to evaluate a genomic association with response. The genomic samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the subject number and stored for up to a maximum 15 years after the last subject visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the subject by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the investigational product. Samples will be destroyed according to a process consistent with local regulation.

10.1.3.4. Samples for Biomarker Long-Term Storage

Collection of biomarker samples for long-term storage is also part of this study. Plasma, serum, whole blood, and CSF samples will be collected. Sample collection, handling, and shipment will occur according to the procedures described in the relevant procedures manual.

Analysis may be performed on biomarker variants thought to play a role in AD pathology to evaluate their association with observed clinical outcomes to solanezumab. Other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to AD and/or determine mechanism of action of solanezumab. Future research could include the evaluation of the effects of solanezumab on Aβ processing and trafficking, tau pathologies and neuronal degeneration (tau levels are known to be elevated in patients with AD [Trojanowski 1996; Green et al. 1999]), and possibly the effects of solanezumab on other analytes that have yet to be identified. Analysis of these data could provide an important biomarker that would guide future decisions by clinicians and researchers.

The stored samples will be coded with the subject number and stored for up to a maximum 15 years after the last subject visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the subject by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the investigational product. Samples will be destroyed according to a process consistent with local regulation. Because of the exploratory nature of these analyses and because the results should not change medical management, neither subjects nor investigators will receive the test results.

10.1.3.5. Magnetic Resonance Imaging

Magnetic resonance imaging of the brain will be performed according to the Study Schedule and as clinically indicated. Each site must be qualified to conduct MRI for the A4 study. The procedures for site qualification and subject scanning will be described in the relevant procedures manual.

All subjects will be scanned using the A4 MRI scanning protocol and must complete the A4 core sequences as described in the relevant procedures manual, to be eligible for randomization in the study. There are additional magnetic resonance sequences that will be acquired depending on scanner type.

A central read will be performed on all MRI scans for subject safety and to assist in determining if the subject is eligible for the study. In instances where more than 4 microhemorrhages are identified or any ARIA-E at screening, it will be flagged for review and the subject will be deemed ineligible for the study. Other findings that are flagged during the central read will be reviewed by the Project Director and Medical Monitors or designees to determine if the subject is eligible to continue. All follow-up MRIs will be reviewed centrally for new occurrence of ARIA-E and ARIA-H that will be flagged for review by the Project Director, Medical Monitors, and site principal investigator. Subjects who develop new ARIA-E or increased ARIA-H but remain asymptomatic may be eligible to continue treatment without interruption.

Volumetric MRI (vMRI) analytic methods will be used to assess change in brain volume over the treatment period.

Functional connectivity MRI methods will be used to assess the integrity of intrinsic brain networks over the treatment period.

10.1.3.6. Florbetapir PET Scan

Florbetapir PET imaging of the brain will be performed using the A4 PET scanning protocol. Each site must be qualified to conduct florbetapir PET for the A4 study. The procedures for site qualification and subject scanning will be described in the relevant procedures manual.

For each scan, the subject will receive a single IV administration of approximately 370 MBq (10 mCi) of florbetapir F 18 (fast IV push), approximately 50 minutes prior to imaging. The injection of the imaging agent will be followed by a saline flush according to the injection procedure described in the relevant procedures manual. The PET procedure can last between 10 and 30 minutes as specified in the relevant procedures manual.

Change in brain amyloid burden (as assessed by florbetapir binding and measured by mean cortical standardized uptake value ratio [SUVr]) will be compared in solanezumab- and placebo-treated subjects for those subjects who undergo baseline and endpoint florbetapir scans.

10.1.4. Secondary Efficacy Clinical Outcome Measures, Open-Label Period

The PACC, ADCS-ADL Prevention Questionnaire, CDR-SB, C3, and CFI described above for the placebo-controlled period of the study will also be evaluated in the open-label extension

period. Additionally, a Clinician Diagnostic Impression (CDI) will be collected at Visit 66 and during the open-label extension period. For the CDI, investigators will be asked to classify the participant's current disease stage according to the following categories: cognitively normal, MCI, or mild AD dementia. Timing for collection of these outcome measures is presented in the Study Schedule (Attachment 1).

10.2. Safety Evaluations

Investigators are responsible for monitoring the safety of subjects 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 subject.

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Attachment 1 lists the schedule of all safety assessments in this study. Attachment 2 lists the laboratory tests that will be performed for this study.

10.2.1. Adverse Events

10.2.1.1. General Information

A clinical study AE is any untoward medical event or unanticipated benefit 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.

Reporting standards for reporting AEs will be provided in the relevant procedures manual and must 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 drug effect.

Any symptomatic ARIA would be considered an AE. Other findings on study-related MRI scans will be at the discretion of the site investigator to determine if it qualifies as an AE.

Any clinically significant findings from ECGs, labs, vital sign measurements, and other procedures must be reported.

Planned medical procedures should not be reported as AEs unless the underlying medical condition has worsened during the course of the study, in which case the worsening of the medical condition (not the procedure) should be reported.

Cases of pregnancy that occur during maternal or paternal exposures to investigational product should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. After the A4 study informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

Investigators will be instructed to report their assessment of the potential relatedness of each AE to items that include, but not limited to, protocol procedure, studied disease state (preclinical AD, elevated brain amyloid), investigational product, and/or drug delivery system.

10.2.1.2. Serious Adverse Events

Serious adverse event collection begins after the subject has signed informed consent. Serious adverse events that occur after consent but before receipt of investigational product must be reported but data from such events will not be submitted to ERBs by the sponsor unless thought to have been possibly caused by a protocol procedure.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

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

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Initial or prolonged inpatient hospitalization
- 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 adverse drug events when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events occurring after a subject has been administered the last dose of study drug will be collected for 30 days after the last dose of study drug, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either study drug, drug delivery system, or a protocol procedure.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.2.1.3. 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.

10.2.2. Columbia Suicide Severity Rating Scale

Consistent with FDA regulatory guidance (FDA 2012), any occurrence of suicide-related thoughts and behaviors will be assessed. The C-SSRS is 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.

The standard version of the scale will be used in this study. The first time the scale is administered in this study (Visit 1), the C-SSRS "Screening/Baseline" version will be used and the findings will be used to assist the clinician in determining eligibility. The C-SSRS will be administered at baseline (Visit 6) and at subsequent visits as outlined in the study schedule. The C-SSRS "Since Last Visit" scale will be used for baseline and all subsequent assessments.

If a suicide-related thought to 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.

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.

10.2.3. Electrocardiograms

For each subject, a 12-lead digital ECG will be collected as replicates (triplicates). Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed when needed to ensure high-quality records.

ECG will be collected in the placebo-controlled period per schedule of events and in the open-label period as unscheduled ECG per investigator discretion.

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 subject is still present, to determine whether the subject meets entry criteria at the

screening and for immediate subject management, should any clinically relevant findings be identified at screening or during subsequent ECG visits as outlined in the Study Schedule.

After enrollment, if a clinically significant increase in the QT/corrected QT interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the subject will be assessed by the investigator for symptoms (for example, palpitations, near syncope, syncope) and to determine whether the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full overread on 1 of the replicates (including all intervals). A report based on data from this overread will be issued to the investigative site. For each set of replicates, the cardiologist will determine the RR and QT intervals, QRS duration, and heart rate on the ECGs that were not fully overread. These data are not routinely reported back to the investigative site. However, any clinically significant finding that was not present on the fully overread ECG will be reported to the investigator, Lilly, and ATRI. All data from the overreads will be placed in the Lilly database as well as transferred to ATRI for analytical and study report purposes.

When there are differences in the ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate subject management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report-writing purposes.

The investigator (or qualified designee) must document his/her review of 1 of the replicate ECGs printed at the time of collection, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

10.2.4. Immunogenicity

Serum for immunogenicity testing will be prepared from blood drawn at designated visits. Serum immunogenicity results and any associated plasma Aβ 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.

Sample handling and shipment of the central laboratory will occur per instructions given to the investigative study site. Samples may be stored for a maximum of 15 years following last subject visit for the A4 study at a facility selected by Lilly to enable further analysis of immune responses to solanezumab. The duration allows Lilly to respond to regulatory requests related to solanezumab.

10.2.5. Neurological Examination

A medically qualified professional will perform a neurological examination that includes an assessment of cranial nerves, strength, coordination, reflexes, sensation, tremor, and gait. Neurological examinations will be performed as clinically indicated, and as indicated in the Study Schedule. If necessary, given the training of the principal investigator, a neurologist will be consulted in the event of significant new findings.

10.2.6. Physical Examination

A medically qualified professional will perform a brief physical examination that consists of a review of the major body systems (that is, skin, head/ears/eyes/nose/throat, cardiovascular, pulmonary, abdomen, musculoskeletal, neurological, and gastrointestinal). Physical examination will be performed at clinically indicated, and as indicated in the Study Schedule.

10.2.7. Safety Laboratory Samples

Blood and urine samples (Attachment 2) will be collected according to the Study Schedule and to determine whether subjects meet inclusion/exclusion criteria and to monitor subject health. Redraws will be permitted if a sample is not viable when received by the central laboratory or if sample collection is not possible during the visit.

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.

10.2.8. Vital Signs

Vital signs, including temperature and weight, should be measured at all clinic visits and recorded in the eCRF according to the Study Schedule. Blood pressure, respiration, and pulse will be measured in the sitting position. Height will be measured at Screening Visit 1.

10.2.9. Subject Medical History/Family History/Concomitant Medications

Information regarding demographics, medical history, and family history will be gathered from the subject and study partner at Screening Visit 1. Concomitant medications will be assessed at every visit.

