Protocol I5T-MC-AACD(f)

A Single- and Multiple-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Intravenous Doses of LY3002813 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

NCT02624778

Approval Date: 14-Dec-2017

1. Protocol I5T-MC-AACD(f)
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LY3002813

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 22 October 2015
Amendment (a) Electronically Signed and Approved by Lilly: 11 March 2016
Amendment (b) Electronically Signed and Approved by Lilly: 09 May 2016
Amendment (c) Electronically Signed and Approved by Lilly: 07 March 2017
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Amendment (e) Electronically Signed and Approved by Lilly: 22 June 2017
Amendment (f) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 14-Dec-2017 GMT

2. Synopsis

Clinical Pharmacology Protocol Synopsis: Study I5T-MC-AACD

<table>
<tr><td colspan="2">Name of Investigational Product: LY3002813</td></tr>
<tr><td colspan="2">Title of Study: A Single- and Multiple-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Intravenous Doses of LY3002813 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease</td></tr>
<tr><td>Number of Planned Patients: Up to 150 patients may be enrolled so that approximately 72 patients complete the study (7 dosing cohorts of 8 to 12 patients).</td><td>Phase of Development: 1b</td></tr>
<tr><td colspan="2">Length of Study:
Part A (Cohorts 1, 2, and 3): screening—approximately 6 weeks; single intravenous (IV) LY3002813 or placebo treatment; 72-week (for Cohorts 1 and 2) and 24-week (for Cohort 3) follow-up.
Part B (Cohorts 4 and 5): screening—approximately 6 weeks; multiple dose IV LY3002813 or placebo treatment every 2 weeks (Q2W) for 24 weeks; 48-week follow-up after dosing.
Part C (Cohorts 6 and 7): screening—approximately 6 weeks; multiple dose IV LY3002813 or placebo treatment every 4 weeks (Q4W) for 72 weeks; 12 weeks follow-up after dosing.</td></tr>
<tr><td colspan="2">Objectives:
<u>Primary Objective</u>
The primary objective is to assess the effect of LY3002813 on brain plaque load using florbetapir imaging.
<u>Secondary Objectives</u>
The secondary objectives are to further evaluate the safety and pharmacokinetics (PK) of single and multiple doses of LY3002813 in Japanese and non-Japanese patients with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) or mild to moderate AD, and to evaluate the immunogenicity of single and multiple doses of LY3002813.
<u>Exploratory Objectives</u>
• To assess the relationship among dosing regimens, PK, pharmacodynamics (PD) from florbetapir scan, immunogenicity, and immune safety.
• To evaluate changes in plasma, serum, and cerebrospinal fluid (CSF) biomarkers following single and multiple doses of LY3002813.
• To evaluate the effects of single and multiple doses of LY3002813 on cognitive function.
• To evaluate changes in magnetic resonance imaging (MRI) measures and 18F-AV-1451 tau positron emission tomography scan.
• To evaluate genetic interactions with study treatment response or any adverse events (AEs).</td></tr>
<tr><td colspan="2">Study Design: This is a 3-part, patient- and investigator-blind, randomized within cohort, placebo-controlled, parallel-group, single- and multiple-dose study in patients with MCI due to AD or mild to moderate AD to assess the safety, tolerability, PK, and PD of single and multiple IV doses of LY3002813.
The study will be conducted in at least 7 cohorts.
• Cohort 1: 10 mg/kg IV single dose
• Cohort 2: 20 mg/kg IV single dose
• Cohort 3: 40 mg/kg IV single dose
• Cohort 4: 10 mg/kg IV Q2W for 24 weeks
• Cohort 5: 20 mg/kg IV Q2W for 24 weeks
• Cohort 6: 10 mg/kg IV Q4W for up to 72 weeks
• Cohort 7: 20 mg/kg IV Q4W for up to 72 weeks</td></tr>
</table>

Each cohort will contain approximately 6 (single dose) or 9 (multiple dose) patients treated with LY3002813 and 2 to 3 patients treated with placebo so that the study can detect target engagement and antidrug antibody (ADA) frequency relative to those observed in Study I5T-MC-AACC.

Diagnosis and Main Criteria for Inclusion and Exclusion:
The study will enroll men or nonfertile women, at least 50 years of age with evidence of memory impairment on the Free and Cued Selective Reminding Test with Immediate Recall (FCSRT-IR), a Mini–Mental State Examination (MMSE) 16 to 30, a Clinical Dementia Rating of 0.5 to 2 and memory box score ≥0.5, no history of macrohemorrhage and no more than 4 microhemorrhages on MRI, and a positive amyloid scan by florbetapir. Patients with contraindication for MRI, presence of >4 microhemorrhages on MRI, or history or evidence on MRI of macrohemorrhage will be excluded. Criteria for Japanese patients: Japanese if recruited at sites in Japan or up to third-generation Japanese if recruited at sites outside of Japan. "Third-generation Japanese" is defined as a patient whose biological grandparents are of exclusive Japanese descent and were born in Japan.

Investigational Product, Dosage, and Mode of Administration:
LY3002813, single and multiple doses, from 10 mg/kg up to 40 mg/kg, IV infusion

Comparator, Dose, and Mode of Administration:
Placebo (saline), IV infusion

Planned Duration of Treatment:
Part A (Cohorts 1, 2, and 3): single dose of LY3002813 or placebo followed by 72 weeks (for Cohorts 1 and 2) and 24 weeks (for Cohort 3) follow-up for each dose level
Part B (Cohorts 4 and 5): 13 doses of LY3002813 or placebo administered Q2W for 24 weeks followed by 48-weeks follow-up
Part C (Cohorts 6 and 7): 19 doses of LY3002813 or placebo administered Q4W for 72 weeks followed by 12-weeks follow-up

Criteria for Evaluation:
Safety: Safety parameters that will be assessed include AEs, concomitant medications, cognitive function, physical and neurological examinations, vital signs, electrocardiogram, safety laboratory values, and MRI scans.
Bioanalytical: Serum and CSF samples will be used to determine concentrations of LY3002813. Serum and CSF concentrations of LY3002813 will be determined by validated enzyme-linked immunosorbent assay.
Pharmacogenomics: A blood sample will be used to test for genetic variants that may influence response to treatment.
Pharmacokinetic/Pharmacodynamic: Blood and CSF samples will be used to determine the concentrations of LY3002813. Cortical standardized uptake value ratio (SUVr) from florbetapir and 18F-AV-1451 positron emission tomography scans will be analyzed to estimate mean change. The CSF results from the lumbar punctures taken pre- and postinfusion will be analyzed to estimate the mean change from preinfusion. The dependent variables are $A\beta_{1-40}$, $A\beta_{1-42}$, total tau, and phospho-tau.

Statistical Evaluation Methods:
Up to approximately 150 patients may be enrolled to ensure that a minimum of approximately 72 patients complete the study. The sample size is customary for studies evaluating safety, PK, and/or PD parameters; at the conclusion of the trial, confidence intervals for PK, PD, and cognition endpoints may be computed in order to evaluate the precision of the estimates where appropriate. In addition, based on prior Lilly clinical trials, 6 patients randomized to each LY3002813 dose and placebo provide over 90% power to detect at least a 17% mean florbetapir SUVr reduction of a dose compared to placebo without multiple comparison adjustment.
Statistical: PK/PD analyses will be conducted on the full analysis set. This set includes all data from all randomized patients receiving at least 1 dose of the investigational product according to the treatment the patients actually received. Safety analyses will be conducted for all enrolled patients, whether or not they complete all protocol requirements. A model-based approach of analysis will be used. Summary statistics, data tabulations, and data graphs by ethnicity (Japanese and non-Japanese) will be provided as appropriate.
Safety: The safety parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

Pharmacokinetic/Pharmacodynamic: Noncompartmental analysis will be conducted, and PK parameter estimates of clearance and half-life will be reported for LY3002813. Compartmental modeling using nonlinear mixed-effects modeling or other appropriate software may be explored, and population estimates for clearance and central volume of distribution may be reported. Depending on the model selected, other PK parameters may also be reported. Exploratory graphical analyses of the effect of dose level or demographic factors on PK parameters may be conducted. Additional modeling may be performed based on the results of the graphical analyses. Exploratory graphical analyses relating LY3002813 serum exposure to LY3002813 CSF concentrations may be conducted. Exploratory analyses may be conducted to describe the relationship between serum or CSF exposure and changes in the florbetapir SUVr, as well as relationships with cognitive endpoints, ADA, AEs, and/or plasma and CSF biomarkers. Additional exploratory analyses of the data may be conducted if deemed appropriate. The relationship between the presence (or absence) of ADAs and clinical parameters (including AEs, PD measurements, and PK estimates of LY3002813) may be assessed. The relationship of ADA titers on these parameters also may be assessed.

Exploratory: Alzheimer's Disease Assessment Scale - Cognitive Subscale, Clinical Dementia Rating—Sum of Boxes, MMSE, Neuropsychological Test Battery, Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment-Activities of Daily Living scale, and FCSRT-IR may be analyzed using a mixed model repeated measure with pre-infusion cognitive measures as a baseline covariate and fixed effects of dose and study visit. In addition, the pre-infusion florbetapir SUVr may be used as a covariate in an exploratory analysis of change from pre-infusion cognitive measures in order to assess the baseline variation and change from baseline variation in the florbetapir SUVr and cognitive measures.

3. Table of Contents

A Single- and Multiple-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Intravenous Doses of LY3002813 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

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4. Abbreviations and Definitions

Term	Definition
Aβ	amyloid-beta (amyloid-β)
AD	Alzheimer's disease
ADA	antidrug antibody
ADAS-cog	Alzheimer's Disease Assessment Scale - Cognitive Subscale
ADCS-MCI-ADL	Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment-Activities of Daily Living
AE	adverse event: Any untoward medical occurrence in a patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE 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.
APOE	apolipoprotein E
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities-edema
ARIA-H	amyloid-related imaging abnormalities-microhemorrhage
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding/masking	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 single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received
C-SSRS	Columbia Suicide Severity Rating Scale
CAA	cerebral amyloid angiopathy
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes

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.
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.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CSE	clinically significant event: a moderate to severe adverse event (AE), abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the patient.
CSF	cerebrospinal fluid
ECG	electrocardiogram
EDTA	ethylene diamine tetraacetic acid
end of trial (study)	End of trial is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board: A board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
FCSRT-IR	Free and Cued Selective Reminding Test with Immediate Recall
FLAIR	fluid attenuation inversion recovery
GCP	good clinical practice: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
IB	Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.
ICF	informed consent form
ICH	International Conference on Harmonisation
informed consent	A process by which a patient 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 patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous
IWRS	interactive web response system
Legal Representative	An individual, study partner, or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical trial.
LP	lumbar puncture
MAD	multiple-ascending dose
MCI	mild cognitive impairment
MMRM	mixed model repeated measure
MMSE	Mini–Mental State Examination
MRI	magnetic resonance imaging
N3pG Aβ	pyroglutamate modification of the third amino acid of amyloid beta
NIAAA	National Institute on Aging-Alzheimer's Association
NTB	Neuropsychological Test Battery

patient	A study participant who has the disease or condition for which the investigational product is targeted.
PET	positron emission tomography
PK	pharmacokinetic
PD	pharmacodynamic
Q2W	every 2 weeks
Q4W	every 4 weeks
QTc	corrected QT interval
randomize	the process of assigning patients to an experimental group according to the randomization schedule for the trial.
re-screen	To screen a patient who was previously declared a screen failure for the same study.
SAE	serious adverse event: Any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
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 trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SAD	single-ascending dose
SC	subcutaneous
SUSARs	suspected unexpected serious adverse reactions
SUVr	standardized uptake value ratio
TEAE	treatment-emergent adverse events
TOMM40	translocase of outer mitochondrial membrane 40
TPO	third-party organization

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5. Introduction

5.1. General Introduction

LY3002813 is an antibody directed at the pyroglutamate modification of the third amino acid of amyloid beta (N3pG Aβ) epitope that is present only in brain amyloid plaques. It is being studied for the treatment of Alzheimer's disease (AD). The mechanism of action of LY3002813 is considered to be the targeting and removal of existing amyloid plaque, which is a key pathological hallmark of AD. The clinical strategy for LY3002813 targets the N3pG Aβ specific to amyloid plaque in the population of mild cognitive impairment (MCI) due to AD or mild to moderate AD patients with existing brain amyloid load, as measured using the amyloid plaque biomarker, florbetapir. This rationale is based on the amyloid hypothesis of AD, which states that the production and deposition of amyloid-β (Aβ) is an early and necessary event in the pathogenesis of AD. Clinical support for this hypothesis comes from the demonstration that parenchymal Aβ levels are elevated before the appearance of symptoms of AD. Furthermore, early in the disease, the presence of brain amyloid appears to increase the risk of conversion from MCI to AD. It is implicit in this hypothesis that enhanced clearance of Aβ plaques will lead to amelioration of AD symptoms and slow progression of AD.

The biomarker florbetapir is a positron emission tomography (PET) ligand that binds to fibrillar amyloid plaque. This biomarker can provide a qualitative and quantitative measurement of brain plaque load in patients with AD or MCI due to AD. The absence of significant florbetapir signal indicates that those patients clinically manifesting MCI or dementia lack evidence of amyloid pathology, which is a hallmark of the disease and the target of LY3002813 treatment. As such, implementation of florbetapir will provide a screening tool for entry into early clinical trials and provide a more homogeneous patient population for assessment of the risk of targeting plaques. Florbetapir PET also provides quantitative assessment of amyloid deposition in the brain and can serve as a pharmacodynamic (PD) biomarker of clearance of amyloid deposits.

The safety of LY3002813 was assessed in a 6-week toxicity study in cynomolgus monkeys, including evaluations of safety pharmacology and toxicokinetics. The administration of LY3002813 in monkeys of up to a maximum dose of 100 mg/kg/week (bolus intravenous [IV]) for 6 weeks resulted in no drug-related findings. Repeat-dose hazard identification studies of up to 6 months' duration were conducted in the aged PDAPP (APPV717F) transgenic mouse model of Aβ deposition to investigate potential effects related to clearance of Aβ from the brain. In addition, a specialized 3-month study to investigate the potential for cerebral amyloid angiopathy (CAA)-associated microhemorrhage was conducted in aged PDAPP transgenic mice. These studies in the PDAPP mouse were conducted with mE8c (LSN3026818), a murine analog

antibody of LY3002813, to avoid limitations due to potential immunogenicity from repeated administration of the humanized antibody to the mouse. No drug-related findings occurred in the hazard identification studies in PDAPP mice at mE8c doses of up to 100 mg/kg/week (the highest dose tested). Treatment of PDAPP mice with mE8c at 12.5 mg/kg/week for 3 months did not exacerbate CAA-associated microhemorrhage at a dose that produced a maximum pharmacological response (reduction in deposited brain Aβ) in these animals.