10.2.10. Assessment of Psychological Well-Being

The Assessment of Psychological Well Being is composed of questions from a validated shortened version (Marteau and Bekker 1992) of the “state anxiety” portion of the State-Trait Anxiety Inventory (Spielberger et al. 1983) and from the Geriatric Depression Scale (Sheikh and

Yesavage 1986). It is a self-report assessment designed to identify symptoms of anxiety and depression in the elderly. The anxiety portion of the assessment consists of 6 questions that the subject indicates on a scale from 1 (not at all) to 4 (very much) on how much of a given anxiety symptom they are currently experiencing to assess anxiety level. The depression portion of the assessment has 15 questions that the subject is asked to answer yes or no based on how they felt over the past week in an effort to assess depression symptoms. The more benign items are asked first. Answers to 5 of the items are negatively oriented for depression (for example, Do you feel full of energy?) and 10 positively oriented (for example, Do you often feel helpless?).

10.2.11. Dose Escalation Safety Cohort

Subjects in the dose escalation safety cohort in the placebo-controlled period (Section 7.1.4) will receive additional safety assessments and monitoring during dose escalation to monitor the safety of higher doses. The additional study procedures and their timing are provided in the dose escalation safety cohort section of the Study Schedule (at the end of Attachment 1) and outlined below.

10.2.11.1. On-Site Post-Infusion Monitoring

Each subject will be observed for 1 hour after the first dose of 800 mg and the first dose of 1600 mg.

10.2.11.2. Safety MRI

An additional safety MRI will be conducted at least 7 days after the second dose of 800 mg and at least 7 days before escalating dose to 1600 mg so results of the central read can be reviewed by the site before the escalation. If a study MRI is scheduled within ±2 months of the dose escalation MRI, the MRI should be conducted according the dose escalation schedule as a substitute for the MRI specified in the main study schedule; an exception is the MRI at endpoint (Visit 66), which should be done according to the Study Schedule regardless of timing relative to dose escalation. If a subject experiences symptoms suggestive of ARIA-E at any time, the investigator may obtain an unscheduled MRI.

10.2.11.3. Electrocardiogram, Hematology, Chemistry, Urinalysis, and Vital Signs

Additional ECGs will be obtained at the visits at which subjects receive their second dose of 800 mg and second dose of 1600 mg.

Additional safety blood draws (hematology, chemistry) and urinalysis will be collected at the visits at which subjects receive their second dose of 800 mg and second dose of 1600 mg.

Vital signs will be monitored before all infusions.

10.2.11.4. PK/PD and Anti-Drug Antibody Assessment

Additional PK/PD and anti-drug antibody samples will be collected at each of the 2 visits at which subjects receive 800 mg and at the first 2 visits and the fourth visit at which subjects receive 1600 mg during the dose escalation period.

10.2.12. Safety Monitoring

In consultation with the regulatory sponsor, Medical Monitors or designees will monitor safety data throughout the course of the study. Serious adverse events will be reviewed within time frames mandated by procedures. The Medical Monitors or designees will periodically review:

- Trends in safety data
- Laboratory analytes including blood hematology, chemistry, and urinalysis
- AEs including monitoring of infusion reactions, ARIA-H, ARIA-E, hemorrhagic stroke, microhemorrhage (cerebral microhemorrhage, cerebellar microhemorrhage, brain stem microhemorrhage) as identified by investigator, cardiac ischemia, cardiac arrhythmias, AEs potentially related to immunogenicity and suicide-related thoughts and behaviors

If a study patient/subject experiences elevated ALT or AST >3X ULN or elevated total bilirubin >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/subject safety and comply with regulatory guidance, the investigator is to consult with the medical monitor regarding collection of specific recommended clinical information, follow-up laboratory tests, and follow-up MRIs. 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 treatment until the imaging abnormalities have resolved. If a subject simultaneously develops more than one of the symptoms suggestive of ARIA-E, then an unscheduled MRI should be performed. 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.

Please refer to Section 12.9 for information on what occurs in the event that an issue may need to be addressed by unblinding at the group level.

10.2.13. 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.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.3. Appropriateness of Measurements

Clinical. The PACC was developed specifically for use in this study (as described in Attachment 3). The measure was applied to data from several large longitudinal studies in clinically normal populations to determine whether it was sensitive to change among subjects who declined from normal to MCI. Several datasets confirmed that the measure is able to detect cognitive decline in individuals who demonstrate clinical decline to the stage of MCI. Although it is unknown how much progression will be observed in the present study, the PACC is believed to be an appropriate measure for assessing change in preclinical AD.

The CFI and ADCS-ADL Prevention Questionnaire are instruments to track early changes in clinical function such as abilities to perform high-level ADL and perception of their own ability to perform cognitively demanding functional tasks. These measures demonstrated significant decline in individuals who progressed to MCI in the ADCS-PI trial.

Other functional outcome measures, including the CDR are well-established in MCI and AD studies, although it is expected that only minimal change will be observed in the CDR-SB over 3 years in individuals who are not functionally impaired at baseline.

Given the lack of trials in preclinical AD, many of the chosen scales do not have the same depth of data and literature characterizing their use and/or responsiveness to treatments in this population that they do for populations with more pronounced AD. Scales were therefore selected with an understanding that further validation and refinement would occur as part of this trial.

Biomarkers and Imaging. There is a large body of evidence supporting CSF Aβ, CSF tau, amyloid imaging, and hippocampal and whole brain volume as biomarkers of AD pathology. Pathologic hallmarks of AD identified at autopsy include the presence of neuritic Aβ plaques, neurofibrillary tangles, and neuronal loss in brain regions important for cognition, such as the hippocampus and temporal cortex (Jack et al. 2011). Tau and phosphorylated forms of tau (P-tau) as measured in CSF and plasma are known to be elevated in patients with AD (Trojanowski 1996; Green et al. 1999; Morris et al. 2005; Thal et al. 2006). Cerebrospinal fluid $A\beta_{1-42}$ concentrations are known to be reduced in patients with AD (Motter et al. 1995; Galasko et al. 1998, Jack et al. 2010). Data will be collected in the A4 study to assess the impact of treatment with solanezumab on these well-established biomarkers of AD pathology. In addition, there is growing evidence that those who are 'cognitively normal' but with brain amyloid accumulation exhibit changes consistent with abnormalities seen in AD dementia, including cortical thinning (Dickerson et al. 2009; Schott et al. 2010; Chételat et al. 2012) and disruption of

functional connectivity (Hedden et al. 2009; Sheline et al. 2010; Mormino et al. 2011); these markers will also be assessed in the A4 study.

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

11. Sample Size and Statistical Methods

11.1. Determination of Sample Size

In order to develop an appropriate measure of cognitive decline in a preclinical population, we tested several combinations of measures using data from longitudinal studies in clinically normal populations, including the ADNI; the AIBL; the ADCS-PI trial; and the HABS (Attachment 3).

Sample size and power at 4.5 years (240 weeks) for the PACC were estimated using data from ADNI and HABS. Estimates were obtained by applying appropriate assumptions regarding treatment difference, SD, and attrition for a 4.5-year study in a preclinical AD population. In ADNI, the difference in the composite change between subjects with and without elevated brain amyloid at 240 weeks was 2.13 (SD=2.85). Similarly, in HABS, the difference in the composite change between subjects with and without elevated brain amyloid at 240 weeks was 2.66 (SD=3.08). Given the ADNI-derived estimate of SD at 240 weeks of SD=2.85 and 30% attrition, the total N=1150 provides 80% power (5% 2-sided alpha) to detect a treatment difference of 0.532 points or 0.532/2.13 = 24.9% of the amyloid group difference. Similarly, based on the HABS estimate of SD at 240 weeks of SD=3.08, the study has 80% power to detect a treatment difference of 0.570 points or 0.570/2.66 = 21.4% of the amyloid group difference.

For the open-label period, the estimated mean PACC difference between cognitively normal subjects with and without elevated brain amyloid at 336 weeks is 2.95 (SD=3.77) based on ADNI and 4.74 (SD=3.99) based on HABS. Accounting for the administrative censoring that will be induced by the common close design of the open-label period, and assuming an overall attrition rate of 30%, about 266 PACCs are expected to be available at 336 weeks. The visit-to-visit correlation is estimated to be about 0.5. Under these pilot estimates, 266 PACCs at 336 weeks would provide 80% power to detect a randomized group (early-start vs delayed-start treatment with solanezumab) difference of about 0.9 PACC points. This change of 0.9 PACC points reflects 30% of the difference between amyloid-positive and -negative participants based on ADNI, and 20% of that difference based on HABS.

Sample size for the study was determined prior to the interruption caused by the COVID-19 pandemic. Applying the NCS approach in simulated trials with a COVID-19 pandemic interruption suggests the study has 94% power to detect an effect size of 0.75 PACC points at 240 weeks.

11.2. Statistical and Analytical Plans

11.2.1. General Considerations

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.

All analyses will follow the modified intent-to-treat (mITT) principle unless otherwise specified. An ITT analysis is an analysis of data by groups to which the subjects are assigned by random

allocation, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. A mITT analysis is an ITT analysis for all subjects who have a baseline and at least 1 postbaseline measure.

Any change to the statistical 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 statistical analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

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

11.2.2. Analysis Populations

The primary and secondary efficacy measures will be analyzed using the mITT population unless otherwise specified.

11.2.3. Handling of Missing Items for Scales

If any of the individual items for the clinical outcomes are missing, every effort will be made to obtain the score for the missing item or items. The methodology for imputation will be provided in the SAP.