The first human dose study of LY3002813 was I5T-MC-AACC (Study AACC). Study AACC was a Phase 1, patient- and investigator-blind, randomized within cohort, placebo-controlled, parallel-group, single-dose followed by multiple-dose, dose-escalation study in patients with MCI due to AD or mild to moderate AD to assess the safety, tolerability, PD, and pharmacokinetics (PK) of single and multiple IV doses of LY3002813. The study included Japanese and non-Japanese patients. Patients with AD were enrolled into the single-ascending dose (SAD) phase and were each administered a single IV dose of LY3002813 (5 dosing cohorts from 0.1 mg/kg IV to 10 mg/kg IV) or placebo followed by a 12-week follow-up period for each dose level. After the follow-up period, the same patients proceeded into the multiple-ascending dose (MAD) phase (5 cohorts) and were administered IV doses of LY3002813 (0.3 mg/kg IV to 10 mg/kg IV; subjects in the 0.1 mg/kg SAD cohort received 0.3 mg/kg in the MAD phase) or placebo approximately once per month for up to 4 doses, depending on the initial dose level. This phase concluded with a 12-week follow-up period. The relative exposure assessment of an unblinded single subcutaneous (SC) dose of 3 mg/kg LY3002813 in AD patients was also performed, followed by a 12-week follow-up assessment study. This cohort did not continue to the MAD phase.

Under a protocol amendment, the PK of an unblinded single IV dose of 1 mg/kg LY3002813 in young, healthy male subjects was assessed to determine whether the absence of the amyloid target affected the PK as compared to amyloid-positive AD patients.

In the SAD portion of Study AACC, it was observed that LY3002813 had a significantly shorter half-life than the approximately 24-day half-life predicted based on data from nonclinical studies (a prediction that was consistent with the expected half-life of an immunoglobulin G1 antibody [Lobo et al. 2004]). After single-dose administration from 0.1 mg/kg to 3.0 mg/kg, the mean terminal elimination half-life was approximately 4 days, increasing to approximately 10 days (243 hours) at the 10-mg/kg dose level. The PK of a single dose of 1.0 mg/kg IV LY3002813 in young, healthy subjects was indistinguishable from the PK in AD patients at the same dose level. In the MAD phase, most patients at dose levels ≤3 mg/kg had serum LY3002813 concentrations below the limits of detection 28 days after dosing; patients receiving 10 mg/kg did have sustained quantifiable concentrations 28 days after dosing.

Greater than 90% of the patients with AD had treatment-emergent antidrug antibodies (ADAs) 3 months after the first dose at all dose groups; titers tended to increase by the end of the MAD phase and persist 3 months after the last dose. Dosing was stopped in the MAD phase of Study AACC because of high prevalence of ADAs and unexpected rapid elimination of the study drug.

Sixteen adverse events (AEs) of mild or moderate infusion related reactions were reported in 6 of 51 patients dosed with LY3002813. Infusion reactions occurred in 1 patient in the 0.3-mg/kg cohort, 2 patients in the 1.0-mg/kg cohort, and 3 patients in the 3.0-mg/kg cohort. The infusion reactions developed in 1 of the 6 patients after the first MAD dose and in 5 of the 6 patients after the second MAD dose. One patient discontinued because of dyspnea due to an infusion reaction (mild severity). All patients with infusion reactions had high peak titers of ADAs. Three patients were rechallenged with premedication (acetaminophen, antihistamine, and/or hydrocortisone) and had milder reactions on rechallenge. Infusion reactions began during the infusion or within 30 minutes of completing the infusion and lasted between 1 minute and 8 hours. Symptoms included chills/shivering (3 patients); flushing (2 patients); hypotension (asymptomatic, 1 patient); dyspnea (1 patient); myalgia (1 patient); rash (1 patient); and fever (1 patient).

LY3002813 was generally well tolerated when administered up to 10 mg/kg. There were no drug-related serious adverse events (SAEs) reported. Aside from the subject who withdrew from the study because of an infusion reaction AE described above, no other subject withdrew from the study because of an AE. There were a total of 88 treatment-emergent adverse events (TEAEs) reported irrespective of causality. The most common TEAEs (n = 2 or greater) were infusion related reaction (n = 16), fall (n = 5), headache (n = 4), upper respiratory tract inflammation (n = 4), upper respiratory tract infection (n = 3), amyloid related imaging abnormalities (ARIAs, n = 2), diarrhea (n = 2), dizziness (n = 2), eczema (n = 2), nausea (n = 2), urinary tract infection (n = 2) and delirium (n = 2). Of these, there were a total of 27 TEAEs that were deemed related to the study drug by the investigator. The most common drug related TEAEs were infusion related reaction (n = 16) and delirium (n = 2). Two cases of asymptomatic amyloid-related imaging abnormalities-microhemorrhage (ARIA-H) were detected by magnetic resonance imaging (MRI): (1) a patient in the 3-mg/kg IV cohort had a right temporal microhemorrhage at baseline; a new asymptomatic right external capsule microhemorrhage was detected by MRI at 6 months and was unchanged 1 month later; (2) a patient in the 3-mg/kg SC single-dose cohort had right temporal, right parietal, and left occipital microhemorrhages and moderate white matter lesions in the cerebrum and pons at baseline; asymptomatic new right parietal microhemorrhage and ischemic white matter lesions were detected by MRI 1 month after dosing and were unchanged 1 month later. There were no clinically significant findings in electrocardiograms (ECGs), vital signs, and safety laboratory tests.

Florbetapir scans were performed at baseline and after the last MAD, separated by approximately 7 months, to assess the PD effects of LY3002813. The change in grey matter standardized uptake value ratio (SUVr) with cerebellum as a reference region was compared across dose cohorts. There was a highly significant reduction in cerebral amyloid by PET at the highest dose ($p<.0002$). The analysis showed consistent reduction in cortical amyloid among patients receiving 3 to 5 doses of 10 mg/kg LY3002813. The mean reduction of 17% in SUVr corresponds to a mean 50% reduction in brain amyloid. Meaningful target engagement (amyloid reduction) was likely not achieved at doses smaller than or equal to 3 mg/kg IV every 4 weeks (Q4W) because of the rapid elimination of LY3002813 and the lack of sustained exposure.

More information about the known and expected benefits, risks, and reasonably anticipated AEs may be found in the Investigator's Brochure (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.

5.2. Rationale and Justification for the Study

This is the second study with LY3002813 in patients with MCI due to AD or mild to moderate AD. Data from Study AACC indicated a dramatic reduction in cerebral amyloid (as assessed by florbetapir PET imaging) in the 6 patients who received 3 to 5 doses of 10 mg/kg of LY3002813 IV over 6 months, without cerebral vasogenic edema or microhemorrhage complications in this dose group. These positive results were accompanied by a high incidence of ADAs at all doses, as well as infusion reactions noted at doses ≤3 mg/kg. Dosing was stopped in the multiple-dose phase of Phase 1 Study I5T-MC-AACC (Study AACC) due to high prevalence of ADAs and unexpected rapid clearance of the study drug.

As a result of the significant target engagement (amyloid reduction by florbetapir PET) that was identified after 3 to 5 doses of LY3002813 10 mg/kg IV over 6 months, the current study is proposed to determine whether different dosing regimens (single-dose, short-term "induction" dosing with higher, more frequent dosing; and chronic dosing for maximal PD effect) can mitigate immunogenicity and immune safety issues, and produce sustained amyloid reduction. The aims of the study are to evaluate the effect of different dosing regimens on ADAs and amyloid plaque removal, and assess the relationship between PK, PD (amyloid removal), immunogenicity, and clinical safety. As a high prevalence of ADAs was observed in Study AACC, a risk management plan for immune safety will be incorporated into the clinical trial including at least 6 hours monitoring after completion of each infusion, a protocol for management of infusion reactions, and standardized data collection for infusion reaction AEs.

A favorable risk/benefit profile and dosing selection will support further development of LY3002813, including: (1) removal of amyloid consistent with Study AACC; (2) persistence of amyloid removal after completion of dosing; (3) acceptable clinical impact of ADAs; (4) manageable risk of clinically significant infusion reactions; and (5) low incidence of amyloid-related imaging abnormalities-edema (ARIA-E) and ARIA-H.

6. Objectives

6.1. Primary Objective

The primary objective is to assess the effect of LY3002813 on brain plaque load using florbetapir imaging.

6.2. Secondary Objectives

The secondary objectives are to:

- further evaluate the safety and PK of single and multiple doses of LY3002813 in Japanese and non-Japanese patients with MCI due to AD or mild to moderate AD
- evaluate the immunogenicity of single and multiple doses of LY3002813

6.3. Exploratory Objective

The exploratory objectives are to:

- assess the relationship among dosing regimens, PK, PD from florbetapir scan, immunogenicity, and immune safety
- evaluate changes in plasma, serum, and cerebrospinal fluid (CSF) biomarkers following single and multiple doses of LY3002813
- evaluate the effects of single and multiple doses of LY3002813 on cognitive function
- evaluate changes in MRI measures and 18F-AV-1451 tau PET scan
- evaluate genetic interactions with study treatment response or any AEs

7. Investigational Plan

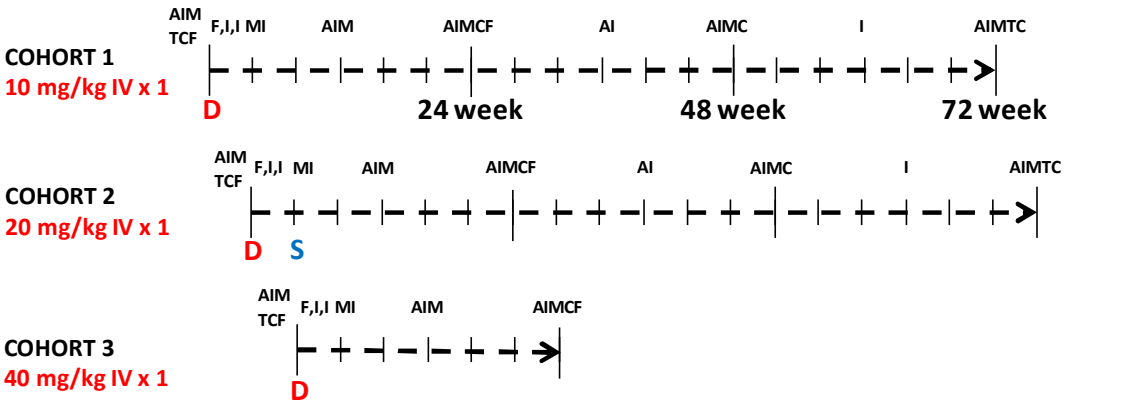
7.1. Summary of Study Design

This is a Phase 1b, patient- and investigator-blind, randomized within cohort, placebo-controlled, parallel-group, single- and multiple-dose study in patients with MCI due to AD or mild to moderate AD to assess the safety, tolerability, PK, and PD of single and multiple IV doses of LY3002813.

This study (Study AACD) will enroll patients with MCI due to AD, mild AD, or moderate AD with amyloid deposition confirmed by florbetapir PET imaging using National Institute on Aging-Alzheimer's Association (NIAAA) work group consensus guidelines (Albert et al. 2011; McKhann et al. 2011). This study will be conducted at sites in in multiple countries, including the United States and Japan. Up to 150 patients may be enrolled so that approximately 72 patients (7 dosing cohorts of 8 to 12 patients) complete the study.

The study will be conducted in at least 7 cohorts (Figure AACD.7.1):

- Cohort 1: 10 mg/kg IV single dose
- Cohort 2: 20 mg/kg IV single dose
- Cohort 3: 40 mg/kg IV single dose
- Cohort 4: 10 mg/kg IV every 2 weeks (Q2W) for 24 weeks
- Cohort 5: 20 mg/kg IV Q2W for 24 weeks
- Cohort 6: 10 mg/kg IV Q4W for up to 72 weeks
- Cohort 7: 20 mg/kg IV Q4W for up to 72 weeks



Abbreviations: f/u = follow up; IV = intravenous; MRI = magnetic resonance imaging; PET = positron emission tomography; Q2W = every 2 weeks; Q4W = every 4 weeks; x = times.

Assessments: **A** = amyloid PET; **I** = immunogenicity; **M** = MRI; **T** = tau PET; **C** = cognition; **F** = cerebrospinal fluid.

D = dosing; **S** = 4 week safety review of Cohort 2.

Follow-up assessments (immunogenicity, **I**; MRI, **M**) 12 weeks after last dose for Cohorts 6 and 7.

Note: vertical lines indicate 4-week intervals. Additional immunogenicity assessments will be performed every 12 weeks up to 48 weeks after the last dose of LY3002813 if the antibody titer has not returned to baseline.

Figure AACD.7.1. Study design.

Cohort 2 will only be initiated after review of safety data from Cohort 1. Thereafter, Cohort 3 will be initiated after review of safety data from Cohort 2. Cohorts 4 and 5 will be initiated after review of safety and PK data from their respective single-dose cohorts. An additional requirement for Cohort 5 is confirmation that at least 2 patients have received at least 3 doses each of LY3002813 safely in Cohort 4. Cohort 6 and Cohort 7 may proceed in parallel with Cohorts 4 and 5, respectively. In addition, Cohort 7 will only be initiated after confirmation that at least 2 patients have received at least 2 doses each of LY3002813 safely in Cohort 6. Safety/PK reviews will occur after a minimum of 4 patients receiving LY3002813 and 1 patient receiving placebo have been dosed. For Cohorts 1 to 3, no more than 1 patient will be dosed on any one particular day. For Cohorts 4 to 7, patients dosed on the same day at any one site should not be dosed simultaneously but should be separated by at least 1 hour. Each cohort will contain approximately 6 (single dose) or 9 (multiple dose) patients treated with LY3002813 and 2 to 3 patients treated with placebo so that the study can detect target engagement and ADA frequency relative to those observed in Study AACC.

The primary target engagement outcome is the reduction of cerebral amyloid as measured by quantitative amyloid PET imaging (florbetapir SUVr) assessed at baseline and at 12 weeks, 24 weeks, 36 weeks, 48 weeks, and 72 weeks after starting treatment. The early postbaseline scans are aimed to assess the time course of amyloid reduction; the later scans are aimed to assess sustainability of amyloid reduction after completion of dosing in Parts A and B, and maximal amyloid removal in Part C.

Safety and PK of LY3002813 will be assessed throughout the study for each cohort. In addition, blood samples for the assessment of immunogenicity will be taken at regular intervals throughout the dosing and follow-up periods. For Cohorts 1 through 3, a CSF sample will be taken by single lumbar puncture (LP) at baseline, another approximately 3 days after dosing to measure the CSF concentration of LY3002813 and CSF biomarkers. For Cohorts 4 through 7, a CSF sample will be taken by single LP at baseline and after 24 weeks dosing, or the last dose if treatment is stopped earlier.

As noted previously, a high prevalence of ADAs was observed in Study AACC; therefore, a risk management plan for immune safety is incorporated into the clinical trial. Other safety monitoring in Study AACD will include serial MRIs beginning at baseline and following dosing according to the study schedule for assessment of amyloid-related imaging abnormalities, AEs, ECGs, vital signs (blood pressure, pulse rate, and temperature), physical examinations, neurological examinations, and safety laboratory tests of blood (including immunogenicity).

Exploratory assessments include CSF, serum, and plasma biomarkers; cognitive function; MRI measures; 18F-AV-1451 tau PET scan (optional for Japan sites); and genetic interactions.

7.1.1. Screening for all Cohorts

At Visit 1, patients will undergo the screening tests outlined in Attachment 1. Upon fulfilling the screening criteria at Visit 1, the patient will undergo a screening MRI (Visit 2) and then a screening florbetapir PET scan (Visit 3), sequentially, provided that the MRI criteria are met before the PET scan occurs. If the patient's eligibility is confirmed by a positive florbetapir PET

scan, then this scan serves as their baseline PET scan. Patients may undergo some or all of the predose testing, including cognitive testing and LP as an outpatient or inpatient (Visit 4). Cognitive testing requires a minimum of 4 hours rest between the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) and Neuropsychological Test Battery (NTB) to avoid test fatigue; ideally, cognitive testing should occur before LP if on the same day, and LP should occur no closer than 24 hours before dosing. However, LP could be performed as a separate visit, and cognitive testing can be performed after a minimum of 24 hours has passed after performing the LP, and patient must be free from any post-LP headache. Patients should be admitted on Day 1, but may be admitted to the site on Day -1 (the day before the first dosing day).

7.1.2. Dosing for all Cohorts

For each dosing day, patients will remain resident at the site for a minimum of 6 hours from the end of infusion, during which time patients will be monitored for safety and, in particular, for infusion reactions. If deemed necessary for safety or feasibility reasons, patients may remain at the site for a longer duration (including an overnight stay), at the discretion of the investigator.

7.1.3. Part A: Single Dose Cohorts (Cohorts 1 through 3)

Safety, PK, and PD will be assessed in Cohorts 1 through 3 after single doses of LY3002813 or placebo. The planned doses are 10, 20, and 40 mg/kg IV for Cohorts 1, 2, and 3, respectively; with 8 patients (6 LY3002813; 2 placebo) planned to be enrolled in each cohort. Dose escalation will only occur after the safety from the preceding cohort has been established in at least 4 patients receiving LY3002813 and 1 receiving placebo. Safety data will be collected at least 1 week after dosing for dose escalation to Cohort 2 and at least 4 weeks after dosing for dose escalation to Cohort 3. Enrollment in Cohorts 2 and 3 will only commence once enrollment into the preceding cohort has completed. Safety, PK, and PD will be assessed at regular intervals for approximately 72 weeks (in Cohorts 1 and 2) or 24 weeks (in Cohort 3) after starting the dosing with study drug (Attachment 1).

7.1.4. Part B: 24-Week Q2W Multiple Dose Cohorts (Cohorts 4 through 5)

Safety, PK, and PD will be assessed in Cohorts 4 and 5, during and after multiple doses of LY3002813 or placebo have been administered Q2W for 24 weeks. The planned doses are 10 and 20 mg/kg IV with 12 patients (9 LY3002813; 3 placebo) planned to be enrolled in each cohort. Cohort 4 (10 mg/kg IV Q2W for 24 weeks) will be initiated after review of the safety (at least 1 week after dosing) and PK data (complete Day 29 visit) from at least 4 patients receiving LY3002813 and 1 receiving placebo in Cohort 1. Cohort 5 (20 mg/kg IV Q2W for 24 weeks) will only be initiated after review of the safety and PK data (at least 4 weeks after dosing) from Cohort 2 in at least 4 patients receiving LY3002813 and 1 receiving placebo, and after confirmation that at least 2 patients have been dosed safely with LY3002813 at least 3 times each in Cohort 4. Safety and PD will be assessed at regular intervals for approximately 48 weeks after completion of 24 weeks of dosing with LY3002813 (Attachment 1).

7.1.5. Part C: Chronic, 72-Week Q4W Multiple Dose Cohorts (Cohorts 6 and 7)

Safety, PK, and PD will be assessed in Cohorts 6 and 7 during and after multiple doses of LY3002813 or placebo have been administered Q4W for up to 72 weeks, or when the LY3002813-induced reduction in amyloid measured by florbetapir reaches the maximum reduction (defined as SUVr <1.1 for 2 consecutive scans) (Joshi et al. 2015). The planned doses are 10 and 20 mg/kg IV with 12 patients (9 LY3002813; 3 placebo) planned to be enrolled in each cohort. Cohort 6 (10 mg/kg IV Q4W) and Cohort 7 (20 mg/kg IV Q4W) may proceed, in parallel with Cohorts 4 and 5, respectively. In addition, Cohort 7 will only be initiated after confirmation that at least 2 patients have received at least 2 doses each of LY3002813 safely in Cohort 6. The maximum dose of 20 mg/kg will not be exceeded. If a patient is deemed to be amyloid negative by florbetapir PET before completion of 18 months' dosing (SUVr <1.1 for 2 consecutive scans), the patient will receive placebo infusion for all subsequent visits and continue the Part C visit schedule, including assessment of sustained amyloid reduction at the scheduled PET scan assessments. Safety, PK, and PD will be assessed for all patients at regular intervals for approximately 12 weeks after completion of 72 weeks of dosing with LY3002813 (Attachment 1).

7.1.6. CSF Sampling for all Cohorts

CSF samples will be obtained by single LP. In Cohorts 1 through 3, the first CSF sample will be collected at baseline and a second collected approximately 3 days after dosing. In Cohorts 4 through 7, a CSF sample will be collected at baseline and a second collected after 24 weeks of dosing, or the last dose if treatment is stopped earlier. Baseline and post-treatment CSF samples will be analyzed for biomarkers. LY3002813 concentrations will only be measured in the post-treatment samples (Attachment 1).

7.1.7. Study Design for Japanese Patients

Sites in Japan will participate in this study to recruit Japanese patients.

At least 2 Japanese patients should be enrolled in each dose cohort for Cohorts 1, 2, 4, and 6. Assuming that the cohorts will be dosed based on safety reviews, it is intended that at least 3 Japanese patients will be enrolled in each dose cohort for Cohorts 3, 5, and 7; however, recruitment to a cohort will not be contingent upon fulfilling these requirements. At least 17 Japanese patients should be enrolled in the study when all cohorts are dosed. Japanese patient enrollment into cohorts should ensure sufficient exposures at applicable doses to support future studies (for example, at least 6 Japanese patients overall exposed to LY3002813, and at least 2 Japanese patients per cohort exposed to LY3002813 at the highest doses to be used in future studies). For the purpose of safety evaluation in Japanese patients during the study, Japanese patients at sites in Japan and up to third-generation Japanese patients at sites outside of Japan will be included. The definition of up-to-third-generation Japanese is defined in Section 8.1.

Evaluation of safety data from patients before dose escalation in Japan must include at least 1 Japanese patient on LY3002813. Therefore, if no Japanese patients are assigned to

LY3002813 in the cohort of patients evaluated before dose escalation, then dose escalation outside Japan will proceed, and additional Japanese patients will be recruited so that at least 1 Japanese patient will be on LY3002813 to allow dose escalation in Japan. To avoid unblinding, there must be at least 2 Japanese patients in a cohort. Once the Japanese patients have adequate 1-week or 4-week safety evaluations (as applicable), then patients in Japan may join in the ongoing dose-escalation cohort.

CSF collection is not required for Japanese patients when the required total number of patients has already been reached for the cohort.

7.2. Discussion of Design and Control

The study will enroll patients with MCI due to AD, mild AD, or moderate AD with amyloid deposition confirmed by amyloid PET imaging using NIAAA work group consensus guidelines (Albert et al. 2011; McKhann et al. 2011). The broad study population is justified for this study because amyloid pathology is well established before the diagnosis of MCI due to AD and does not differentiate during the later stages of disease. Thus, patients within this spectrum are essentially uniform for the purpose of testing LY3002813 effects on target engagement (Jack et al. 2010). Safety, PK, and PD were assessed in this study population in Study AACC for doses of up to 10 mg/kg. Japanese patients are included in this study to help enable the inclusion of Japanese patients in potential subsequent phases of development.

The single-dose arms in Part A are intended to be used to assess whether target engagement can be achieved after a single dose of 10 mg/kg LY3002813 or greater, given that there was evidence of a robust PD signal after only 3 doses of 10 mg/kg LY3002813. The multiple-dose arms will be used to assess a dose response and a time course of amyloid reduction based on florbetapir scans at baseline and at 12- to 24-week intervals. Twenty-four weeks of dosing in Part B is proposed to approximate the maximum duration of dosing leading to amyloid reduction in Study AACC; amyloid scans at 12 weeks and 24 weeks will be used to assess the time course of amyloid removal and identify whether shorter treatment duration (12 weeks) is sufficient. Sustainability of amyloid reduction after completion of 24 weeks of dosing will be assessed by florbetapir PET at 36, 48, and 72 weeks. The higher dose and more frequent dosing (Q2W) may reduce the incidence of immunogenicity identified in Study AACC. If a 12- or 24-week dosing duration is sufficient for amyloid removal, then the risks of immunogenicity and infusion reactions will potentially be limited to that treatment period. Chronic high-dose treatment (Q4W for up to 72 weeks) in Part C will assess the time course of the maximal PD effect and the opportunity to treat until maximum amyloid removal.

Multiple doses of 10 mg/kg IV were safe and tolerated in Study AACC. Although infusion reactions were observed in 6 out of 51 patients dosed with LY3002813, there were no infusion reactions in the 10 mg/kg dose cohort, despite the presence of ADAs. Clinical dosing of single dose of 20 mg/kg or multiple dosing of 10 mg/kg in Study AACD will only be initiated after safety review of the single 10-mg/kg dose of LY3002813.

MRI safety monitoring will occur 4 weeks after the first dose, every 12 weeks from the first dose, and up to 12 weeks after the last dose, with acquisition of sequences appropriate for

detecting vasogenic edema and microhemorrhage. These MRIs and MRIs at additional time points (ie, at 24 weeks, 48 weeks, and 72 weeks) will also provide volumetric and other imaging biomarker assessments. Microhemorrhages are believed to indicate a higher risk for macrohemorrhage as well as for the presence of significant amyloid angiopathy, and there appears to be a risk of microhemorrhage with antiamyloid treatment in preclinical models and in humans (eg, bapineuzumab, gantenerumab, aducanumab [Black et al. 2010]) as well. Although there was no evidence of ARIA-E by MRI at up to 10 mg/kg LY3002813 in Study AACC, this study will continue to monitor ARIA-E (and ARIA-H). The screening MRI scan will be used to exclude patients with >4 microhemorrhages. The 12-week interval between MRI scans is considered appropriate given the lack of ARIA-E observed up to 10 mg/kg LY3002813 in Study AACC.

8. Study Population

8.1. Criteria for Enrollment

Eligibility of patients for study enrollment will be based on the results of a screening medical history, physical and cognitive examination, clinical imaging tests, and the research disease diagnostic criteria (Attachment 1). The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented at screening.

Screening tests may occur up to 56 days before study drug administration except for the following:

Exceptions to the 56-day screening window: the maximum interval of time allowed from performance of screening tests to dosing is presented below. If the interval is greater than what is allowed, then that test may be repeated to meet enrollment criteria before dosing. Note that stable medical therapy for 2 months is a requirement before dosing regardless of the time elapsed for screening criteria.

1) MRI: 70 days
2) Free and Cued Selective Reminding Test with Immediate Recall (FCSRT-IR), Mini–Mental State Examination (MMSE), and Clinical Dementia Rating (CDR): 90 days
3) Florbetapir imaging enrollment: 160 days

Note that patients recruited at the Japan sites must be Japanese. Up to third-generation Japanese patients recruited at sites outside Japan can be counted as Japanese patients. To be considered as Japanese per protocol, patients outside of Japan should be up to third-generation Japanese, which is defined as all of the patient's biological grandparents are of exclusive Japanese descent and were born in Japan.

Individuals who do not meet the criteria for participation in this study may be re-screened. Individuals may be re-screened up to 1 time upon sponsor review. The interval between re-screenings should be at least 1 week. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and is assigned a new identification number.

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

8.1.1. Inclusion Criteria

Patients are eligible for enrollment in the study only if they meet all of the following criteria:

[1] Patients must meet all the research disease diagnostic criteria for MCI due to AD or mild to moderate AD below, consistent with NIAAA research diagnostic guidelines (Albert et al. 2011; McKhann et al. 2011):

a) gradual and progressive change in memory function reported by patients or informants over more than 6 months

b) objective evidence of significantly impaired episodic memory characteristic of hippocampal dysfunction on testing: FCSRT-IR: *<27 for free recall* (The episodic memory impairment can be isolated or associated with other cognitive changes at the onset or as the disease advances.) (Auriacombe et al. 2010; Grober et al. 2010)

c) CDR = 0.5 to 2 and memory box score ≥0.5

d) MMSE score 16 to 30

e) positive florbetapir scan (central read)

[2] men or nonfertile women, at least 50 years of age. Nonfertile is defined as hysterectomy and/or bilateral oophorectomy, or amenorrhea for at least 1 year.

[3] have up to 2 reliable study partners, who will each provide written informed consent to participate, who are in frequent contact with the patient (defined as at least 10 hours per week) and 1 of whom at any 1 occasion will accompany the patient to the study visits, or will be available by telephone at designated times. If a patient has more than 1 study partner, it is preferred that 1 of them will be primarily responsible for the CDR and ADCS-MCI-ADL assessments.

The study partner(s) is/are required to accompany the patient for signing consent, on all dosing days and for all days that the Columbia Suicide Severity Rating Scale (C-SSRS)/Self-Harm Supplement Form and cognitive and functional scales are administered. If the study partner(s) is/are not able to accompany the patient in person because of an unavoidable circumstance, they must be available by telephone for the following assessments:

- AEs and concomitant medications
- relevant portions of the C-SSRS/Self-Harm Supplement Forms
- CDR and ADCS-MCI-ADL (primary study partner if possible)

If any study partner familiar with the study cannot continue, 1 replacement for each study partner is allowed, or more at the investigator's discretion. The replacement(s) will also need to sign a separate informed consent on the first visit that he/she accompanies the patient to participate.

Study partners must be able to communicate with site personnel and be willing to comply with protocol requirements, and in the investigator's opinion must have adequate literacy to complete the protocol-specified questionnaires.

[4] have adequate premorbid literacy, vision, and hearing for neuropsychological testing in the opinion of the investigator

[5] have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site

[6] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

8.1.2. Exclusion Criteria

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

[7] are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[8] are Lilly employees or employees of third-party organizations (TPOs) involved with the study

[9] have participated, within the last 30 days (for sites in Japan, 4 months) of screening, in a clinical trial involving an investigational product (other than the investigational product used in this study). If the previous investigational product has a long half-life, 3 months (for sites in Japan, 4 months) or 5 half-lives (whichever is longer) should have passed.

[10] are persons who have previously completed or withdrawn from this study. This exclusion criterion does not apply to patients who are allowed to re-screen before randomization.