11.2.4. Subject Disposition

The reasons for discontinuation will be collected when the subject's participation in the study ends and will be summarized by treatment group. The percentage of subjects discontinuing will be compared between groups. The median time to discontinuation will also be compared between treatment groups. The comparisons will be done for the overall percentage of subjects who discontinue and also for specific reasons for discontinuation.

11.2.5. Subject Characteristics

Baseline and demographic characteristics will be summarized by treatment group and overall. Summaries will be provided for continuous and categorical measures.

11.2.6. Prior and Concomitant Therapy

Prior medications are defined as those that stop before randomization. Concomitant medications are defined as those being taken on or after randomization. A summary of concomitant medications will be presented as frequencies and percentages for each treatment group. Fisher's exact test will be used to test for treatment differences between groups.

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

Prior and concomitant medications will also be listed.

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

11.2.7. Protocol Violations

Protocol violations will be analyzed as frequency tables between solanezumab and placebo. Listings of subjects with significant protocol violations will also be provided.

11.2.8. Analysis of Primary Outcome (Placebo-Controlled Period)

The primary objective of this study is to test the hypothesis that IV infusion of solanezumab will slow cognitive decline in preclinical AD as compared with placebo.

The original mITT analysis (that is, all participants as randomized to treatment who have a baseline and at least 1 postbaseline measure) for the primary outcome will be retained and conducted at the end of the treatment period, although the dose will be increased during the study; in other words, the primary analysis will include all data for the solanezumab group as the treatment group versus placebo. As with the original analysis plan, the hypothesis for this analysis will be tested against an alpha level of .05.

The details of this analysis including the analytic method and model are presented below.

An NCS analysis will be used to assess the difference between treatment groups in change from baseline for the PACC score at 4.5 years. The composite score at baseline and each post-baseline visit will be the dependent variable. Time will be treated as a continuous variable with values equal to years between baseline and follow-up exam dates. We will assume an unstructured covariance structure. The fixed effects will include the following terms: (i) NCS basis expansion terms (two terms), (ii) NCS basis expansion terms-by-treatment interaction (two terms), (iii) PACC test version administered, (iv) age, (v) education, (vi) APOE 4 carrier (yes/no), and (vii) baseline florbetapir cortical SUVr. The model is constrained to not allow a difference between treatment group means at baseline.

The null hypothesis is that the treatment difference between solanezumab and placebo for the PACC score at 240 weeks is equal to zero. The primary analysis will be carried out in the mITT population that is randomized and has a baseline score and at least 1 postbaseline assessment. If the unstructured covariance structure matrix results in a lack of convergence, the following structures will be used in sequence:

- heterogeneous Toeplitz covariance structure
- heterogeneous autoregressive order 1 covariance structure
- heterogeneous compound symmetry covariance structure, and
- compound symmetry covariance structure.

The sensitivity analyses of the effect of dose change on clinical outcomes are included in Section 11.2.9.2.

11.2.9. Analysis of Secondary Outcomes (Placebo-Controlled Period)

11.2.9.1. Clinical Outcomes

Similar to the primary analysis, each of the secondary efficacy outcomes will be assessed using an NCS analysis. These secondary efficacy outcomes include MMSE, ADCS-ADL Prevention

Questionnaire, CDR-SB, CFI, and C3. For each secondary efficacy measure, the baseline score and scores at each post-baseline visit during the treatment period will be analyzed using NCS.

Also similar to the primary analysis, all data from all patients regardless of dose increase will be included for the solanezumab and placebo groups.

Each of the secondary efficacy outcomes will be assessed using an MMRM analysis. These secondary efficacy outcomes include MMSE, ADCS-ADL Prevention Questionnaire, CDR-SB, CFI, and C3. For each secondary efficacy measure, scores at each post-baseline visit during the treatment period will be analyzed using MMRM.

An additional MMRM analysis, termed a slopes analysis, will be conducted examining the change from baseline score on the PACC at each scheduled postbaseline visit. The slope analysis will treat time from randomization as a continuous variable.

11.2.9.2. Sensitivity Analyses

Sensitivity analyses of the effect of dose change on clinical outcomes will be conducted as noted in the SAP.

1. An MMRM analysis will be performed separately on the PACC and other clinical measures after censoring all observations after the dose increase. In other words, change from baseline for the clinical measure will be obtained only through the last available value prior to first dose escalation for each subject.

   The null hypothesis is that the treatment difference between solanezumab and placebo for the PACC score is equal to zero. Since the timing (visit) of dose escalation will vary for each subject, a specific endpoint for comparison between treatment groups will not be available. Therefore, the hypothesis will be tested using the p-value obtained for the overall treatment effect.

2. Additionally, we will implement a sensitivity analysis to estimate the potential differences in the treatment effect for the original dose and the higher dose by modeling the effects of a time-varying dose indicator variable (with values placebo, low, and high). The time-varying dose indicator variable will be fitted as a separate variable to the ITT model of change from baseline on the primary measure (PACC) and other secondary measures.

   The fixed effects in the model for the sensitivity analysis will be constructed as follows:

   Change from baseline = baseline score + dose+ visit + dose-by-visit interaction + age + education + baseline cortical SUVr

   The coefficient for this new time-varying dose indicator variable will provide estimates to

compare and contrast all dose groups at the relevant time points at which the different doses were assigned.

3. Another sensitivity analysis will include the mean dose for each subject as a separate co-variable. The fixed effects in the model will be the following:

   Change from baseline = baseline score + treatment + visit + treatment-by-visit interaction + age + education + baseline cortical SUVr + mean dose.

Additional sensitivity analyses will be included in the SAP.

11.2.9.3. Biomarker Outcomes

Analysis of Plasma. Change in plasma Aβ and P-tau, GFAP, and Neurofilament light chain after treatment will be compared between treatment groups. This analysis will be done separately for each plasma Aβ and P-tau parameter.

Analysis of vMRI Data. Change in vMRI data after treatment will be compared between treatment groups. This analysis will be done separately for each vMRI parameter.

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 compared between treatment groups.

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 $A\beta_{1-40}$ and $A\beta_{1-42}$ species and total tau and P-tau peptides, GFAP Neurofilament light chain, will be compared between treatment groups.

11.2.10. Open-Label Period

When change from baseline is assessed, subjects will be included in the summary only if both a baseline and a postbaseline measure are available. For efficacy analyses (noninferiority and superiority analyses), the baseline will be the last non-missing observation collected prior to the initiation of treatment in the placebo-controlled period, generally, Visit 6.

Treatment group comparisons used in the statistical analysis will be the treatment group to which the subjects were randomized in the placebo-controlled period (subjects randomized to solanezumab [early start] versus patients randomized to placebo [delayed start]).

For analyses using MMRM, an unstructured covariance matrix will be used to model the within-patient variance–covariance errors. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. The Kenward–Roger approximation will be used to estimate the denominator degrees of freedom.

In the event that the primary contrast for the placebo-controlled period at 240 weeks is statistically significant, delayed-start analyses will proceed based on the methods described by Liu-Seifert and colleagues (2015). Several efficacy measures (PACC, ADCS-ADL Prevention Questionnaire, CDR-SB, C3, and CFI) will be analyzed separately using a noninferiority hypothesis in an MMRM model, in which the specific hypothesis is that the advantage of solanezumab treatment demonstrated in the placebo-controlled period is sufficiently maintained in the open-label period. This randomized/delayed-start analysis will assess whether solanezumab has a persistent effect on disease course. That is, the hypothesis is that subjects originally randomized to receive placebo and later switched to solanezumab at the start of the open-label period do not "catch up" to subjects originally randomized to receive solanezumab in the placebo-controlled period. This may be understood as a comparison of the treatment difference at the end of the placebo-controlled period with the treatment difference at the end of the open-label period.

The noninferiority margin for this hypothesis is specified as 50% of the treatment difference observed at the end of the placebo-controlled period. The hypothesis will be tested by constructing a 90% one-sided CI of the difference in LS means at the last visit in the open-label period. If the lower limit of the CI rules out the difference that would have been obtained if 50% of the observed difference had been lost, the disease progression for the treatment groups will be considered parallel, indicating that the treatment effect is independent of symptomatic effects. The interim noninferiority analysis of the PACC up to Week 336 in the open-label period will be considered the main efficacy analysis for the open-label period.

In addition to the noninferiority test, superiority of early-start subjects compared with delayed-start subjects at the 336-week analysis in the open-label period will also be assessed. The PACC, ADCS-ADL Prevention Questionnaire, CDR-SB, C3, and CFI will be analyzed.

11.2.11. Gatekeeping Strategy

Given continuing evolution in the field regarding assessment of clinical meaningfulness in a preclinical AD population, a formal gatekeeping strategy is not currently planned. If a gatekeeping strategy is used, it will be specified in an SAP before database lock.

11.2.12. Pharmacokinetic/Pharmacodynamic Analyses

The distribution of observed plasma solanezumab concentrations will be graphically compared to simulated solanezumab concentrations generated by a population 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 subjects with treatment-emergent immunogenicity will be plotted as a

function of time, along with mean plasma solanezumab concentrations in all subjects. 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 subjects will also be presented on the graph. If this graphical analysis demonstrates a trend in plasma solanezumab concentrations in subjects with treatment-emergent immunogenicity relative to the overall trial population, additional work may be performed to characterize this trend.

11.2.13. Safety Analyses

All analyses will depend on the analysis populations being specified. For the analyses and summary statistics, the 2 analysis populations to be used are randomized subject population and placebo-controlled population. The randomized subject population will include all randomized subjects in the A4 study and will include observations across both the placebo-controlled period and the open-label period. The placebo-controlled population will include all enrolled subjects who have entered the placebo-controlled period of the A4 study and will be limited to observations collected during the placebo-controlled period of the study.