[11] are persons who have previously participated in a study investigating LY3002813 and received active treatment with LY3002813

[12] are persons who have previously participated in a study with active and/or passive immunization against Aβ (not including LY3002813)

[13] have had gamma globulin therapy within the last 6 months

[14] have allergies to either humanized monoclonal antibodies, diphenhydramine, epinephrine, or methylprednisolone

[15] have a history of 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, and/or exfoliative dermatitis)

[16] have known allergies to LY3002813, related compounds, or any components of the formulation; or history of significant atopy

[17] have a clinically significant abnormality in the 12-lead ECG, including left bundle branch block, second or third degree heart block, or Bazett's corrected QT interval ≥470 msec for male patients or ≥480 msec for female patients, or intend to use drugs known to significantly prolong the QT interval within 14 days or 5 half-lives, whichever is longer, of a scheduled 18F-AV-1451 PET scan, or have a medical history of a risk factor of torsades de pointes

[18] have an unacceptable blood pressure or pulse rate, as determined by the investigator (Note: patients may be on a stable hypertension medication)

[19] show evidence of suicidal ideation within the last 6 months as assessed by the C-SSRS

[20] show evidence of clinically significant active neuropsychiatric disease, deemed to be a risk to patient participation in the study, in the opinion of the investigator

[21] show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies

[22] Exclusion Criterion [22] has been deleted

[23] are women who are lactating

[24] have used stable medical therapy for less than 2 months for any concurrent medical condition that is not exclusionary

[25] have donated blood of more than 500 mL within the last 30 days before dosing. For patients in Japan: have donated blood ≥400 mL in the last 3 months (male patients) or in the last 4 months (female patients), or any blood donation (including apheresis) within the last 1 month, or total volume of blood donation within 12 months is 1200 mL (male patients) or 800 mL (female patients) at screening

[26] have an average weekly alcohol intake that exceeds 21 units per week (male patients up to age 65) and 14 units per week (male patients over 65 and female patients), or are unwilling to stop alcohol consumption 48 hours before dosing until each discharge from the site (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

[27] have a known history of alcohol or drug abuse (as defined by the *Diagnostic and Statistical Manual, Fourth Edition, Text Revision* [APA 2000]) within 2 years of enrolling or a positive result regarding use of illicit drugs on the drug screening test

[28] have current serious or unstable illnesses including hepatic disease (cirrhosis, hepatitis A, B, or C [presence of antibody to hepatitis B surface antigen in the setting of hepatitis B immunization is not an exclusion; the presence of hepatitis C antibody a normal liver function tests and a negative hepatitis C polymerase chain reaction is also not an exclusion]); renal, gastroenterologic, respiratory, cardiovascular disease (active ischemic heart disease [stable or unstable angina], intermittent atrial fibrillation); endocrinologic disease (stable non-insulin-dependent diabetes or stable thyroid disease is not an exclusion); neurologic disease (other than AD); psychiatric disease (including suicidal ideation); immunologic, infectious (HIV, tuberculosis, Lyme, or hematologic disease (including transfusion within past year), or other conditions that, in the investigator's opinion, could interfere with the analyses of safety in this study.

[29] have a history of uncontrolled asthma, significant autoimmune disease (rheumatoid arthritis, systematic lupus erythematosus), hereditary angioedema, or common variable immune deficiency

[30] have any contraindications for MRI, including claustrophobia or the presence of contraindicated metal (ferromagnetic) implants/cardiac pacemaker

[31] have a head MRI (central read) demonstrating either greater than 4 cerebral microhemorrhages on T_2*-weighted gradient-echo sequence (regardless of their anatomical location), or a single area of superficial siderosis, or prior evidence of macrohemorrhage, or any other major intracranial pathology except: atrophy, meningiomas without mass effect, benign pituitary microadenomas, and/or mild to moderate white matter hyperintensities on fluid attenuation inversion recovery (FLAIR)

[32] have a history of intracranial hemorrhage; cerebrovascular aneurysm or arteriovenous malformation; or carotid artery occlusion, stroke, or epilepsy

Exclusion criteria [33] to [36] only apply to patients who will require an LP during the study:

[33] have criteria that would preclude an LP, such as allergy to all local anesthetics (such as lidocaine); have a local infection at the site of the LP; have ≤100 GI/L (100,000/mm^3) platelets, clinically significant coagulation abnormality, or significant active bleeding; treatment with an anticoagulant or treatment with 2 or more antiplatelet agents or other drugs that affect coagulation or platelet function within 14 days before lumbar puncture

[34] show clinically significant abnormalities in lumbar spine previously known or determined by screening lumbar x-ray or fluoroscopy (if conducted) that are considered incompatible with LP by the investigator and/or the person conducting the LP (if not the investigator)

[35] in the opinion of the investigator have a history of clinically significant back pain, back pathology, and/or back injury (for example, degenerative disease, spinal deformity, or spinal surgery) that may predispose to complications or technical difficulty with LP

[36] have medical or surgical conditions in which LP is contraindicated

Exclusion criteria [37] to [41] apply to all patients:

[37] have poor venous access that would preclude IV drug delivery or multiple blood draws

[38] have screening clinical laboratory test results with unacceptable deviations that are judged to be clinically significant by the investigator

[39] have a history within the past 5 years of a primary or recurrent malignant disease with the exception of resected cutaneous squamous cell carcinoma in situ, basal cell carcinoma, cervical carcinoma in situ, or in situ prostate cancer with a normal prostate-specific antigen after resection

[40] are being monitored for radiation due to occupational exposure to ionizing radiation, or exposure to ionizing radiation within last 12 months from an investigational study

[41] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

8.1.3. Rationale for Exclusion of Certain Study Candidates

Criteria [7] and [8] prevent conflict of interest in study participants. Criteria [9] through [41] exclude medical conditions, medication intolerance, and concomitant medication use that may constitute a risk for the patient and/or may confound the assessment of study endpoints.

8.2. Discontinuation

The reason for, and date of, discontinuation will be collected for all patients. All randomized patients who discontinue, regardless of whether or not they received investigational product, will have procedures performed as shown in the Study Schedule (Attachment 1).

8.2.1. Discontinuation of Patients

8.2.1.1. Patients Inadvertently Enrolled

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Lilly clinical pharmacologist or clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the investigator and Lilly clinical pharmacologist or CRP agree it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly clinical pharmacologist or CRP does not agree with the investigator's determination it is medically appropriate for the patient to continue. The investigator must obtain documented approval from Lilly clinical pharmacologist or CRP to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

8.2.1.2. Discontinuations from Investigational Product or from the Study

Patients will be discontinued from the investigational product and/or from the study in the following circumstances:

- 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 patient should be discontinued from the study

  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the other agent

- patient or study partner decision
  - the patient requests to be discontinued from the study
- sponsor decision
  - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- AE
  - if a clinically significant event (CSE) occurs, the investigational product is to be discontinued and appropriate measures taken. Lilly or its designee should be alerted immediately. A CSE will be defined as a moderate to severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the patient. Refer to Section 10.6.
  - a clinically significant systemic hypersensitivity reaction occurs following administration of the LY3002813 (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension), that requires parenteral medication, does not respond to symptomatic medication, or results in clinical sequelae or an anaphylactic reaction
  - Appearance of clinically significant new cerebral ischemic or hemorrhagic events by MRI, as judged by the investigator and agreed by the clinical pharmacologist/CRP
  - Appearance of symptomatic or asymptomatic ARIA-E (also known as cerebral vasogenic edema)
  - Appearance of symptomatic ARIA-H, including superficial siderosis, or an asymptomatic increase in the number of cerebral microhemorrhages >4 over baseline

Where possible, subjects who discontinue the investigational product because of an AE will continue with safety, PK, PD, and other assessments as per protocol and as deemed appropriate by the investigator and the Lilly clinical pharmacologist/CRP.

8.2.1.3. Suspension or Termination of Dosing for Either Dose Escalation or within a Dose Cohort

Dosing within a cohort, or dose escalation to a higher dose cohort (Cohorts 3, 5, 7), may be suspended or terminated if any of the following scenarios occur within a given dose cohort as determined by the unblinded Lilly CRP or clinical pharmacologist:

1) ≥2 patients experience an SAE that is considered related to LY3002813 administration. This would include:

   a) signs and/or symptoms consistent with meningoencephalitis

   b) fixed-focal neurological deficit

2) ≥2 patients experience evidence of clinically significant new cerebral ischemic or hemorrhagic events by MRI, as judged by the investigator and agreed by the clinical pharmacologist/CRP

3) ≥2 patients experience asymptomatic or symptomatic ARIA-E

4) ≥2 patients experience symptomatic ARIA-H, including superficial siderosis, or an asymptomatic increase in the number of cerebral microhemorrhages >4 over baseline

5) ≥2 patients develop clinically significant acute infusion AEs considered related to LY3002813 during or within 6 hours of completing the infusion that do not resolve with a reduced infusion rate and/or supportive care

6) ≥2 patients experience similar CSEs considered related to LY3002813. A CSE will be defined as a moderate to severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the patient.

7) 50% or more patients at a dose level experience moderate or severe AEs that impair normal activities, but do not meet the CSE criteria, and are considered related to study treatment

8) If an SAE occurs during the infusion of the study drug, irrespective of causality, the drug is discontinued immediately. No redosing or completion of dosing is considered for that patient. If the infusion SAE is considered related to LY3002813, then the remaining cohort is not dosed.

It is important to note that when the above criteria are met, the dosing at the same and higher dose levels may be suspended or terminated, but any ongoing dose level that is below the dose that triggered the stopping rule may continue when considered appropriate by the sponsor.

Any cohort that has been suspended may be re-initiated at a later date if a review of all available safety data by the sponsor supports this action. The decision to re-initiate the cohort, together with the supporting safety data, will be documented and shared with the investigators, institutional review board, and regulatory agencies, as appropriate. If multiple dose levels are involved, the original dose-escalation plans will be adhered to.

In the event of an SAE that is related to the investigational product, other than precautionary inpatient observation, dosing may be suspended, for that cohort and/or higher cohorts.

Refer to the Study Schedule (Attachment 1) for data collected at the time of discontinuation and follow-up.

8.2.1.4. Patients Lost to Follow-up

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

8.2.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for any reason consistent with applicable laws, regulations, and GCP.

8.2.3. Discontinuation of the Study

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

9. Treatment

9.1. Treatment Materials and Supplies

Table AACD.1 provides a summary of the investigational product to be used for this study.

Table AACD.1. Investigational Product Regimens

Product:	LY3002813	Placebo
Dose:	Each vial can deliver 120 mg	Not applicable
Formulation:	Lyophilized powder in vial	

Drug substance for Study AACD was manufactured using a revised manufacturing process to improve process performance (changes in clone, cell culture, and purification processes). Changes to the product quality are not expected to affect the PK, PD, or clinical characteristics of the antibody which will be assessed in the current study.

9.2. Treatment Administration

The investigator or designee is responsible for:

- explaining the correct use of the investigational agent(s) to the patients
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- and returning all unused medication to Lilly or its designee at the end of the study

Note: in some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

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

All clinical trial material provided to the investigator will be stored in a secure place, and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the investigational products will be fully documented and verified by a second person. Detailed records of the amounts of the investigational product received, dispensed and remaining at the end of the study will be maintained. Detailed instructions for the preparation and handling of LY3002813 will be provided by the sponsor in a pharmacy manual.

The actual time of all dose administrations will be recorded in the patient's case report form (CRF).

Minimum dosing time based on dose is listed below:

Dose (mg/kg)	minimum infusion time (hr)
10	1.00
20	1.50
40	2.0

LY3002813 is a yellow color when reconstituted. To ensure blinding, the syringe and pump tubing may be covered (for instance, with aluminum foil) or sites can use local procedures.

The minimum observation period in the site is 6 hours after the end of the infusion; however, this site stay may be extended for safety or feasibility reasons (including an overnight stay), at the discretion of the investigator.

Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the dose and for at least 6 hours after dosing.

Study procedures scheduled relative to dosing time are to occur from time of start of infusion. For example, 3 hours postdose would be 3 hours after the start of the IV infusion.

9.2.1. Method of Assignment to Treatment

A patient number will be assigned to each patient after the ICF is signed and dated. This identification number must appear on all patient-related documents. Assignment to treatment groups will be determined by a computer-generated random sequence within each dose cohort using an interactive web response system (IWRS).

9.2.2. Florbetapir Dosage and Administration

Up to 6 florbetapir scans will be performed, approximately 12-24 weeks apart. At each florbetapir PET scanning visit, patients will receive a single IV administration of approximately 185 MBq (5 mCi) of florbetapir 18F, to be given 50 minutes before the imaging session. The injection of the imaging agent will be followed by a saline flush according to the injection procedure described in the image management plan or, if using molecular neuroimaging for imaging core laboratory, the technical operations manual.

9.2.3. 18F-AV-1451 Dosage and Administration

A total of two 18F-AV-1451 PET scans will be performed approximately 72 weeks apart, except for Cohort 3 where scans will be approximately 24 weeks apart. During this study, patients will receive a single IV administration of approximately 240 MBq (6.5 mCi) of 18F-AV-1451. At approximately 75 minutes following injection, a continuous 30 minute brain scan (6 acquisitions, each of 5 minutes in duration) will be performed.

Previously conducted 18F-AV-1451 PET scans can be used as baseline measurements, if the sponsor approves. During these previous scans, patients might receive a single IV administration of approximately 240 MBq (6.5 mCi) or 370 MBq (10.0 mCi) of 18F-AV-1451. For each patient, the baseline data originally collected for previous Lilly and Avid Radiopharmaceuticals

studies can only be entered/sent for Study AACD after the patient signs the ICF agreeing to participate in this study.

18F-AV-1451 is an investigational tracer and was positive in the in vitro human ether-a-go-go-related gene (hERG) assay. However, the cardiovascular assessments performed during the dog toxicology studies showed no evidence that 18F-AV-1451 prolongs the QT interval at high multiples of relevant clinical doses. Nonetheless, until sufficient human cardiovascular data are available, subjects with a history of risk factors for torsades de pointes and subjects who intend to use drugs known to significantly prolong the QT interval within 14 days or 5 half-lives, whichever is longer, of a scheduled 18F-AV-1451 PET scan are excluded from studies with this tracer.

9.2.4. Radiation Doses Associated with PET Imaging

The estimated exposure to ionizing radiation per patient enrolled in this study (effective dose) is summarized in Table AACD.2. This includes contributions from florbetapir and 18F-AV-1451 scans, along with low-dose CT scans required for attenuation correction. The injected doses for florbetapir and 18F-AV-1451 are lower than typically used, in order to minimize the overall radiation exposure to the patients. However, the duration of each PET scan will be longer than typically performed in order to preserve the final image quality and ensure robust image quantification.

For florbetapir PET scans with regard to the baseline (screening) and endpoint (or early discontinuation) scanning visits only, if the image is not interpretable because of technical artifact (scanner failure, patient motion), the patient may be asked to schedule an additional scan and have a second scan performed. Each patient will only undergo up to 1 additional PET scan beyond those scheduled in this protocol. In this case, the patient would be exposed to an additional 3.92 mSv of ionizing radiation.

In a previously conducted and accepted 18F-AV-1451 scan, the patient might have been administered with 370 MBq (10.0 mCi) rather than 240 MBq (6.5 mCi) of 18F-AV-1451. In this case, the patient would be exposed to an additional 2.9 mSv of ionizing radiation.

Table AACD.2. Radiation Doses Associated with PET Imaging

	Injected Radioactive Dose per Scan, mCi	Injected Radioactive Dose per Scan, MBq	Effective Dose (mSv) per Scan	Number of Scans in First Year	Effective Dose (mSv) in First Year	Number of Scans in Second Year	Effective Dose (mSv) in Second Year	Effective dose (mSv) for Both Years
18F-AV-1451 scan	6.5	240.5	6.20	1	6.20	1	6.20	12.40
Florbetapir scan	5.0	185.0	3.92	4	15.68	2	7.84	23.52
Totals				5	21.88	3	14.04	35.92

Abbreviations: CT = computed tomography; PET = positron emission tomography.

Note: Doses shown include radiation exposure from the radiotracer and also assume a nonclinical CT scan is obtained (estimated at 0.4 mSv) as part of the PET scan attenuation correction process when the scan is done on a PET/CT scanner.