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, MRI scans, ECGs, immunogenicity measures, and the C-SSRS during the treatment period. Safety analyses of the open-label extension will span across both the placebo-controlled study period and the open-label study period in order to be able to compare early-start safety risks to early-start efficacy benefits.

For safety assessments, 3 separate sets of analyses will be conducted: 1 set of analyses for all data when the subjects were on 400 mg Q4W, 1 set of analyses for all data when the subjects were receiving doses higher than 400 mg Q4W, and 1 set of analyses for all data (regardless of dose).

11.2.13.1. Study Drug Infusion

Summary statistics will be provided for the total number of subjects who received complete infusions, duration of complete infusion, and volume of complete infusion by treatment group at each visit. The proportions of subjects who received complete infusion between treatments will be compared between treatment groups. Duration of complete infusion and volume of complete infusion will also be compared between treatment groups.

Frequencies and percentages of reasons why infusion was incomplete or not done will also be presented.

11.2.13.2. Adverse Events

Adverse events will be coded according to established Medical Dictionary for Regulatory Activities (MedDRA) terms and summarized by MedDRA System Organ Class and Preferred Term.

Treatment-emergent adverse events will be defined as events that first occurred or worsened on or after the first infusion.

An overview of AEs, including the number and percentage of subjects who died, suffered SAEs, discontinued due to AEs, and who suffered TEAEs, will be provided. Comparison between treatments will be performed.

Summaries of AEs by decreasing frequency of preferred term within system organ class will be provided for the following:

- Preexisting conditions
- TEAEs
- TEAEs by maximum severity
- TEAEs occurring in greater than 5% of subjects by Preferred Term
- SAEs

A summary of TEAEs by visit will also be provided.

In addition, the proportion of subjects within specific clusters of TEAEs, such as infusion-related reactions, hemorrhagic stroke and cerebral microhemorrhage, cardiac ischemia-related events, cardiac arrhythmia-related events, and suicidal ideation or behaviors will be summarized and treatment comparisons will be conducted.

Preexisting conditions, TEAEs, SAEs, and discontinuations due to AEs will be listed.

11.2.13.3. Laboratory Analyses

Laboratory measurements will be analyzed using continuous data (change from baseline) and categorical data (proportion of treatment-emergent abnormalities).

11.2.13.4. Electrocardiograms

The ECG measurements will be analyzed using continuous data (change from baseline) and categorical data (proportion of treatment-emergent abnormalities).

11.2.13.5. Vital Signs

Vital sign measurements (including temperature and weight) will be analyzed using continuous data (change from baseline) and categorical data (proportion of treatment-emergent abnormalities).

11.2.13.6. Immunogenicity

Immunogenicity data (anti-solanezumab) after treatment will be compared between the treatment groups.

11.2.13.7. Amyloid-Related Imaging Abnormalities: Magnetic Resonance Imaging

The incidence of ARIA-E will be summarized. Change in ARIA-E status from baseline, to each postbaseline MRI will be compared between treatment groups.

The incidence of ARIA-H will be summarized. Change in ARIA-H status from baseline to each postbaseline MRI will be compared between treatment groups.

11.2.13.8. Columbia Suicide Severity Rating Scale

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent occurring during treatment, based on the C-SSRS, will be summarized. In particular, for each of the following events, the number and percentage of patients with the event will be enumerated by treatment: completed suicide, nonfatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (no plan) without intent to act, nonspecific active suicidal thoughts, wish to be dead, and self-injurious behavior without suicidal intent.

Results will be summarized for "at any time" (irrespective of baseline) and "treatment emergent" (new or worsening since baseline) events.

In addition, the number and percentage of patients who experienced at least 1 component of various composite measures will be presented. Composite endpoints are defined below.

- Suicidal ideation: A "yes" answer at any time during treatment to any 1 of the 5 suicidal ideation questions on the C-SSRS.
- Suicidal behavior: A "yes" answer at any time during treatment to any 1 of the 5 suicidal behavior questions on the C-SSRS.

11.2.14. Subgroup Analyses

To assess the effects of various demographic and baseline characteristics, subgroup analyses of the efficacy outcomes will be performed.

11.2.15. Interim Analyses

An interim analysis for futility may be conducted. If an interim analysis for futility is conducted, the details will be described in the SAP prior to the analysis. Only the data and safety monitoring board (DSMB) 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 subjects.

Unblinding details will be specified in the unblinding plan section of the SAP or a separate unblinding plan document.

12. Informed Consent, Ethical Review, and Regulatory Considerations

12.1. Informed Consent and HIPAA Compliance

12.1.1. Informed Consent

The investigator is responsible for ensuring that the subject and study partner(s) understand the potential risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each subject before the performance of any protocol procedures and before the administration of investigational product. The investigator is also responsible for ensuring that study partners provide informed consent.

As used in this protocol, the term "informed consent" includes all consent and assent given by subjects and study partners.

12.2. Ethical Review

The ATRI must approve all ICFs before they are submitted to the ERB and used at investigative sites. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP. Standard ATRI Regulatory Affairs procedures will be followed tracking, monitoring and assisting with ERB reviews at the sites.

As part of study initiation, documentation of ERB approval of the protocol and the ICF must be provided to ATRI as part of the regulatory packages before the study may begin at the investigative sites. The standard ATRI Regulatory Approval process will be followed. The ERB(s) will review the protocol as required.

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

12.3. Confidentiality

An identification code assigned by the investigator to each subject will be used in lieu of the subject's name in order to protect the subject's identity when reporting AEs and/or other trial-related data.

In addition, information about study subjects will be kept confidential and managed according to the requirements of HIPAA. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (that is, that the subject is alive) at the end of their scheduled study period.

12.4. Inclusion of Women and Minorities

Special efforts will be made to encourage minority enrollment, with a requirement to screen at least one out of every 5 subjects from an under-represented minority, and minority recruitment will be monitored throughout the study. Minority enrollment will be facilitated through minority outreach effort coordinated by the Recruitment and Retention group at the ATRI. Each site will be encouraged to employ specific efforts (for example, media and community outreach activities) to attract appropriate minority subjects to the trial. Spanish translation is available for a variety of instruments deployed in this trial. The success of minority recruitment is based on the specific efforts of each site (for example, media and community outreach efforts) as well as the criteria for entry. This trial has been designed to maximize minority participation in both ways. No subject will be excluded due to their sex, race, or ethnic group.

12.5. Regulatory Considerations

This study will be conducted in accordance with:

[1] 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

[2] the ICH GCP Guideline [E6]

[3] applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

12.6. Site Personnel Requirements

12.6.1. Roles and Responsibilities

At a minimum, 3 staff members (Site Principal Investigator, Study Coordinator, Psychometrician) will be required to conduct the protocol at each site. Additional functions are

outlined below that may be covered by one staff member at certain sites; for other sites there will be multiple staff assigned. Details will be provided in the relevant procedures manual.

- Site Principal Investigator. This person is responsible for ensuring that the local ERB approves the protocol and oversees all site activity for the study; this person may also serve as the study physician. See also Section 12.6.2.
- Study Physician. This person is responsible for conducting or supervising the amyloid disclosure process, and clinical evaluation of all subjects, including physical and neurological examinations, reviewing AEs, interpreting laboratory results; ensuring enrollment and protocol adherence. The study physician will supervise project personnel and ensure that raters maintain a high level of skill and accuracy in conducting assessments.
- Study Coordinator. This person will be responsible for managing the day-to-day conduct of the trial, ensuring accurate administration of all instruments, maintaining online data and scheduling study procedures, processing laboratory samples, serving as liaison with the clinical monitor, and coordinating clinic visits. The study coordinator may perform several ratings, including the CDR.
- Rater/Psychometrician. This person will have at least 1 year experience administering cognitive assessments to older and cognitively impaired subjects.
- CDR Rater: This person must have a current rater certification through Washington University and should have at least 2 years of clinical experience in interviewing and assessing older and cognitively impaired subjects, and will render the CDR rating based on clinical judgment of study subject and study partner.
- Regulatory: This person will be responsible for managing all regulatory related documents for the duration of the trial, including submitting all required regulatory documents to ATRI regulatory affairs.
- Billing Remittance and Statement: This person will be responsible for reviewing and verifying payments from the ATRI are in alignment with procedures completed, along with accepting and processing payments from the ATRI.
- MRI Contact: This person will be responsible for conducting necessary scan for site qualification purposes using the appropriate scanning sequence. As well as conducting subject MRI scans per protocol and ensuring the scans are uploaded to the A4 portal in a timely manner.
- PET Contact: This person will be responsible for conducting necessary scan for site qualification purposes and as needed to assess for drift using the appropriate scanning sequence. As well as conducting subject PET scans per protocol and ensuring the scans are uploaded to the A4 portal in a timely manner.

12.6.2. Investigator/Rater Requirements

Physicians with expertise in neurology, geriatrics, or psychiatry will participate as investigators in this clinical study. Contact information for investigators, clinical laboratories, and other medical and/or technical department(s) and/or institutions involved in the clinical study are maintained in the study records.

Cognitive assessments must be administered by an individual trained in the use of these instruments. Investigators and site personnel who will perform ratings will be trained and approved by ATRI or its designee prior to participating in the study. In most cases, evaluation and notification will occur at the investigator meeting. Individuals who do not attend the rater evaluation and training portion of the investigator meeting and who wish to perform the ratings in this study must be appropriately trained prior to performing any ratings. If possible, the measurements should be performed on a given subject by the same rater at each visit. The primary investigator has the responsibility of selecting who will administer the instruments at the site, as long as all training requirements have been met by those raters.