9.3. Rationale for Selection of Dose

Three to 5 IV doses of 10 mg/kg LY3002813 administered over 24 weeks or less were tolerated without any drug-related SAEs or infusion reactions reported in Study AACC and demonstrated target engagement (reduction of florbetapir PET) after 3 to 5 months of treatment. Therefore, doses of 10 mg/kg will be administered to assess the reproducibility and extent the amyloid-lowering findings with 10 mg/kg IV dosing in Study AACC. Doses greater than 10 mg/kg will be administered to explore the maximal effect of LY3002813 on reducing cerebral amyloid. The single-dose arms in Part A are intended to be used to assess whether target engagement can be achieved after a single dose. The multiple-dose arms will be used to assess a dose response and a time course of amyloid reduction based on florbetapir scans at baseline and 12- to 24-week intervals. Twenty-four weeks of dosing is proposed in Part B to approximate the maximum duration of dosing leading to amyloid reduction in Study AACC; amyloid scans at 12 weeks and 24 weeks will be used to assess the time course of amyloid removal and identify whether shorter treatment duration (12 weeks) is sufficient. Sustainability of amyloid reduction after completion of 24 weeks of dosing will be assessed by florbetapir PET at 36, 48, and 72 weeks. The higher dose and more frequent dosing (Q2W) may reduce the incidence of immunogenicity identified in Study AACC. If a 12- or 24-week dosing duration is sufficient for amyloid removal, then the risks of immunogenicity and infusion reactions will potentially be limited to that treatment period. Chronic high-dose treatment (Q4W for up to 72 weeks) in Part C will be used to assess the time course of the maximal PD effect and the opportunity to treat until maximum amyloid removal.

Multiple doses of 10 mg/kg IV were safe and tolerated in Study AACC. Clinical doses of 20 mg/kg and 40 mg/kg are 5- and 2.5-fold lower than the highest dose tested in monkeys (100 mg/kg/week), which was a no-observed-effect level. The ability to project human exposures at doses above 10 mg/kg is questionable, as the exposure at 10 mg/kg did not appear to be proportional with the exposures seen at lower doses. The clearance of LY3002813 appeared to be decreasing, and the half-life increasing, at the 10 mg/kg dose level relative to what was observed at lower doses. It is unclear whether this trend will continue at higher doses. Accordingly, in estimating the exposures that may be encountered at doses greater than 10 mg/kg, the clearance predicted based on nonclinical data (11.3 mL/h) was used, which is much more conservative than the clearance observed to date clinically (26.3 mL/h at the 10 mg/kg dose level). These exposure projections suggest that a dose of 40 mg/kg may result in exposure that exceeds that which was achieved at the no-observed-effect level in the 6-week monkey study (Table AACD.3). However, the monkey is an “off-target” species (does not possess deposited N3pG Aβ); further, the animal data did not predict the human findings with respect to PK or immunogenicity.

Table AACD.3. Margin of Safety for Intravenous Administration of LY3002813 Based on Administered (QW) Dose and Measured or Predicted Exposure

	Dose (mg/kg)	Dose Multiple[a]	AUC(0-168hr) (μg•hr/mL)	Exposure Multiple (AUC[0-∞])[a]
Human[b]	0.1	1000	199	715
	10	10	27000	5.3
	20	5	124000	1.1
	40	2.5	248000	0.6
Monkey NOEL[c]	100	--	142219	--

Abbreviations: AACC = I5T-MC-AACC; AUC = area under the concentration-time curve; AUC(0-∞) = area under the concentration versus time curve from time 0 to infinite time; FDA = Food and Drug Administration; IV = intravenous; MW = molecular weight; NOEL = no-observed-effect level; QW = every week.

[a] Dose multiple is the dose in animals/dose in humans based on mg/kg. For biological products administered IV with an MW >100,000 Da, scaling doses on a mg/kg basis is the preferred approach (FDA guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers; Rockville, Maryland, United States FDA 2005).
Exposure multiple is the AUC in animals/AUC in humans (Study AACC interim data).

[b] AUC(0-∞) exposure (geometric mean) in humans (0.1 and 10 mg/kg dose levels, based on Study AACC interim data, 20 mg/kg and 40 mg/kg AUC(0-∞) extrapolated using the predicted human clearance based on nonclinical data (11.3 mL/hr), which is more conservative than the clearance values observed in Study AACC)

[c] NOEL determined in a 6-week repeat-dose toxicity study (IV once per week) in cynomolgus monkeys (Study 8242713). The AUC(0-166hr) exposure for monkeys is the average of values for males and females on Day 36.

9.4. Dose Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the maximum tolerated dose is determined or until the maximum dose for each dosing frequency has been shown to be well tolerated. If the minimal intolerable dose is reached for any dose/dosing frequency, then the dose level that is tolerated below this minimal intolerable dose at each dosing frequency will be designated as the maximum tolerated dose for that dosing frequency.

Safety data from Cohort 1 is the minimum requirement for the dose escalation to Cohort 2. Safety data from Cohort 2 is the minimum requirement for the dose escalation to Cohort 3. Safety and PK data (maximum concentration, area under the concentration-time curve, and clearance) from Cohort 1 are the minimum requirements for initiating Cohort 4. Safety and PK data from Cohort 2 and confirmation that at least 2 patients have been dosed safely for at least 3 doses each in Cohort 4 are the minimum requirements for initiating Cohort 5. In addition, Cohort 7 will only be initiated after confirmation that at least 2 patients have received at least 2 doses each of LY3002813 safely in Cohort 6. Safety/PK reviews will occur after a minimum of 4 patients receiving LY3002813 and 1 patient receiving placebo have been dosed. Additional safety reviews may be added. If available at the time of dose escalation decision, immunogenicity and additional PK data may be used as supporting data for dose escalation. No dose escalation can occur without prior discussion and agreement between the investigator and the study team.

9.4.1. Dose Escalation Method

Safety data (in particular AEs, SAEs, ECGs, vital signs, neurological examinations, and adverse laboratory abnormalities) will be independently assessed by the investigator and will be considered related to the investigational product unless there is clear evidence that the event is not related. The assessment of AE relatedness is detailed in Section 10.6.1.

After review of these data, an agreement on initiation of subsequent cohorts as detailed above will be made by the investigator and sponsor. Additional criteria for initiation of Cohort 5 are described in Section 9.4 above. Criteria for termination of dosing for either dose escalation or within a dose cohort are in Section 8.2.1.3.

9.5. Specific Restrictions/Requirements

Throughout the study, patients may undergo medical assessments and review of compliance with restrictions before continuing in the study.

Alcohol

Patients will not be permitted to consume alcohol from 48 hours before visits until after leaving the site. Patients will not exceed their habitual alcohol consumption during the study.

Exercise

Patients should avoid strenuous exercise and/or activity from 48 hours before visits until after leaving the site and 24 hours after LP.

Hydration

Patients should be adequately hydrated throughout the study. Therefore, patients should be encouraged to drink several glasses of water each day.

Cerebrospinal Fluid Collection by Lumbar Puncture

On LP days, movement may be restricted for an appropriate amount of time after the LP, as determined by the investigator. Patients may also be required to stay overnight at the site for monitoring following completion of the LP procedure. Dosing cannot proceed if post-LP headache is present.

Contraception

Male patients with partners of childbearing potential must agree to use at least 1 effective method of contraception for the duration of the study and 6 months following the last dose of study drug. At least 1 effective method of contraception will be used (for example, condoms with spermicide, oral contraceptives, intrauterine device, male sterilization, etc). The patient may choose to use a barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method. Thus, each barrier method must include use of a spermicide [ie, condom with spermicide, diaphragm with spermicide, female condom with spermicide]. It should be noted, however, that the use of male

and female condoms as a double barrier method is not considered acceptable because of the high failure rate when these barrier methods are combined.)

9.5.1. Special Treatment Considerations

9.5.1.1. Premedication for Infusions

Premedication for dosing is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigators (see Section 9.7). The patient may be premedicated for subsequent infusions. If infusion reactions are observed, but review of the data suggests that dosing may continue, administration of acetaminophen (500 to 1000 mg) and/or an antihistamine, and/or methylprednisolone (or other corticosteroid) may be administered orally 30 to 60 minutes before starting the infusion for subsequent patients.

The decision to implement premedication for infusions in subsequent cohorts will be made by the investigator and sponsor, and it will be recorded in the study documentation, along with the dose-escalation decision.

Any premedication given will be documented as a concomitant therapy (see Section 9.7).

9.5.1.2. Management of Infusion Reactions

There is a risk of an infusion reaction with any biological agent; therefore, all patients should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. In the event that a significant infusion reaction occurs, the following guidance should be followed:

- the investigational product infusion should be slowed or stopped, depending on the symptoms/signs present
    - if slowed, the infusion should be completed at the slower rate, as tolerated and documented in the CRF
    - if stopped, no further attempts to administer the investigational product will be made, and this will be documented in the CRF
- supportive care should be employed in accordance with the symptoms/signs. Management of the infusion reaction should proceed according to the severity of the reaction as per the flowchart in Attachment 5. This may include, but is not limited to, rescue medications such as diphenhydramine, epinephrine, and/or methylprednisolone.

Stored serum samples for possible immune safety laboratory testing (including but not limited to Beta tryptase, total immunoglobulin E, and immune complex testing) will be collected at time points indicated in the Study Schedule (Attachment 1).

Additional, unscheduled stored serum samples for possible immune safety laboratory testing (including but not limited to β tryptase, total immunoglobulin E, and immune complex testing) should also be collected approximately 60-120 minutes and 4-6 weeks after moderate or severe infusion reactions.

Standardized clinical information from the infusion should be collected in the CRF.

9.5.1.3. Recognition and Management of Cerebral Vasogenic Edema

Antiamyloid therapies that have some similarities to LY3002813 have been associated with cerebral vasogenic edema (ARIA-E) with and without microhemorrhage (ARIA-H). Most of these cases are asymptomatic and have been detected by routine brain MRI. When symptoms are present in association with these imaging abnormalities, they have been reported to include headache, gait instability, dizziness, tremor, worsening cognitive function, alteration of consciousness, seizures, unsteadiness, and/or vomiting. In most cases (even when symptomatic), these imaging abnormalities have not required treatment other than discontinuation of the investigational compound, and imaging abnormalities have resolved. Infrequently, high-dose steroid therapy has been administered in the presence of prominent symptoms.

If the symptoms above are reported and vasogenic edema is suspected, then the abnormality is best detected by FLAIR sequences on MRI and microhemorrhages are best detected with the T_2*-weighted gradient-echo sequence on MRI. An unscheduled MRI with these sequences should be obtained upon suspicion of cerebral vasogenic edema. It is recommended that MRI be repeated with these sequences every 2 to 4 weeks until resolution of vasogenic edema is documented. For asymptomatic or mild symptoms, the patient can be observed; for moderate symptoms, the use of oral or IV steroids can be considered. In the case of severe symptoms, it is recommended that the patient be hospitalized for close observation; the use of IV steroids, such as high-dose dexamethasone or a similar agent, should be considered. Such medications, if used, should be entered into the concomitant medications CRF. If asymptomatic or symptomatic vasogenic edema occurs, the patient must not receive further dosing and should undergo discontinuation procedures.

Patients who present with new clinically asymptomatic microhemorrhages should have a repeat MRI approximately every 4 weeks until stabilization.

9.6. Blinding

This is a patient- and investigator-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. Refer to Attachment 4 for details on the blinding/unblinding plan.

Emergency codes will be available to the pharmacy. A code, which reveals the treatment group for a specific study patient, may be opened during the study only if the patient's well-being requires knowledge of the patient's treatment assignment.

If a patient's study treatment assignment is unblinded, the patient must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist or CRP for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study patient's emergency code.

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

Upon completion of the study, all codes must be returned to Lilly or its designee.

9.7. Concomitant Therapy

Stable medical therapies within the guidelines of the inclusion/exclusion criteria are allowed; however, additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. The use of local anesthetics for performance of LP does not constitute a violation of 2 months of stable medical therapy.

For all cohorts, if an infusion reaction occurs, rescue medications including, but not limited to, diphenhydramine, epinephrine, and/or methylprednisolone may be administered at the discretion of the investigator. Administration of medications before an infusion to prevent a reaction does not cause a discontinuation of the patient from the study. If the need for concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the investigator after consultation with a Lilly CRP or clinical pharmacologist. All medication used during the course of the study must be documented.

Concomitant therapy administered to treat an infusion reaction or as premedication for infusions should be documented.

10. Sample Collection and Safety Data Collection

Attachment 1 lists the schedule for sample collections in this study.

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

Attachment 3 summarizes the blood volumes for all blood sampling during the study.

10.1. Laboratory Samples

Blood, urine, and CSF samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Routine clinical laboratory tests will be analyzed by a central laboratory selected by Lilly or local laboratory (screening, coagulation and CSF protein, glucose, and cell counts).

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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. Samples for Pharmacokinetic and Pharmacodynamic Evaluations

10.2.1. Pharmacokinetic Samples

At the visits and times specified in the Study Schedule, 1 venous blood sample of approximately 4 mL will be collected for each PK assessment (Attachment 1). These blood samples will be used to determine the serum concentrations of LY3002813. The actual date and time (24-hour clock time) of each sampling will be recorded. On the day of dosing, every attempt should be made to collect samples at the specified time; however, failure to do so will not constitute a protocol violation.

A maximum of 3 blood samples per patient may be drawn at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor.

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

Time points for PK may be modified based on interim PK results.

10.2.2. Cerebrospinal Fluid Samples

For patients undergoing LP, a lumbar x-ray or fluoroscopy may be conducted at screening to perform the procedure or rule out potential contraindication to a LP, such as significant osteoarthritic disease and bone overgrowth. If an x-ray or fluoroscopy was done within 12 months of screening, this may be used.

A qualified physician (eg, anesthesiologist or neurologist) will perform the LP under local anesthesia. At each LP, a maximum of 15 mL (including up to 5 mL for local laboratory testing) of CSF will be collected. The first 5 mL of CSF will be collected and sent to a local laboratory for testing of white blood cell count, red blood cell count (where possible), total protein, and glucose. In addition, each CSF sample will be visually inspected for evidence of blood contamination. The results of the visual inspection and local laboratory CSF analyses are to be documented on the electronic CRF (eCRF). Grossly evident blood by visual inspection will be reported as positive and documented in the CRF. The remaining CSF will be collected to measure concentrations of $A\beta_{1-40}$, $A\beta_{1-42}$, total tau, and phospho-tau measurements, as well as LY3002813 (see below) in patients who are randomly assigned to receive LY3002813. All other remaining CSF will be stored for exploratory work (Section 10.2).

Patients will be carefully monitored for post-LP headaches. The investigator may use hydration, analgesics, and blood patch to treat the headache, as clinically indicated.

Any sample that shows visual or laboratory evidence of blood contamination may be excluded from the PK and statistical analyses if the level of contamination is estimated to be sufficient to produce misleading results.

10.2.3. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Serum and CSF concentrations of LY3002813 will be determined using a validated enzyme-linked immunosorbent assay method. It is not intended that samples collected from placebo-treated patients will be analyzed. Samples will be analyzed at a laboratory approved by the sponsor and stored within the United States.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 2 years following last patient visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism and/or protein binding work.

10.2.4. Plasma Samples

Ethylene diamine tetraacetic acid (EDTA) plasma from a 6 mL collection tube will be analyzed for Aβ species, which includes $A\beta_{1-40}$ and $A\beta_{1-42}$. Other fragments of amyloid precursor protein processing or Aβ plaque species may be analyzed.