12.7. Protocol Signatures

The regulatory sponsor's responsible medical officer, the ATRI Director, and the Project Director will approve the protocol, confirming that, to the best of their 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 ATRI.

12.8. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report 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 number of qualified, enrolled subjects will be considered when determining the coordinating investigator for the clinical study report. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

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

12.9. Data and Safety Monitoring Board

The DSMB will review the safety of all subjects on an ongoing basis. The initial task of the DSMB will be to review the protocol and consent forms to identify any necessary modifications. If modifications are necessary, revisions will be reviewed by the DSMB prior to its recommendation on initiation of the project. The DSMB, based on its review of the protocol, will identify the data parameters and format of the information to be regularly reported. The

DSMB will be informed of the occurrence of any SAEs and immediately notified of fatal or life threatening events. The DSMB may at any time request additional information. The DSMB will initially be provided with data blinded to treatment status, but they may request unblinded data if there is a safety concern. The DSMB and NIA representative will meet in person or by conference call on a quarterly basis. Based on the review of safety data, the DSMB will make recommendations regarding the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed. The Board will also be informed in a real-time basis of all immediately reportable AE (FDA-defined serious AE). All reports are stripped of identifying information. Using the ATRI Safety Review Process and the DSMB, there is substantial oversight and case review to alert the investigators, in a timely manner, to any safety issues that may arise. For further details, please refer to the DSMB charter.

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Attachment 1. A4 Study Schedule

Study Schedule, A4 Protocol, Visits 1 through 5 (Screening Period)

Visit Purpose: / Category / Procedure	Consent and general eligibility	PET amyloid imaging	Amyloid status disclosure	MRI	Fasting LP (optional)[d]
Visit No.:	SC V1	SC V2	SC V3	SC V4	SC V5
Tolerance Interval for Screening Period	← ← ← ← ← ← ← ≤90 days → → → → → → →				
Consent and HIPAA Authorization	X				
Safety Assessments					
Demographics, subject medical history/family history, preexisting symptoms	X				
Concomitant medications	X				X
Adverse events	X	X		X	X
C-SSRS[a]	X				
Assessment of Psychological Well Being	X				
Physical/neurological examination	X				
Vital signs	X				
Electrocardiogram	X				
Screening MRI				X	
Amyloid Disclosure Assessments					
Views & Perceptions of Amyloid Imaging Scale	X		X (post disclosure)		
Concerns about Alzheimer's Disease Scale	X		X (post disclosure)		
Future Time Perspective Scale	X		X (post disclosure)		
Impact of Events Scale[b]			X		

continued on next page

Study Schedule, A4 Protocol, Visits 1 through 5 (Screening Period) (completed)

Visit Purpose: / Category / Procedure	Consent and general eligibility	PET amyloid imaging	Amyloid status disclosure	MRI	Fasting LP (optional)[d]
Visit No.:	SC V1	SC V2	SC V3	SC V4	SC V5
Tolerance Interval for Screening Period	← ← ← ← ← ← ← ≤90 days → → → → → → →				
Efficacy/Health Outcomes/Imaging/LP					
PACC (version SC)[f]	X				
C3[e]	X		X (before disclosure)		
CDR	X				
CFI (self and study partner)	X				
ADCS-ADL Prevention Questionnaire (self and study partner)	X				
Florbetapir PET scan		X			
Amyloid status disclosure			X		
Fasting LP (optional)[d]					X
Collection of Laboratory Specimens					
Clinical chemistry, hematology, HbA1c	X				
Urinalysis	X				
Blood for APOE Genotyping	X				
Addendum 1 Blood Samples[c]	X		X[c]		

Abbreviations: ADCS-ADL Prevention Questionnaire = Alzheimer's Disease Cooperative Study – Activities of Daily Living Prevention Questionnaire; PACC = Preclinical Alzheimer's Cognitive Composite; APOE = apolipoprotein E gene; C3 = Computerized Cognitive Composite; CDR = Clinical Dementia Rating; CFI = Cognitive Function Index; C-SSRS = Columbia Suicide Severity Rating Scale; HbA1c = hemoglobin A1c; HIPAA = Health Insurance Portability and Accountability Act; LP = lumbar puncture; MRI = magnetic resonance imaging; PET = florbetapir positron emission tomography; SC = screening; SC V = screening visit.

a If C-SSRS indicates suicide-related behavior has occurred, the Lilly Self Harm Form is to be completed and follow-up must occur by a site clinician.

b Administered by phone within 3 business days of SC V3.

c See Addendum 1 for details; Addendum 1 blood samples to be taken under fasted conditions.

d Optional LP is available in US, Canada, and Japan only.

e The C3 will be optional in Japan.

f Every effort should be made to administer the PACC before all other procedures on the same day.

Study Schedule, A4 Protocol, Visits 6 through 66 (Placebo-Controlled Period)[a]

Category / Procedure	Rand																					Early Term[i]
Visit No[a].:	V6	V9	V12	V15	V18	V21	V24	V27	V30	V33	V36	V39	V42	V45	V48	V51	V54	V57	V60	V63	V66	
Week:	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240	
Tolerance Interval for Visit (days)		±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	
Infusion[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Safety Assessments																						
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Psychological Well Being	X	X		X		X		X		X		X		X		X		X		X	X	X
C-SSRS[b]	X	X		X		X		X		X		X		X		X		X		X	X	X
Physical/neurological examination	X							X							X						X	X
Vital signs	X	X	X	X	X			X		X		X		X		X		X		X	X	X
Electrocardiogram	X	X	X		X					X					X						X	X
MRI[c]		X						X							X						X	X
Amyloid Disclosure Assessments																						
Future Time Perspective Scale		X		X				X							X						X	X
Concerns about AD Scale		X		X				X							X						X	X
Efficacy and Health Outcomes Measures																						
PACC (version SC, A, or B, as shown)[d,j]	A		B		SC		A		B		A		B		A		SC		B		A	X
C3[g,j]		X		X		X		X		X		X		X		X		X		X		X
CDR[j]					X					X					X			X			X	X
CFI (self and study partner)[j]					X					X					X			X			X	X
ADCS-ADL Prevention Questionnaire (self and study partner)[j]					X					X					X			X			X	X
RUI-B[j]	X				X					X					X						X	X
Florbetapir PET scan																					X	X
Fasting LP (optional)[f]																					X	X
Research Satisfaction Survey	X				X					X					X						X	X
Clinician Diagnostic Impression (CDI)																					X	

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Study Schedule, A4 Protocol, Visits 6 through 66 (Laboratory Specimens, Placebo-Controlled Period)[a] (completed)

Procedure	Rand																					Early Term[i]
Visit No.[a]:	V6	V9	V12	V15	V18	V21	V24	V27	V30	V33	V36	V39	V42	V45	V48	V51	V54	V57	V60	V63	V66	
Week:	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240	
Tolerance Interval for Visit (days)		±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	
Collection of Laboratory Specimens[e]																						
Clinical chemistry, hematology, HbA1c	X	X	X		X					X					X						X	X
High sensitivity C-reactive protein	X	X	X		X					X					X						X	X
Urinalysis					X					X					X						X	X
Immunogenicity specimen	X	X	X		X					X					X						X	X
Plasma for solanezumab	X	X	X		X					X					X						X	X
Plasma for biomarker long-term storage	X	X	X		X					X					X						X	X
Serum for biomarker long-term storage	X	X	X		X					X					X						X	X
Whole blood for biomarker long-term storage	X									X					X						X	X

Abbreviations: AD = Alzheimer's disease; ADCS-ADL Prevention Questionnaire = Alzheimer's Disease Cooperative Study – Activities of Daily Living Prevention Questionnaire; PACC = Preclinical Alzheimer's Cognitive Composite; AE = adverse event; CFI = Cognitive Function Index; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; EOS = end of study; HbA1c = hemoglobin A1c; LP = lumbar puncture; MRI = magnetic resonance imaging; PET = positron emission tomography; Rand = randomization; RUI-B = Resource Use Inventory, Brief version; SC = screening; V = Visit.

[a] At all visits not shown on the table (Visits 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43, 44, 46, 47, 49, 50, 52, 53, 55, 56, 58, 59, 61, 62, 64, and 65), infusion and collection of AE and concomitant medication information will occur.

[b] If C-SSRS indicates suicide-related behavior has occurred, the Lilly Self Harm Form is to be completed and follow-up must occur by a site clinician.

[c] If MRI is done on the same day as cognitive and other assessments, then it should be done after cognitive and other tests. MRI may be done before other visit procedures, including cognitive and other tests, but in that case MRI must be done at least 1 day before other visit procedures. The V66 MRI may be done up to 4 weeks before other V66 procedures, but must be done after the completion of V65.

[d] Every effort should be made to administer the PACC before all other procedures on the same day. PACC version at early term visit should be the next version in series (not including SC).

[e] Blood samples should be collected before beginning infusion. Record the date and times of sample collection on the Lab Requisition Form.

[f] Optional LP is available in US, Canada, and Japan only. The postbaseline LP should be performed during the same time of the day as the baseline LP and fasting status must be recorded for all LPs.

[g] The C3 will be optional in Japan.

[h] Visit intervals are every 4 weeks ±10 days throughout the trial. In addition, there are to be a minimum of 14 days between infusions once a subject is receiving solanezumab at doses of 800 or 1600 mg Q4W.

[i] Depending on the timing of the most recent visit, not all procedures/tests may be required at early termination. Consult medical monitor for early terminations.