10.2.5. Pharmacodynamic Evaluations

See Section 10.5.2 for further details.

10.3. Samples for Biomarker Research

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic 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, where local regulations and ERBs allow, a 1-time blood sample will be collected for pharmacogenetic analysis (Attachment 1).

Collection of samples for other biomarker research is also part of this study. Blood and CSF samples will be collected as specified in the Study Schedule.

The CSF, plasma, and serum stored samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to AD and or other neuropathological conditions.

Blood samples for biomarker research are required and will be collected from all patients in this study as specified in the Study Schedule (Attachment 1).

Samples will be tested for the apolipoprotein E (APOE) genotype (ε2, ε3, ε4) and translocase of outer mitochondrial membrane 40 (TOMM40) poly-T polymorphism to determine whether these genetic variants are associated with response to LY3002813. APOE genotype, which is in linkage disequilibrium with TOMM40, has been demonstrated even in small sample sizes to be associated with vasogenic edema complications; thus, the analysis of these genes is planned. In addition, where local regulations allow, the sample will be stored and analysis may be performed on other genetic variants thought to play a role in response to LY3002813, response to antidementia concomitant therapy, and/or molecular subtypes of AD to test their association with observed clinical outcomes when taking the study drug. While it is unlikely that signals from small trials can be suggested by genetic variance, samples may be saved for analysis particularly for retrospective review if future studies detect associations or other researchers report significant findings. At the current time, possible target genes include, but are not limited to, FcγRII, FCγRIII, CLU, CR1, PICALM, MAPT, BIN1, PSEN1, and PSEN2.

CSF samples remaining after local laboratory studies, LY3002813 PK, amyloid species, and tau species testing are complete may be retained as stored samples for a maximum of 15 years for use as described above. The following list of potential exploratory biomarkers does not preclude future molecules of interest but may include VILIP-1, YKL40, β-amyloid fragments, interleukins, tumor necrosis factor alpha, and inflammatory cytokines.

EDTA plasma from a 6-mL collection tube and serum from a 6-mL collection tube will each be aliquoted into 5 respective 0.5-mL aliquot volumes for a total of 10 aliquots (5 EDTA plasma and 5 serum). These samples will be stored for biomarker research and development. The following list of potential exploratory biomarkers does not preclude future molecules of interest

but may include VILIP-1, YKL40, β-amyloid fragments, interleukins, tumor necrosis factor alpha, and inflammatory cytokines.

ABI Tempus™ tubes (3 mL blood) for ribonucleic acid extraction and exploratory gene expression will be collected/processed and stored for future analysis.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3002813. These investigations may be limited to a focused candidate gene study or, if appropriate, genome wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic 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.

Other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to disease process, pathways associated with disease state, and/or mechanism of action of the investigational product(s).

The samples will be coded with the patient number and stored for up to a maximum of 15 years after the last patient 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 patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the investigational product.

An 11-mL blood sample for pharmacogenetic evaluation is a required part of this study, unless country-specific laws and regulations prohibit this type of testing. A 3-mL tube will be used for APOE genotypes and TOMM40 polymorphisms, a 4-mL tube will be used for DNA extraction, and a 4-mL tube of whole blood will be stored. These samples will be used to test for genetic variants that may influence response to treatment.

Samples will be destroyed according to a process consistent with local regulation.

10.4. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against the investigational product. Additional samples may be collected if there is a possibility that an AE is immunologically mediated. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of the investigational product. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the investigational product.

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to the investigational product. The duration allows the sponsor to respond to regulatory requests related to the investigational product.

10.4.1. Additional Immunogenicity and Safety Visits for all Cohorts

If the immunogenicity titer at the last scheduled assessment or discontinuation visit is positive, then additional safety assessments (concomitant medications, AEs, laboratory values, vital signs, ECGs) and samples for immunogenicity and PK should be taken every 12 weeks until the titer returns to baseline (comes within a single 2-fold dilution of the baseline titer) or up to 48 weeks after the last dose of LY3002813 if the antibody titer has not returned to baseline within 48 weeks after the last dose. In the case of a patient whose result is positive at baseline with a 1:10 titer and then subsequently develops a treatment-emergent ADA response that increases to much higher titers, the antibody titer would need to decline to a titer of 1:20 or less to be considered a "return to baseline." In contrast, if the patient's result is "not detected" at baseline (in an assay with a 1:10 minimal required dilution), the titer would need to decline to either "detected" with a 1:10 titer or a result of "not detected" to be considered a "return to baseline."

10.5. Exploratory Evaluations

10.5.1. Cognitive and Functional Scales

The test of cognitive function, ADAS-cog, NTB, MMSE, Clinical Dementia Rating - Sum of Boxes (CDR-SB), Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment-Activities of Daily Living (ADCS-MCI-ADL) scale, and FCSRT-IR will be performed during the study at the times specified in the Study Schedule (Attachment 1). These tests are performed as a safety and exploratory measure to document any substantial change associated with treatment, as it is not anticipated that these tests should have significant changes associated with LY3002813 in this small patient population and short time window. Cognitive and functional tests that are performed on the same day should be done in a specific order. Screening tests should be completed in this order: 1) MMSE, 2) FCSRT-IR, and 3) CDR. The other scales, if done on the same day, should be performed in this order: 1) NTB, 2) ADCS-MCI-ADL, and 3) ADAS-cog. The study partner (or 1 of the study partners if there are 2) should be present or available by telephone for the assessment of CDR and ADCS-MCI-ADL (this should be the primary study partner for ADCS-MCI-ADL).

10.5.1.1. Alzheimer's Disease Assessment Scale-Cognitive Subscale

The ADAS was designed as a rating scale for the severity of the dysfunction in the cognitive and noncognitive behavior characteristic of persons with AD (Rosen et al. 1984). The cognitive subscale of the ADAS (ADAS-cog[11]) consists of 11 items assessing areas of function most typically impaired in AD: orientation, verbal memory, language, and praxis. The scale ranges from 0 to 70, with higher scores indicating greater disease severity. An extended ADAS-cog (the ADAS-cog[14]) which includes measurements of delayed free recall, digit cancellation, and maze completion will be used in this study (Mohs et al. 1997). A conversion code of 0 to 10 for delayed free recall and 0 to 5 for both digit cancellation and maze completion provide a total ADAS-cog[14] score that ranges from 0 to 90.

10.5.1.2. Neuropsychological Test Battery

The NTB is a cognitive tool for clinical trials in the field of AD. The NTB is a collection of several written and oral tests that examines verbal and nonverbal brain functions. The NTB shows linear annual cognitive changes across a wide range of MMSE scores as compared to the ADAS-cog and is more sensitive than the ADAS-cog among patients with mild impairment (Harrison 2007).

10.5.1.3. Mini-Mental Scale Examination

The MMSE is one of the most widely used screening instruments for cognitive impairment and provides a total score ranging from 0 to 30, with lower scores indicative of greater cognitive impairment (Folstein et al. 1975).

10.5.1.4. Clinical Dementia Rating

The CDR is a clinical staging instrument for Dementia (Morris 1993). It characterizes 6 domains of cognitive and functional performance: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semistructured interview of the patient and a reliable informant or collateral source (eg, a family member). The CDR table provides descriptive anchors that guide the clinician in making appropriate ratings based on interview data and clinical judgment. In addition to ratings on a 5-point scale for each domain (except for personal care, which is rated on a 4-point scale), an overall CDR score is derived by standard algorithm. This score is useful for globally staging the level of impairment: 0 indicates no impairment; 0.5, 1, 2, and 3 indicate very mild, mild, moderate, and severe dementia, respectively.

10.5.1.5. Clinical Dementia Rating–Sum of Boxes

The CDR-SB is considered a more detailed quantitative general index than the global score and has reasonable accuracy to discriminate between patients with very early AD and those with MCI.

10.5.1.6. Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale

The ADCS-MCI-ADL is a 24-item questionnaire that attempts to detect milder functional impairments and represent a modification of the original activities of daily living scale (Galasko et al. 1997).

10.5.1.7. Free and Cued Selective Reminding Test with Immediate Recall

The FCSRT-IR is a 16-item instrument version of controlled learning (Grober and Buschke 1987). FCSRT-IR performance as an indicator of early AD comes from correlations with abnormalities in structural and functional imaging and with neurofibrillary lesions in parahippocampal regions that are the earliest targets of AD pathology.

10.5.2. Imaging

A total of two 18F-AV-1451 PET scans will be performed, approximately 72 weeks apart, except for Cohort 3 where scans will be approximately 24 weeks apart. 18F-AV-1451 PET scan should be performed at least 24 hours apart from the florbetapir scan (for further details on florbetapir imaging see Section 9). The change in grey matter SUVr will be compared to total dose

exposure. Additional approaches for tau PET quantitation may be applied based on emerging data.

MRI changes in brain volume over the course of the study will be explored. Over an approximate span of 72 weeks, except for Cohort 3, which will be 24 weeks, screening MRI and up to 8 post-baseline MRIs will be performed, mostly for safety monitoring (i.e., occurring 4 weeks after the first dose, every 12 weeks starting from the first dose, and up to 12 weeks after the last dose). However, additional MRI scans are included for exploratory evaluation of brain structural changes (including, but not limited to, whole brain, ventricle, and hippocampal volumes), white matter and tissue microstructure changes, and functional connectivity in brain networks at baseline, 24 weeks, 48 weeks, and 72 weeks as applicable.

10.6. Safety Evaluations

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

The investigator is responsible for the appropriate medical care of patients during the study. Planned safety assessments and measures are detailed in Section 10.6.3, but additional assessments and safety tests may be performed at the investigator's discretion.

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

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical trial records throughout the study.

Safety monitoring in will include MRIs, AEs, ECGs, vital signs (blood pressure, pulse rate, and temperature), physical and neurological examinations, C-SSRS, and safety laboratory tests (including LP clinical laboratory tests).

For Part A, MRI safety monitoring will consist of a baseline MRI, a Week 4 postdosing MRI, and a Week 12 postdosing MRI, with sequences appropriate for detecting vasogenic edema and microhemorrhage. MRIs at baseline, 24 weeks, 48 weeks, and 72 weeks are for volumetric assessment. Additional MRI measures may be obtained at these ARIA-related and/or MRI time points.

For Parts B and C, MRI safety monitoring will consist of a baseline MRI, a Week 4 postdosing MRI, and a Week 12 postdosing MRI, as well as MRIs every 12 weeks until 48 weeks (Part B) and 12 weeks (Part C) after the last dose. MRIs at baseline, 24 weeks, 48 weeks, and 72 weeks are for volumetric assessment. Additional MRI measures may be obtained at these ARIA-related and/or MRI time points.

Determination of the number of microhemorrhages will be required to be assessed on a 1.5T or 3T MRI, as the greatest understanding of the number of microhemorrhages and their relationship to disease are associated with these magnet strengths.

Dose-escalation methods are presented in Section 9.4 and stopping criteria are presented in Section 8.2. Safety evaluations of Cohorts 1 and 2 will be performed after a minimum of 5 patients (4 patients on LY3002813 and 1 patient on placebo) have concluded the 4-week period and completed all required testing. Any remaining patients not reviewed for the Cohort 1 and Cohort 2 evaluations will undergo a 4-week safety evaluation when all have completed 4-week safety assessments.

Regular safety evaluations across all cohorts will be performed at 3-monthly intervals. All new data as listed above will be included, in addition to the local CSF laboratory tests. Each geography (which may mean separate meetings in the United States and in Japan) will meet as described above to determine whether stopping rules are met.

10.6.1. Adverse Events

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

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

Cases of pregnancy that occur during maternal (note: fertile women are excluded from the study) or paternal exposures to the investigational product should be reported. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

Any clinically significant findings from ECGs, laboratory tests, vital sign measurements, physical or neurological examination, and PET/MRI that result in a diagnosis should be reported as an AE to Lilly or its designee.

In addition, all AEs occurring after the patient receives the first dose of the investigational product must be reported to Lilly or its designee via designated data transmission methods.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, investigational product, and/or drug delivery system via designated data transmission methods.

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the investigational product, the following terminologies are defined:

- **related**: a direct cause and effect relationship between the study treatment and the AE is likely
- **possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **unrelated**: without question, the AE is definitely not associated with the study treatment

As per Lilly's standard operating procedures all "related" and "possibly related" AEs and SAEs will be defined as related to the investigational product.

Study site personnel must alert Lilly or its designee within 24 hours of the investigator **unblinding** a patient's treatment group assignment for any reason.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via designated data transmission methods the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.6.2. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

SAE collection begins after the patient has signed informed consent and has received investigational product. If a patient experiences an SAE after signing informed consent, but

prior to receiving investigational product, the event will NOT be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

SAEs occurring up to and including the patient's last study visit will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at the sponsor.

The investigator does not need to actively monitor patients for AEs once the trial has ended unless specified in the protocol. However, if an investigator becomes aware of SAEs occurring to a patient after the patient's participation in the trial has ended, the investigator should report them to the sponsor, regardless of the investigator's opinion of causation, and the SAEs will be entered in the pharmacovigilance system at the sponsor.

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.

10.6.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the reference safety section of 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.

10.6.3. Other Safety Measures

10.6.3.1. Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the Study Schedule and as clinically indicated (Attachment 1). Other elements of the physical examination may be included on an optional or symptom-directed basis.

10.6.3.2. Vital Signs

Blood pressure and pulse rate will be measured as specified in the Study Schedule and as clinically indicated (Attachment 1).

Blood pressure and pulse rate should be measured after at least 5 minutes sitting.

If the patient feels unable to stand, supine vital signs only will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted and agreed upon between the sponsor and investigator.

Body temperature (axillary in Japan) will be measured as specified in the Study Schedule and as clinically indicated (Attachment 1).

Additional vital signs may be measured during each study period if warranted and agreed upon between the sponsor and investigator. If orthostatic measurements are required, patients should be supine for at least 5 minutes and stand for at least 3 minutes.

10.6.3.3. Body Weight

Body weight will be recorded as specified in the Study Schedule and as clinically indicated (Attachment 1).

10.6.3.4. Electrocardiograms

For each patient, a single12-lead digital ECG will be collected according to the Study Schedule (Attachment 1). ECGs must be recorded before collecting any blood for safety or PK tests. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

All ECGs, except for the screening ECG, will be obtained in triplicate at approximately 1-minute intervals.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high quality records. All ECGs recorded should be stored at the investigational site.

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

If a clinically significant quantitative or qualitative change from baseline is identified (including, but not limited to, changes in QT/corrected QT [QTc] interval from baseline) after enrollment, the investigator will determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining whether any change in patient 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. Any new clinically relevant finding should be reported as an AE.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted before completion of the final study report (in which case the overread data would be used).

10.6.3.5. Neurological Examinations

A directed neurological examination will be performed by a physician, nurse practitioner, or physician's assistant (for Japan, physician only) at the time points specified in the Study

Schedule (Attachment 1). If abnormalities are noted at these time points, additional examinations should be performed at daily intervals until the patient has returned to baseline. The examiner should be familiar with the patient's baseline examination. Mandated elements of the examination include inspection for tremor, extraocular movements, brachial and patellar deep tendon reflexes, finger-nose pointing, and Romberg sign.

Table AACD.4 presents the scoring of the neurological examination findings. For patients with mild (1+) tremor or nystagmus at baseline, increases in these findings should not be scored at a higher level unless the examiner judges them to be significantly exacerbated compared to baseline.