[j] Efficacy measures (including PACC, C3, CDR-SB, CFI, ADCS-ADL Prevention Questionnaire, and RUI-B) that are not collected at the scheduled visit may be collected at a subsequent visit within 8 weeks of the scheduled visit window. If the PACC is collected at a subsequent visit, it must be the same version that was missed (SC, A, or B).

Study Schedule, A4 Protocol, Dose Escalation Safety Cohort

Dose (mg)	800	800	1600	1600	1600	1600
Week relative to first dose of 800 mg:	0	4	8	12	16	20
Consent and HIPAA Authorization[a]	X					
Vital signs	X	X	X	X	X	X
Electrocardiogram		X		X		
MRI[b]			X			
Plasma for solanezumab (PK/PD)	X	X	X	X		X
Immunogenicity specimen	X	X	X	X		X
Clinical chemistry, hematology, urinalysis		X		X		
Infusion (800 mg)[c]	X	X				
Infusion (1600 mg)[c]			X[d]	X[d]	X[d]	X[d]
1-Hour Post-Infusion Monitoring	X		X			

Abbreviations: HIPAA = Health Insurance Portability and Accountability Act; MRI = magnetic resonance imaging; PD = pharmacodynamics; PK = pharmacokinetics.

[a] Consent and HIPAA authorization can take place at time point 0 or any time before the first dose of 800 mg is given.

[b] Additional safety MRI will be conducted at least 7 days after the second dose of 800 mg and at least 7 days before escalating dose to 1600 mg so results of the central read can be reviewed by the site before the escalation. If the MRI cannot be read before the first scheduled dose of 1600 mg, the subject should continue to receive 800 mg until such time that the MRI central read is available, which will not be considered a protocol deviation. If a study MRI is scheduled within ±2 months of the dose escalation MRI, the MRI should be conducted according the dose escalation schedule as a substitute for the MRI specified in the main study schedule; an exception is the MRI at endpoint (Visit 66), which should be done according to the Study Schedule regardless of timing relative to dose escalation.

[c] Infusion occurs after all other procedures at each visit.

[d] Dosing at 1600 mg every 4 weeks to continue through the remaining duration of the study.

Study Schedule, A4 Protocol, Visits 66 through 117 (Open-Label Extension Period)

Category / Procedure																			Early Term[a]
Visit No[b].:	V66	V69	V72	V75	V78	V81	V84	V87	V90	V93	V96	V99	V102	V105	V108	V111	V114	V117	
Week:	240	252	264	276	288	300	312	324	336	348	360	372	384	396	408	420	432	444	
Tolerance Interval for Visit (days)[c]	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	±10	
Informed Consent[d]	X																		
Infusion (every 4 weeks)	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Safety Assessments																			
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[e]		X		X		X		X		X		X		X		X		X	X
MRI[f]			X																
Efficacy and Health Outcomes Measures																			
PACC (version A or B, as shown)[g]			B		A		B		A		B		A		B		A		X[g]
CDR[h]					X				X				X				X		X
CFI (self and study partner)[h]					X				X				X				X		X
C3[h,i]		X		X		X		X		X		X		X		X		X	X
ADCS-ADL Prevention Questionnaire (self and study partner)[h]					X				X				X				X		X
RUI-B[h]					X				X				X				X		X
Clinician Diagnostic Impression					X				X				X				X		X

Abbreviations: AD = Alzheimer's disease; ADCS-ADL Prevention Questionnaire = Alzheimer's Disease Cooperative Study – Activities of Daily Living Prevention Questionnaire; PACC = Preclinical Alzheimer's Cognitive Composite; AE = adverse event; CFI = Cognitive Function Index; C-SSRS = Columbia Suicide Severity Rating Scale; MRI = magnetic resonance imaging; V = Visit.

[a] Depending on the timing of the most recent visit, not all procedures/tests may be required at early termination. Consult medical monitor for early terminations. If the open-label period is ended early because of lack of efficacy in the placebo-controlled period, all participants should have an early termination visit within 3 months of site notification.

[b] The open-label period uses a common close design such that subjects will complete the study period at approximately the same time, up to V117 (444 weeks) or when primary analyses of the A4 study placebo-controlled period are completed and reviewed, whichever comes first. At all visits not shown on the table (Visits 67, 68, 70, 71, 73, 74, 76, 77, 79, 80, 82, 83, 85, 86, 88, 89, 91, 92, 94, 95, 97, 98, 100, 101, 103, 104, 106, 107, 109, 110, 112, 113, 115, and 116), infusion and collection of AE information will occur.

[c] Visit intervals are every 4 weeks ±10 days throughout the trial. In addition, there are to be a minimum of 14 days between infusions.

[d] Prior to administration of study drug, confirm approval from the coordinating center has been granted, that the open-label period informed consent has been obtained, and that all V66 (Week 240) assessments, including MRI and florbetapir PET, have been completed. Consent may be obtained any time before the V66 infusion. Subjects may enter the open-label period of the study and receive their first open-label infusion of study drug up to 12 weeks following completion of the placebo-controlled period Visit 66 assessments and procedures.

[e] If C-SSRS indicates suicide-related behavior has occurred, the Lilly Self Harm Form is to be completed and follow-up must occur by a site clinician.

[f] The MRI and florbetapir and flortaucipir (if applicable) PET scans at V66 must be completed before the infusion and can be completed up to 4 weeks before V66.

[g] The PACC should be administered before all other procedures on the same day. PACC version at the early term visit should be the next version in series (not including SC). If the PACC is not collected at the scheduled visit, the missed version should be collected at the next possible subsequent visit within 8 weeks of the scheduled visit window.

[h] If the CDR-SB, CFI, C3, ADCS-ADL Prevention Questionnaire, or RUI-B is not collected at the scheduled visit, the assessment may be collected at a subsequent visit within 8 weeks of the scheduled visit window.

[i] The C3 will be optional in Japan.

Attachment 2. A4 Protocol Clinical Laboratory Tests

Clinical Laboratory Tests for A4 Protocol

Hematology[a,b,c]	**Clinical Chemistry**[a,c] **Serum Concentrations of:**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count	Chloride
MCV	Total bilirubin[d]
MCHC	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	ALT/SGPT[d]
Lymphocytes	AST/SGOT[d]
Monocytes	GGT
Eosinophils	BUN
Basophils	Creatinine
Platelets[a,e]	Uric acid
	Phosphorus
Coagulation Panel[c,e]	Calcium
PT	Glucose, nonfasting or fasting
INR	Total protein
PTT	Albumin
	Cholesterol
CSF[f,g]	CK
Glucose	
Protein	
Cell count with differential	
Urinalysis[a,c]	**Other Tests**
Color	Urine pregnancy[h]
Specific gravity	APOE genotyping[a,c,i]
pH	Serologies if needed[c,d]
Protein	C-reactive protein[c]
Glucose	HbA1c[a]

Ketones
Blood
Leukocyte esterase

Clinical Laboratory Tests for A4 Protocol Abbreviations and Footnotes

Note: Laboratory tests may be ordered by the primary investigator at any time during the study when they are deemed clinically indicated.

Abbreviations: APOE = Apolipoprotein E gene; ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; BUN = blood urea nitrogen; CK = creatine kinase; CSF = cerebrospinal fluid; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; hCG = human chorionic gonadotropin; INR = International Normalized Ratio; MCHC = mean cell hemoglobin concentration; MCV = Mean cell volume; PT = Prothrombin Time; PTT = Partial Thromboplastin Time; SGOT = serum glutamic oxalo-acetic transaminase; SGPT= serum glutamic pyruvate transaminase; ULN = upper limit of normal; WBC = white blood cells.

[a] Assayed by central laboratory.

[b] Reflex assessment of cell morphology by peripheral smear will be performed when predefined hematology limits are exceeded.

[c] 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.

[d] If a study subject experiences elevated ALT or AST >3X ULN or elevated total bilirubin >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 subject safety and comply with regulatory guidance, the investigator is to consult with the Medical Monitor regarding collection of specific recommended clinical information and follow-up laboratory tests.

[e] Optional, for subjects who undergo a lumbar puncture. If desired, coagulation profile (including PT/INR and PTT) and platelet count are obtained from a local laboratory up to 4 weeks before the lumbar puncture.

[f] Assayed by local laboratory.

[g] Cerebrospinal fluid samples are only collected from subjects undergoing LP.

[h] Urine pregnancy tests are ordinarily required on the day of florbetapir PET imaging in females of childbearing potential to rule out pregnancy. Because such females are excluded from participation by exclusion criterion [24], this is not routinely necessary in this study. However, if there is any concern that a subject is not fully menopausal (for example, has had suspected menses in the past 12 months), conduct a pregnancy test; this test must be negative in order to proceed with florbetapir dose administration.

[i] Neither subjects nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results.

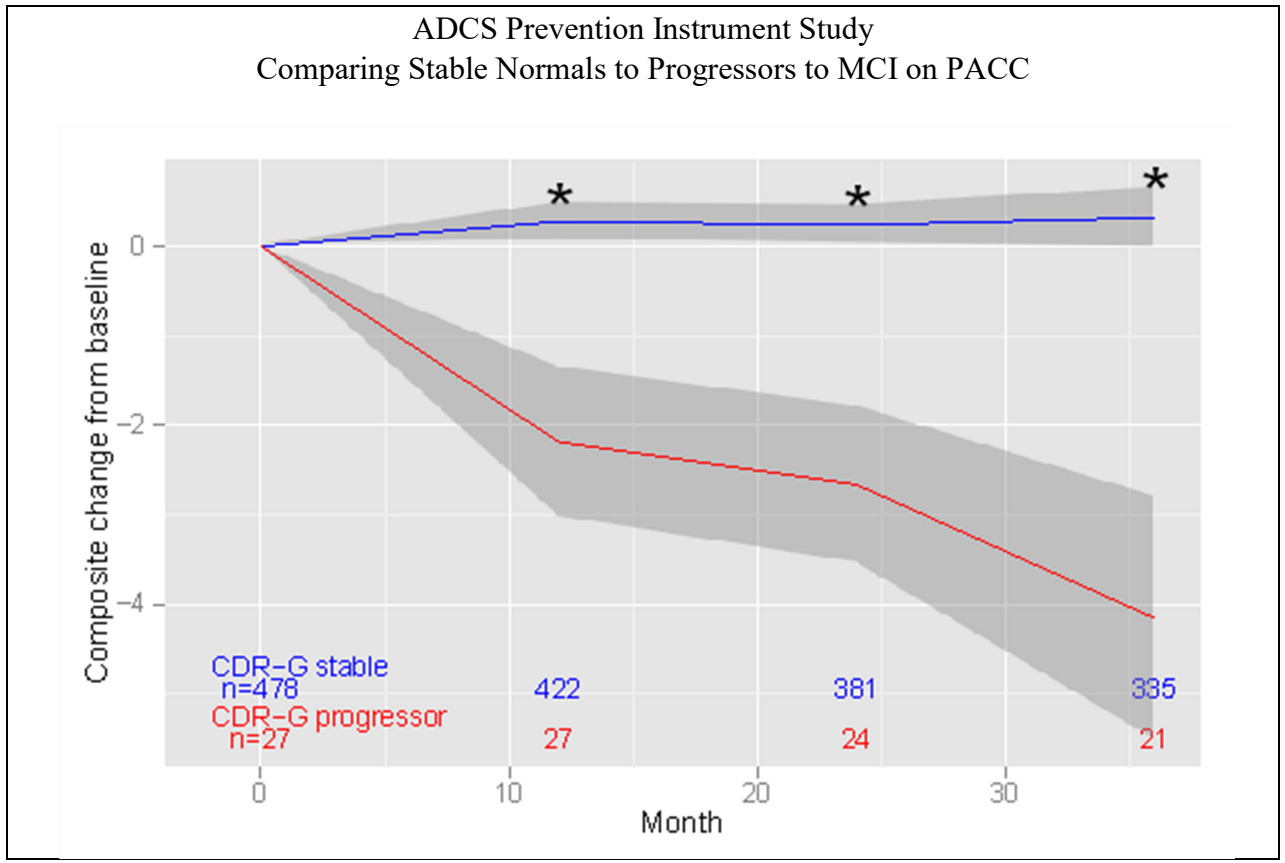
Attachment 3. Development of the PACC Measure

Based on review of the literature from cohort studies data from "normal controls" who progressed to mild cognitive impairment or AD dementia, we determined that a composite measure sensitive to change in preclinical AD would likely require assessment of these key domains: episodic memory, executive function, and orientation. Previous studies have reported evidence that both list learning and paragraph recall measures of episodic memory decline 7 to 10 years prior to the diagnosis of MCI or AD dementia (Elias et al. 2000; Grober et al. 2008; Derby et al. 2013). Recent data from amyloid imaging studies have reported decline in multiple cognitive domains looking retrospectively at cognitive trajectories over 8 to 10 years prior to PET amyloid imaging (Resnick et al. 2010; Landau et al. 2012; Snitz et al. 2013) and prospectively over 1- to 3-year longitudinal follow-up (Morris et al. 2009; Doraiswamy et al. 2012; Knopman et al. 2012; Lim et al. 2012b; Kawas et al. 2013).

In order to test the hypothesis that a composite measure including episodic memory measures, timed executive function and a global measure would be sensitive to detect decline from clinically normal to the stage of mild cognitive impairment, we tested several combinations of measures using data from longitudinal studies in clinically normal populations, including the Alzheimer's Disease Neuroimaging Initiative (ADNI); the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL); and the ADCS-PI trial.

Evidence Supporting Use of the Proposed Composite. We examined whether the proposed combination of measures (memory, timed executive function, and global) would demonstrate greater decline in individuals progressed to MCI (CDR 0.5) compared with those who remained normal (CDR 0) in two datasets: the ADCS-PI and ADNI.

Figure A4.3 illustrates the 3-year change in the proposed composite (PACC) among those who declined from Normal (defined as CDR 0) to MCI (CDR 0.5 plus cognitive decline) as compared with those whose CDR score remained stable at 0 in the ADCS-PI trial. Figure A4.4 shows ADNI data from a very similar composite cognitive measure for Normals who remained stable compared to those who progressed to a diagnosis of MCI over 3 years. Both datasets demonstrate the sensitivity of a composite that included episodic memory, timed executive function, and global measures (including orientation) to detect cognitive decline in individuals who demonstrate clinical decline to the stage of MCI.

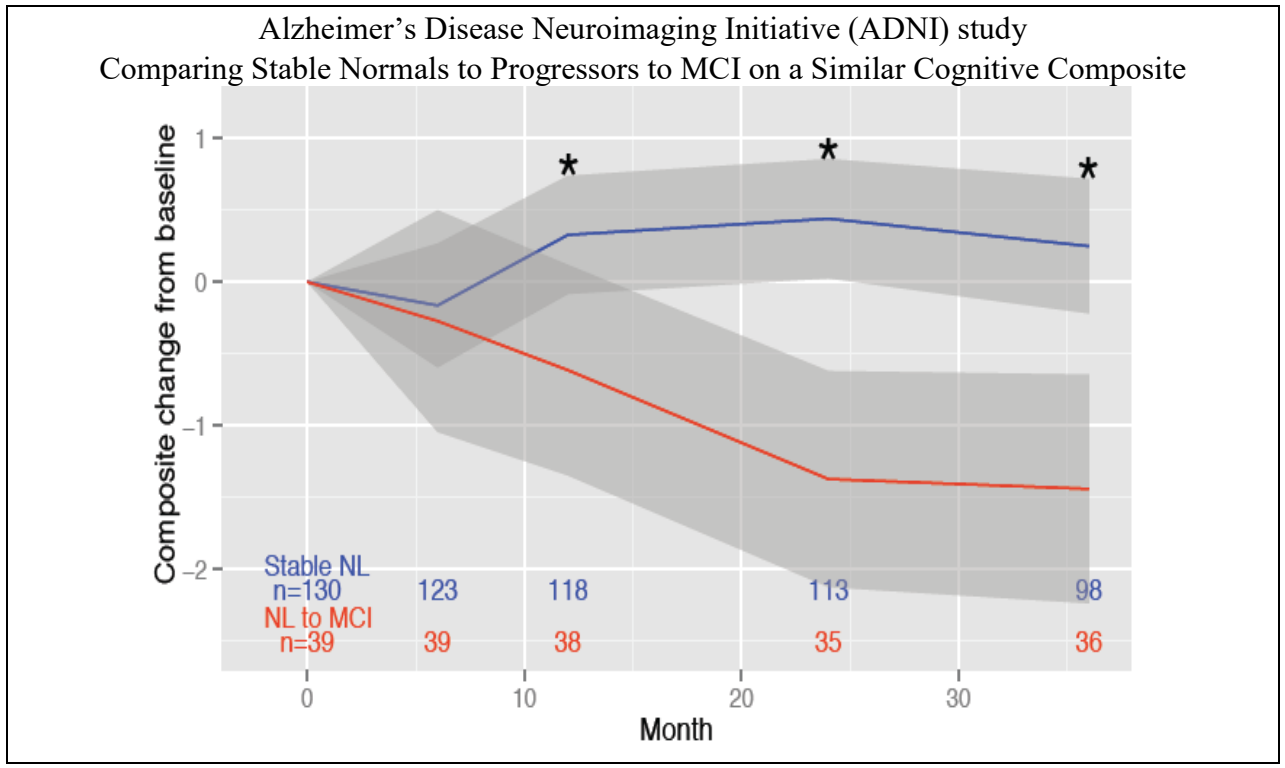


The shaded regions represent 95% confidence intervals for the estimates at each time point. CDR-G stable refers to subjects whose global CDR score remained at 0 throughout the trial; [C]DR-G progressors were those whose global CDR score changed from 0 to 0.5.

* $p<0.05$ For the test of the group difference at the indicated time.

Abbreviations: ADCS = Alzheimer Disease Cooperative Study; CDR-G = Clinical Dementia Rating – Global score.