Table AACD.4. Scoring of Neurological Examinations

Score	0	1	2	3	4
Tremor	Absent	Visible with limb extension and/or careful inspection	Visible without limb extension.	Interferes with motor function	
Nystagmus	Absent	1-3 beats on lateral gaze	>3 beats on lateral gaze.	Present on forward gaze	
Reflexes (brachial or patellar)	Absent	Trace	Normal	Increased	Clonic
Finger-nose	Normal	Abnormal			
Romberg sign	Absent	Present			

10.6.3.6. Columbia Suicide Severity Rating Scale (Cohorts 1 through 7)

By industry guidance regarding suicidality (FDA), any assessment of suicide-related thoughts and behaviors must map to the Columbia Classification Algorithm for Suicide Assessment (Posner et al. 2007). The C-SSRS was developed by the National Institute of Mental Health trial group to map directly to the Columbia Classification Algorithm for Suicide Assessment and therefore was chosen to assess suicide-related thoughts and behaviors in this study.

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine whether a suicide-related thought or behavior has occurred. The C-SSRS will be administered as specified in the Study Schedule (Attachment 1) by appropriately trained site personnel.

The C-SSRS is available in adult and child versions; however, there is no version of the C-SSRS for a cognitively impaired population. The adult version contains a more elaborate "Intensity of Ideation" section that requires memory of past thoughts in a temporal context, and a cognitively impaired population may be unable to give an accurate response. The child version of the C-SSRS has condensed this section into 1 question. This reason, and also the suggested wording for the scale questions having been simplified, resulted in the child version being chosen for this study.

The child version of the C-SSRS should be administered to the patient with the study partner present or available by phone. Responses from both the study partner and patient should be

considered when administering the scale. The response from the study partner may be provided over the phone. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation should be performed by a study physician, and appropriate medical care should be provided.

The Lilly Self-Harm Supplement Form should be completed every time the C-SSRS is administered. If the investigator determines that suicide-related behaviors have occurred, the Lilly Self-Harm Supplement Form will be used to collect additional information to allow for a more complete assessment of these behaviors. Patients with any clinically significant change as determined by the investigator will be referred to a psychiatrist.

10.6.3.7. Magnetic Resonance Imaging

MRI scans will be obtained at time points indicated in the Study Schedule (Attachment 1).

MRI safety monitoring will consist of MRIs with sequences appropriate for detecting vasogenic edema and microhemorrhage (ARIA-E and ARIA-H). The number of microhemorrhages detected on the baseline MRI scan will serve as 1 factor in the exclusion criteria (that is, exclusion of patients with >4 microhemorrhages). Microhemorrhages might indicate a higher risk for macrohemorrhage, as well as the presence of significant amyloid angiopathy, and there appears to be a risk of microhemorrhage with some antiamyloid treatments in preclinical models and possibly in humans as well.

The determination of the number of microhemorrhages will be required to be assessed on a 1.5T or 3T MRI using a T_2*-weighted gradient-echo sequence. Additional FLAIR images will be performed to evaluate for the presence of vasogenic edema. All baseline and safety imaging will be analyzed by a central reader blinded to treatment.

10.6.3.8. Special Procedure/Subjective Procedure

The CSF samples acquired via LP will be collected at time points indicated in the Study Schedule (Attachment 1).

10.6.3.9. Immunogenicity Samples

Samples for immunogenicity testing will be collected at time points indicated in the Study Schedule (Attachment 1). Serum samples will be used to determine antibody production against LY3002813. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3002813. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3002813. Samples may be stored for a maximum of 15 years following last patient visit to enable further analysis of immune responses to LY3002813. The duration allows the sponsor to respond to regulatory requests related to the study drug.

10.6.4. Safety Monitoring

The Lilly clinical pharmacologist or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or research physician will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist when appropriate, and periodically review:

- trends in safety data
- laboratory analytes
- AEs
- MRI
- ECGs
- neurological exams
- physical exams
- C-SSRS data
- immune safety monitoring:
    - data form for infusion reactions (safety developing)
    - blood samples collected, as able, following infusion reactions (see Attachment 1 for listing of exploratory testing)

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the sponsor or data monitoring committee, if formed, (an advisory group for this study formed to protect the integrity of data; refer to Section 11.3) can conduct additional analyses of the safety data.

10.6.5. Complaint Handling

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

Complaints related to unblinded comparator drugs or concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or its designee 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.

10.7. Appropriateness and Consistency of Measurements

All of the measurements in this study will be performed using standard, validated methods.

10.8. Compliance

Every attempt will be made to select patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study. The time and day of drug administration will be recorded. Drug accountability records will be maintained by the study site.

The specifications in this protocol for the timings of safety, PK, and PD sampling are given as targets, to be achieved within reasonable limits. Modifications may be made to the time points based upon the safety and PK information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.

Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

11. Sample Size and Data Analyses

11.1. Determination of Sample Size

Up to approximately 150 patients may be enrolled so that approximately 72 patients complete the study. Cohorts 1, 2, and 3 are each planned to have approximately 8 patients (6 LY3002813; 2 placebo) complete the study. Cohorts 4 and 5 are each planned to have approximately 12 patients (9 LY3002813; 3 placebo) complete the study. Also, Cohorts 6 and 7 are each planned to have approximately 12 patients (9 LY3002813; 3 placebo) complete the study.

The sample size is customary for studies evaluating safety, PK, and/or PD parameters; at the conclusion of the trial, confidence intervals for PK, PD, and cognition endpoints may be computed in order to evaluate the precision of the estimates where appropriate. Based on prior Lilly clinical trials, 6 patients randomized to each LY3002813 dose and placebo provide over 90% power to detect at least a CCI mean SUVr reduction of a dose compared to that of placebo without multiple comparison adjustment. Based on Fixed and Adaptive Clinical Trial Simulator simulations, there is over 90% success rate that at least 1 LY3002813 dose separates from placebo with a success criterion of Pr (mean SUVr reduction of LY3002813 dose < mean SUVr reduction of placebo) >CCI. If more patients are needed to determine safety, target engagement, PK, dosing, and/or race differences, then up to a total of 10 additional patients may be added.

Patients who are randomized but who do not complete the 12-week safety and PET assessments may be replaced.

11.2. Data Analysis Plans

11.2.1. General Considerations

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

PK/PD analyses will be conducted on the full analysis set. This set includes all data from all randomized patients receiving at least 1 dose of the investigational product according to the treatment the patients actually received. Safety analyses will be conducted for all enrolled patients, whether or not they complete all protocol requirements.

Summary statistics, data tabulations, and data graphs by ethnicity (Japanese and non-Japanese) will be provided as appropriate.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Analyses will be fully detailed in the statistical analysis plan. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post hoc analyses and incomplete disclosures of analyses.

11.2.2. Study Participant Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

11.2.3. Study Participant Characteristics

Patient age, sex, weight, height, smoking habits, APOE4 status, and/or other demographic characteristics will be recorded and may be used in the PK, PD, and safety analyses as quantitative or classification variables. These characteristics will be listed and summarized at baseline, with the exception of weight, which will also be summarized over time.

11.2.4. Pharmacokinetic Analyses

11.2.4.1. Pharmacokinetic Parameter Estimation

Noncompartmental analysis will be conducted, and PK parameter estimates of clearance and half-life will be reported for LY3002813. Compartmental modeling using nonlinear mixed-effects modeling or other appropriate software may be explored, and population estimates for clearance and central volume of distribution may be reported. Depending on the model selected, other PK parameters may also be reported. Exploratory graphical analyses of the effect of dose level or demographic factors on PK parameters may be conducted. Additional modeling may be performed based on the results of the graphical analyses. Exploratory graphical analyses relating LY3002813 serum exposure to LY3002813 CSF concentrations may be conducted.

Additional exploratory analyses of the data may be conducted if deemed appropriate.

Interim PK analyses may be conducted using noncompartmental analysis and/or compartmental modeling.

11.2.5. Pharmacodynamic Analyses

PD and cognition endpoints as function of visit or time will be summarized and/or plotted as appropriate; further details will be given in the statistical analysis plan. As there will not be sufficient information to make informative comparisons to placebo within the Japanese population, all analyses will be conducted on the overall population unless otherwise specified. As the analyses are considered exploratory, changes to the planned analyses will not require a protocol amendment.

11.2.5.1. Imaging Analyses

Statistical assessment of the SUVr will be analyzed by a mixed model repeated measure (MMRM). The planned analyses is an MMRM using at least compound symmetry covariance structure with fixed effects of treatment doses (LY3002813 and placebo), study visit, and interaction between treatment and visit. A baseline covariate adjustment may be used. The primary comparison is between LY3002813 and placebo for change from baseline in composite SUVr or percent change in composite SUVr at last PET imaging visit. This analysis may be repeated for SUVrs in individual brain regions if needed.

In addition to the MMRM analysis, a Bayesian posterior probability may be computed for each LY3002813 dose compared to placebo. For each dose, the credible interval will be computed for each dose relative to placebo.

Changes in volume (including, but not limited to, whole brain, ventricle, and hippocampus), brain tissue microstructure, and functional connectivity in brain networks captured by MRI over the course of the study will be explored; exploratory evaluation of whole brain and anatomically localized structural and functional changes will be summarized. MRI will be obtained every 12-24 weeks; therefore, an MMRM may be conducted fitting treatment and study visit as fixed effects.

Additionally, the relationship between LY3002813 serum exposure and imaging endpoints may be explored graphically or by a modeling approach.

11.2.5.2. Pharmacodynamic Cerebrospinal Fluid Estimation

The CSF results from the LPs taken pre- and postdose will be analyzed to estimate the mean change and percent change from predose. The dependent variables are $A\beta_{1-40}$, $A\beta_{1-42}$, , total tau, and phospho-tau.

11.2.5.3. Cognition and Functional Analyses

ADAS-cog, NTB, MMSE, CDR-SB, ADCS-MCI-ADL, and FCSRT-IR will all be summarized and may be analyzed using an MMRM with preinfusion cognitive measures as a baseline covariate and fixed effects of dose and study visit.

11.2.5.4. Plasma Aβ

Plasma Aβ will be analyzed to estimate the mean change from predose. The dependent variables will be $A\beta_{1-40}$ and $A\beta_{1-42}$.

Dosing regimen will be a fixed effect in the model and time may be included as a repeated effect. These analyses are considered exploratory in order to estimate whether there is mean change following doses of LY3002813. If required, a logarithmic transformation may be considered.

11.2.6. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory analyses may be conducted to describe the relationship between serum or CSF exposure and changes in the florbetapir SUVr, as well as relationships with cognitive endpoints, ADA, AEs, and/or plasma and CSF biomarkers. It is intended that these analyses will be graphical in nature as a function of LY3002813 dose, exposure, and/or time from study entry; however, the relationship may also be described using a modeling approach, if appropriate.

11.2.7. Safety Analyses

11.2.7.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed; if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product, as perceived by the investigator. Symptoms reported to occur

before randomization will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of investigational product-related SAEs will be reported.

11.2.7.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

A shift table for each dose group will be constructed to assess the MRI measurement pre- and postdose for changes and additions of vasogenic edema and microhemorrhages.

Suicide-related thoughts and behaviors based on the C-SSRS will be listed by patient. Only time points and patients that show ideation/behavior of suicide will be displayed (ie, all "no" responses will not be displayed).

Exploratory analyses of Fridericia's corrected QT interval data from ECG monitoring in a Phase 1 trial are performed to judge the extent and/or risk of QT prolongation. There will be an exploratory assessment of potential prolongation by examining mean change in Fridericia's corrected QT interval as a function of serum drug concentration obtained and an inspection of the upper confidence limit relative to a value of 10 msec, which is consistent with International Conference on Harmonisation (ICH) guidance. Frequency tables of QTc changes from baseline and large QTc values may also be obtained in accordance with ICH guidance.

11.2.7.3. Evaluation of Immunogenicity

Antibody formation will be summarized over time. If trends following the dosing of LY3002813 are observed, then a mixed effect model will be done fitting dose, study visit, and interaction between study visit and dose as fixed effects and the dependent variable as the change from baseline in antibody formulation following dosing of LY3002813. If a neutralization assay is performed, the frequency of neutralizing antibodies will be determined. The relationship between the presence (or absence) of ADAs and clinical parameters (AEs, PD measurements, and PK estimates) may be assessed.

11.3. Interim Analyses

The Lilly study team will review data obtained on an ongoing basis, to assure patient safety.

It is intended that a safety review of Cohort 2 data will be conducted to enable the enrollment of Cohorts 3, 5, and 7. This review is described in Section 7.1.3.

There are 4 planned interim reviews of PK and/or safety data. Interim reviews of safety data include AEs, clinical laboratory data, ECGs, vital signs, and imaging data. ADA titers will also be reviewed, if available.

The first interim review (PK data only) will occur after a minimum of 4 patients receiving LY3002813 in Cohort 1 complete Visit 10 (Day 29). The second interim review (PK data only)

will occur after a minimum of 4 patients receiving LY3002813 in Cohort 2 complete Visit 10 (Day 29). The third interim review (safety and PK data) is planned to occur after a minimum of 4 patients receiving LY3002813 in Cohort 3 (40 mg/kg IV single dose) complete Visit 12 (Day 85). Safety data will include data up to Visit 13 (Day 169). The fourth interim review (safety and PK data) is planned to occur after a minimum of 4 patients receiving LY3002813 in Cohort 4 and also in Cohort 5 (for a total of 8 patients) have completed Visit 16 (Day 141). Safety data will include data up to Visit 18 (Day 169).

Additional interim data reviews may also be conducted to summarize data for internal decision making and/or supporting subsequent clinical studies/regulatory agency/IB annual updates, as required.

There will be regular reviews of PD data by the Lilly study team, after a minimum of 4 patients on LY3002813 complete each scheduled florbetapir scan in each cohort.

In addition, safety will be reviewed by the Lilly study team on an ongoing basis. Safety review meetings will be conducted regularly with investigators.

12. Data Management Methods

12.1. Data Quality Assurance

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

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

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

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

12.2. Data Capture Systems

12.2.1. Source Data and Case Report Form

A source document is the first record of data. These can be paper (for example, ECG tracing or patient diary), a paper CRF on which the data is initially recorded, or data captured directly on an investigator site electronic system (for example, Holter Monitor record data files or electronic health record). The site must retain all source records and must maintain a record of any data where source data are directly entered into the paper CRF.

Data may then be entered into either an electronic or paper CRF and the process will be documented and communicated by the sponsor to the investigator site before first patient visit.

Some investigator site data may be collected directly in the paper CRF whereas other data that is collected by the site on paper or electronic records may be transferred to the paper CRF.

Lilly does not allow direct source data entry into Lilly computer systems, with the exception of the investigator site systems at the Lilly CRU.

If an electronic patient reported outcomes instrument record will be used to collect source data, that data will be identified and documented by each site in the site's study file.

For data handled by a data management TPO, CRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the sponsor.

For data handled internally, CRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

12.2.2. Ancillary Data

Data managed by a central vendor will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse and TPO's system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly data warehouse and the TPO's system.

PD data that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Electrocardiogram data will be stored electronically in the central database system of Lilly's central review organization. Data will subsequently be transferred from the central review organization system to the TPO's system.

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

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

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

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

The investigator is ultimately responsible for ensuring that informed consent is given by each patient before the study is started. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of the investigational product.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites(s). All ICFs must be compliant with the ICH guideline on GCP.