Figure A4.3. **MMRM estimates of change on the ADCS Preclinical Alzheimer Cognitive Composite, controlling for age, for stable and progressing subjects from the ADCS Prevention Instrument (PI) study.**

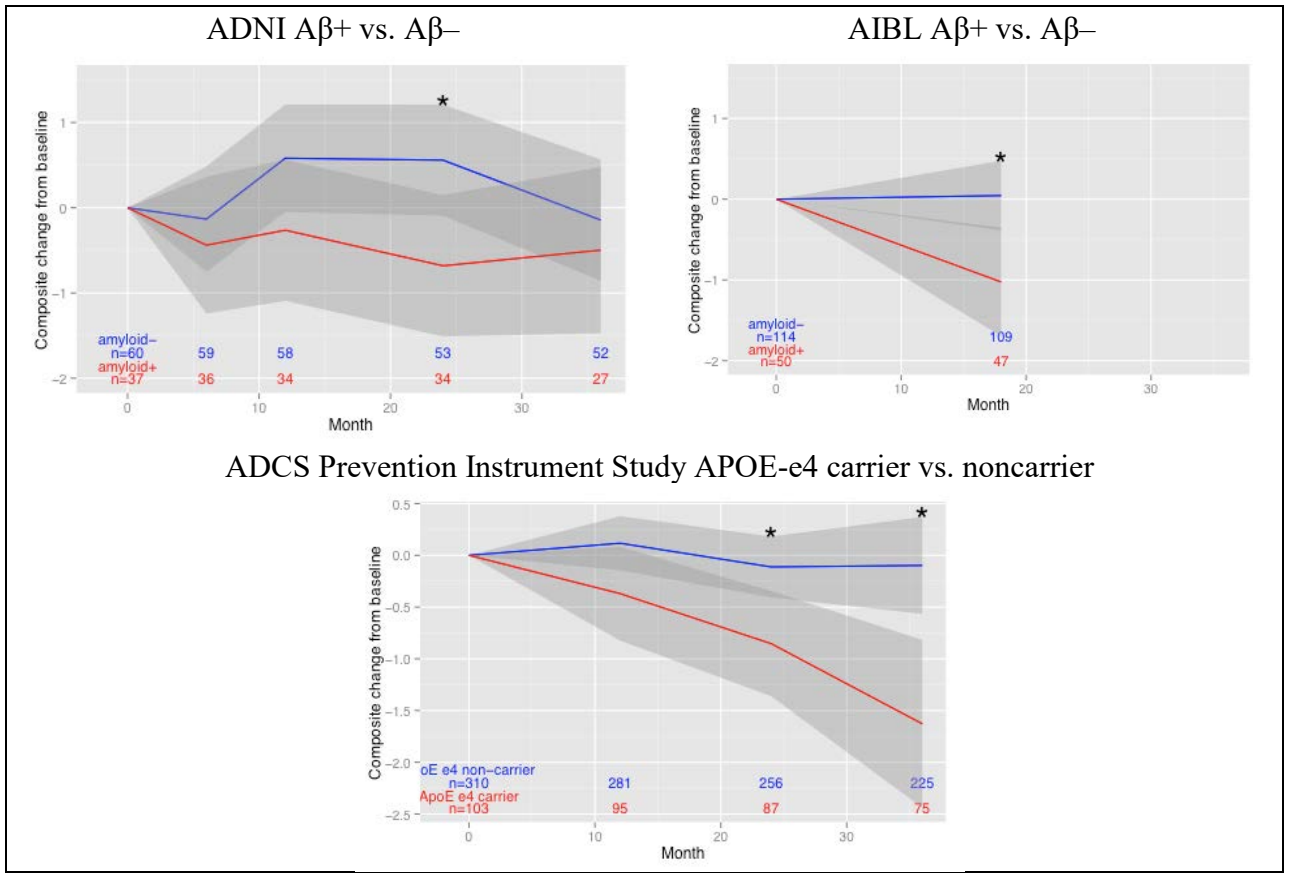


The shaded regions represent 95% confidence intervals for the estimates at each time point.
* $p<0.05$ For the test of the group difference at the indicated time.
Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; LMIIa = Logical Memory test, part IIa; MCI = mild cognitive impairment; MMRM = mixed model repeated-measure; NL=normal; RAVLT = Rey Auditory Verbal Learning Test.

Figure A4.4. MMRM estimates of change on the ADNI data, using a similar Composite (RAVLT for list learning, LMIIa, Digit Symbol, and MMSE), controlling for age, comparing for stable NL subjects versus NL subjects who progressed to MCI in ADNI.

Data from normal controls with elevated brain amyloid deposition and normal controls without elevated brain amyloid deposition were compared in the ADNI and AIBL datasets. For these power analyses, we only considered clinically normal older individuals (CDR 0) with baseline Logical Memory Delayed Recall scores of less than 15 to capture individuals at the highest risk of imminent

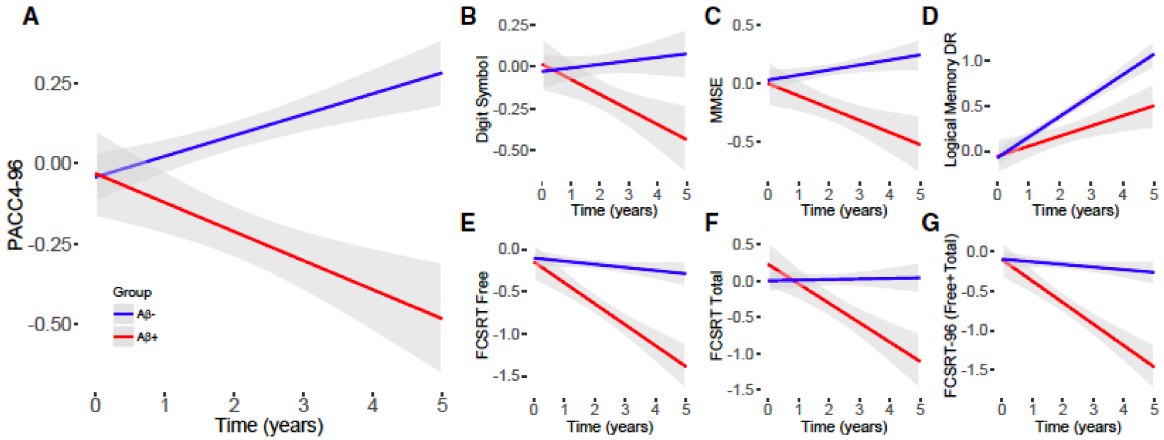
cognitive decline. In the ADCS Prevention Instrument study, biomarkers of amyloid were not collected. Therefore, we considered APOE ε4 carriers (at least one allele) versus noncarriers in the ADCS-PI trial (see Figure A4.5).



The shaded regions represent 95% confidence intervals for the estimates at each time point.
* p<0.05 For the test of the group difference at the indicated time.
Abbreviations: Aβ = amyloid-β peptide; ADCS = Alzheimer Disease Cooperative Study; ADNI = Alzheimer's Disease Neuroimaging Initiative; AIBL = Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing.

Figure A4.5. MMRM estimates of change on the ADCS Preclinical Alzheimer Cognitive Composite, controlling for age, from ADNI, AIBL, and the ADCS Prevention Instrument (PI) study.

The Harvard Aging Brain Study (HABS) is a longitudinal study of aging and preclinical Alzheimer's disease. The HABS is following approximately 300 clinically normal older (CDR=0; 73.5±6.0 years) individuals, characterized on the basis of baseline amyloid PET imaging. In a recent study (Mormino et al. 2017), we investigated amyloid-beta (Aβ)-related longitudinal cognitive change, examining several variations of the Preclinical Alzheimer Cognitive Composite (PACC). Aβ+ CN demonstrated longitudinal decline on all individual PACC components, and all PACC variations. Aβ group differences emerged after 1 to 2 years when both Free and Total Recall FCSRT scores were included in the PACC (see Figure A4.6). Decline in PACC was also associated with progression to CDR 0.5. These results confirm the ability of the PACC to capture both early and late cognitive decline during the preclinical stages of AD, which may prove advantageous in prevention trial design.



Abbreviations: HABS = Harvard Aging Brain Study; PACC = preclinical Alzheimer cognitive composite.
Source: Mormino et al. (2017).

Figure A4.6. **Longitudinal change by Aβ status for the PACC and individual components tests in HABS participants. Aβ-related decline is significant for the PACC4-96 (A) as well as on all individual components (B–G). Z-scores are shown on the y-axis for all tests.**

Development of the PACC composite measure for the A4 trial has been publicly presented at an AlzForum webinar (Developing Outcome Measures for Pre-Dementia Trials – 28 February 2013) and published in 2014 (Donohue et al. 2014). This combination of tests measuring word list learning, paragraph recall, timed executive function and global cognition, including orientation to time, is also strongly supported by work done for the Alzheimer's Prevention Initiative (API) by Drs. Suzanne Hendrix and Jessica Langbaum, using longitudinal cohorts from Rush University and the Colombian PS-1 kindred data (Langbaum et al. 2011). These data were also presented by Dr. Hendrix in the AlzForum webinar (Developing Outcome Measures for Pre-Dementia Trials – 28 February 2013). Further description of development of the PACC has been reported by Mormino and colleagues (2017).

Evidence Supporting Selection of Individual Components.

- *Episodic Memory.* Across multiple datasets (ADNI, AIBL, ADCS-PI, and summary data from Washington University), we found evidence that a combination of a list learning memory measure and paragraph recall consistently provided the greatest sensitivity to detect decline in elevated brain amyloid (or APOE ε4) individuals. Although the available datasets used different list-learning measures, the results were quite consistent. We chose to use the FCSRT for the list-learning test for the A4 study, as this measure was particularly powerful in detecting decline in individuals who progressed to MCI during the ADCS-PI trial (Salmon et al. in press), 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). In addition, 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). The Delayed Paragraph Recall score on the Logical Memory IIa was chosen as the paragraph recall test because there is extensive data using this measure in ADNI and other cohorts (Crane et al. 2012; Derby et al. 2013).
- *Executive Function.* We also found that the addition of a timed executive function measure, such as Digit-Symbol, added power to detect decline, consistent with previous reports that slowing of processing speed and executive dysfunction are seen in very early AD (Albert 1996; Storandt et al. 2009).
- *Orientation/Other Cognitive Domains.* Although the MMSE has not been typically thought of as a sensitive measure for early detection, the MMSE score (or the Modified MMSE [Teng and Chui 1987]) consistently added power to detect decline in all of the cohorts that have been examined.

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