The investigator must give assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

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

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

13.3. 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) ICH GCP Guideline [E6]

3) applicable laws and regulations

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

Some of the obligations of the sponsor will be assigned to a TPO.

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

13.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

13.3.2. Protocol Signatures

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

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

13.3.3. Final Report Signature

The final report coordinating investigator or designee will sign the 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 investigator with the most enrolled patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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

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Attachment 1. Protocol AACD Study Schedule

Schedule of Activities, Protocol I5T-MC-AACD, Visit 1 through Visit 3 (Screening Period), All Cohorts

Procedure			
Visit No.:	**V1[c]**	**V2**	**V3**
Day Relative to First Dose	**-56***	**-30***	**-15***
Entry and Administrative/Every Visit			
Informed consent (before procedures/tests)	X		
Patient number assigned	X		
Demographics, height, and habits	X		
Inclusion/exclusion review	X		
Previous/concomitant medications	X		
Preexisting conditions/AEs	X		
Vital signs and weight[d]	X		
Cognitive Assessments			
CDR	X		
FCSRT-IR	X		
MMSE	X		
Safety Assessments[c]			
Physical/neurological examination	X		
12-lead digital ECG[e]	X		
C-SSRS (child)/SHSF[f]	X		
Laboratory Assessments			
Coagulation tests (local laboratory)	X		
Clinical chemistry, electrolytes, hematology, urinalysis (local laboratory)[g]	X		
Imaging			
Lumbar x-ray or fluoroscopy (if required to rule out potential contraindications to an LP)	X		
MRI[i]		X	
Florbetapir PET scan			X

Schedule of Activities, Protocol I5T-MC-AACD, Part A: Cohorts 1 and 2 (Single Dose), Visit 4 through Visit 17

Procedure															
Visit No.:	**V4[a]**	**V5[b]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ED**
Day Relative to First Dose	**-4**	**1**	**4**	**6**	**8**	**15**	**29**	**57**	**85**	**169**	**253**	**337**	**421**	**505**	
Week			**1**	**1**	**1**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	
Tolerance Interval for Visit (days)	**±4***	**0**	**0**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	
Entry and Administrative/Every Visit															
Body weight	X						X		X	X		X		X	X
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Preexisting conditions/AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication administered[l]		X													
Cognitive Assessments															
ADAS-Cog	X									X		X		X	X
ADCS-MCI-ADL24	X									X		X		X	X
NTB	X									X		X		X	X
CDR										X		X		X	X
FCSRT-IR										X		X		X	X
MMSE										X		X		X	X
Safety Assessment															
Vital signs	X	X[m]	72 hrs	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[d]/SHSF[f]	X	X				X	X	X	X	X	X	X	X	X	X
Physical/neurological examination		X[p]				X	X	X	X					X	X
12-lead digital ECG[e]	X[m]	X[m]	72 hrs	X	X	X	X	X	X					X	X
Imaging															
MRI[h,i]							X		X	X		X		X	X
Florbetapir PET scan									X	X	X	X		X	X
18F-AV-1451 PET scan	X[x]													X[j]	X[j]
Laboratory Assessments															
LP[n]	X		X												
ABI tempus tube/blood RNA	X				X										
Pharmacogenetic sample[o]	X														

Schedule of Activities, Protocol I5T-MC-AACD, Part A: Cohorts 1 and 2 (Single Dose), Visit 4 through Visit 17

Procedure															
Visit No.:	**V4[a]**	**V5[b]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ED**
Day Relative to First Dose	**-4**	**1**	**4**	**6**	**8**	**15**	**29**	**57**	**85**	**169**	**253**	**337**	**421**	**505**	
Week		**1**	**1**	**1**	**1**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	
Tolerance Interval for Visit (days)	**±4***	**0**	**0**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	
Laboratory Assessments (continued)															
Clinical chemistry, electrolytes, hematology, urinalysis[g]		X	X	X	X	X	X	X	X					X	X
Coagulation tests (at local laboratory, prior to LP, except the V6 LP)[y]	X														
Serum LY3002813 PK[q]		predose, end of infusion, 3, 24, 48 hrs	72 hrs	X	X	X	X	X	X	X	X	X	X	X	X
Plasma Aβ	X		X												
Serum for immunogenicity[s]	X				X	X	X		X	X	X	X	X	X	X
Aliquoted plasma (EDTA) and serum for storage	X				X										
Stored serum for possible exploratory immune safety laboratory tests[t]	X								X						X

Schedule of Activities, Protocol I5T-MC-AACD, Part A: Cohort 3 (Single Dose), Visit 4 through Visit 13

Procedure											
Visit No.:	**V4[a]**	**V5[b]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**ED**
Day Relative to First Dose	**-4**	**1**	**4**	**6**	**8**	**15**	**29**	**57**	**85**	**169**	
Week			**1**	**1**	**1**	**2**	**4**	**8**	**12**	**24**	
Tolerance Interval for Visit (days)	**±4***	**0**	**0**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±7**	
Entry and Administrative/Every Visit											
Body weight	X						X		X	X	X
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Preexisting conditions/AEs		X	X	X	X	X	X	X	X	X	X
Study medication administered[l]		X									
Cognitive Assessments											
ADAS-Cog	X									X	X
ADCS-MCI-ADL24	X									X	X
NTB	X									X	X
CDR										X	X
FCSRT-IR										X	X
MMSE										X	X
Safety Assessment											
Vital signs	X	X[m]	72h	X	X	X	X	X	X	X	X
C-SSRS[d]/SHSF[f]	X	X				X	X	X	X	X	X
Physical/neurological examination		X[p]				X	X	X	X	X	X
12-lead digital ECG[e]	X[m]	X[m]	72h	X	X	X	X	X	X	X	X
Imaging											
MRI[h,i]							X		X	X	X
Florbetapir PET scan									X	X	X
18F-AV-1451 PET scan	X[x]									X[j]	X[j]
Laboratory Assessments											
LP[n]	X		X								
ABI tempus tube/blood RNA	X				X						
Pharmacogenetic sample[o]	X										
Clinical chemistry, electrolytes, hematology, urinalysis[g]		X	X	X	X	X	X	X	X	X	X
Coagulation tests (at local laboratory, prior to LP, except the V6 LP)[y]	X										
Serum LY3002813 PK[q]		predose, end of infusion, 3, 24, 48h	72h	X	X	X	X	X	X	X	X
Plasma Aβ	X		X								
Serum for immunogenicity[s]	X				X	X	X		X	X	X
Aliquoted plasma (EDTA) and serum for storage	X				X						
Stored serum for possible exploratory immune safety laboratory tests[t]	X								X		X

Schedule of Activities, Protocol I5T-MC-AACD, Part B: Cohorts 4 and 5 (Multiple Dose), Visit 4 through Visit 22

Procedure																				
Visit No.:	**V4[a]**	**V5[b]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**ED**
Day Relative to First Dose	**-4**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**253**	**337**	**421**	**505**	
Week		**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**36**	**48**	**60**	**72**	
Tolerance Interval for Visit (days)	**±4***	**0**	**±1**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	
Entry and Administrative/Every Visit																				
Body weight[d]	X				X				X						X	X	X		X	X
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Preexisting conditions/AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication administered[l]		X		X	X	X	X	X	X	X	X	X	X	X	X					
Cognitive Assessments																				
ADAS-Cog	X														X		X		X	X
ADCS-MCI-ADL24	X														X		X		X	X
NTB	X														X		X		X	X
CDR															X		X		X	X
FCSRT-IR															X		X		X	X
MMSE															X		X		X	X
Safety Assessment																				
Vital signs	X	X[m]	X	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X	X	X	X	X
C-SSRS[d]/SHSF[f]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical/neurological examination		X[p]		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X
12-lead digital ECG[e]	X[m]	X[m]		X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X			X	X
Imaging																				
MRI[h,i]					X				X						X	X	X		X	X
Florbetapir PET scan									X						X	X	X		X	X
18F-AV-1451 PET scan	X[x]																		X[j]	X[j]
Laboratory Assessments																				
LP[n]	X														72 hrs					X[z]
ABI tempus tube/blood RNA	X				X											X	X		X	X
Pharmacogenetic sample[o]	X																			

Schedule of Activities, Protocol I5T-MC-AACD, Part B: Cohorts 4 and 5, Visit 4 through Visit 22

Procedure																				
Visit No.:	**V4[a]**	**V5[b]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**ED**
Day Relative to First Dose	**-4**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**253**	**337**	**421**	**505**	
Week		**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**36**	**48**	**60**	**72**	
Tolerance Interval for Visit (days)	**±4***	**0**	**±1**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**		
Laboratory Assessments (continued)																				
Clinical chemistry, electrolytes, hematology, urinalysis[g]		X		X	X	X	X	X	X	X	X	X	X	X	X	X				X
Coagulation tests (at local laboratory, prior to LP)[y]	X														X					X
Serum LY3002813 PK[q]		predose, end of infusion, 3, 24, 48, 72 hrs	X	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	predose, end of infusion,3, 24, 48, 72 hrs	X[r]	X[r]	predose, end of infusion, 72 hrs	X	X	X	X	X
Plasma Aβ	X	72 hrs													X					X
Serum for immunogenicity[s]	X		X	X	X				X						X	X	X	X	X	X
Aliquoted plasma (EDTA) and serum for storage	X				X											X	X		X	X
Stored serum for possible exploratory immune safety laboratory tests[t]	X								X						X	X				X

Schedule of Activities, Protocol I5T-MC-AACD, Part C: Cohorts 6 and 7 (Chronic Dose), Visit 4 through Visit 25

Procedure	**Rand**																					
Visit No.:	**V4[a]**	**V5[b]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**
Day Relative to First Dose	**-4**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**
Week		**1**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**
Tolerance Interval for Visit (days)	**±4***	**0**	**±1**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Entry and Administrative/Every Visit																						
Body weight[d]	X				X		X			X				X			X			X		
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Preexisting conditions/AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication administered[l,w]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cognitive Assessments																						
ADAS-Cog	X									X						X						X
ADCS-MCI-ADL24	X									X						X						X
NTB	X									X						X						X
CDR										X						X						X
FCSRT-IR										X						X						X
MMSE										X						X						X
Safety Assessment																						
Vital signs	X	X[m]		X	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]
C-SSRS[d]/SHSF[f]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical/neurological examination		X[p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead digital ECG[e]	X[m]	X[m]		X	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]
Imaging																						
MRI[h,i]					X		X			X			X			X			X			X
Florbetapir PET scan							X			X			X			X						X
18F-AV-1451 PET scan	X[x]																					X[j]
Laboratory Assessments																						
LP[n]	X									72 hrs												
ABI tempus tube/blood RNA	X				X											X	X	X	X	X		
Pharmacogenetic sample[o]	X																					

Schedule of Activities, Protocol I5T-MC-AACD, Part C: Cohorts 6 and 7 (Chronic Dose), Visit 4 through Visit 25

Procedure	**Rand**						M3			M6				M9			M12			M15		
Visit No.:	**V4[a]**	**V5[b]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**
Day Relative to First Dose	**-4**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**
Week		**1**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**
Tolerance Interval for Visit (days)	**±4***	**0**	**±1**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Laboratory Assessments (continued)																						
Clinical chemistry, electrolytes, hematology, urinalysis[g]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation tests (at local laboratory, prior to LP)[y]	X									X												
Serum LY3002813 PK[q]		predose, end of infusion, 3, 24, 48, 72 hrs	X	X	X[r]	X[r]	X[r]	X[r]	predose, end of infusion 3, 24, 48, 72 hrs	predose, end of infusion 72 hrs	X[r]		X[r]			X[r]			X[r]			X[r]
Plasma Aβ	X	72 hrs								X												
Serum for immunogenicity[s]	X		X	X	X		X			X			X			X			X			X
Aliquoted plasma (EDTA) and serum for storage	X				X								X			X			X			X
Stored serum for possible exploratory immune safety laboratory tests[t]	X						X			X			X									X

Schedule of Activities, Protocol I5T-MC-AACD, Part C: Cohorts 6 and 7 (Chronic Dose), Visit 26 through Visit 27

Procedure	**M18**	**FU**	
Visit No.:	**V26**	**V27**	**ED**
Day Relative to First Dose	**533**	**589**	
Week	**76**	**84**	
Tolerance Interval for Visit (days)	**±7**	**±7**	
Entry and Administrative/Every Visit			
Body weight		X	X
Previous/concomitant medications	X	X	X
Preexisting conditions/AEs	X	X	X
Cognitive Assessments			
ADAS-Cog$_{14}$			X
ADCS-MCI-ADL24			X
NTB			X
CDR			X
FCSRT-IR			X
MMSE			X
Safety Assessment			
Vitals	X	X	X
C-SSRS[d]/SHSF[f]	X	X	X
Physical/neurological examination	X	X	X
12-lead digital ECG[e]	X	X	X
Imaging			
MRI[h,i]			X
Florbetapir PET scan			X
18F-AV-1451 PET scan			X[j]
Laboratory Assessments			
LP[n]			X[z]
ABI tempus tube/blood RNA			X

Schedule of Activities, Protocol I5T-MC-AACD, Part C: Cohorts 6 and 7 (Chronic Dose), Visit 26 through Visit 27

Procedure	**M18**	**FU**	
Visit No.:	**V26**	**V27**	**ED**
Day Relative to Study Medication Start	**533**	**589**	
Week	**76**	**84**	
Tolerance Interval for Visit (days)	**±7**	**±7**	
Laboratory Assessments (continued)			
Clinical chemistry, electrolytes, hematology, urinalysis[g]	X	X	X
Coagulation tests (at local laboratory)[y]			X
Serum LY3002813 PK[q]	X	X	X
Plasma Aβ	X	X	X
Serum for immunogenicity[s]	X	X	X
Aliquoted plasma (EDTA) and serum for storage	X	X	X
Stored serum for possible exploratory immune safety laboratory tests[t]		X	X

Abbreviations: Aβ = amyloid-beta; ADAS-cog = Alzheimer 's Disease Assessment Scale-Cognitive Subscale; ADCS-MCI-ADL24 = Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment-Activities of Daily Living, 24-item questionnaire, AE = adverse event; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; ED = early discontinuation; EDTA = ethylene diamine tetraacetic acid; FCSRT-IR = Free and Cued Selective Reminding Test with Immediate Recall; FU = follow-up; hr = hours; IWRS = interactive web response system; LP = lumbar puncture; M = month; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NTB = Neuropsychological test battery; PET = positron emission tomography; PK = pharmacokinetics; RAND = randomization; RBC = red blood cells; RNA = ribonucleic acid; SHSF = Self-Harm Supplement Form; V = visit; WBC = white blood cells.

*Approximate days and may be highly variable.

a Patients may be admitted on Day -1, to perform these tests, at the discretion of the site. Note that the ADAS-cog and NTB testing must be separated from each other by 4 hours to avoid testing fatigue and all cognitive tests must be performed before LP if on the same day and LP must be performed no closer than 24 hours from dosing.

b Patients will remain at the site for at least 6 hours after the end of infusion. Any patient discharged before the 24-, 48-, and 72-hour procedures will be required to return to the site for procedures at the respective time points.

c Screening tests may occur up to 56 days before the study drug administration apart from the exceptions presented in Section 8.1.

d Performed before dosing.

e A single ECG will be obtained at screening and will not be transmitted to central vendor. All other ECGs will be done in triplicate and transmitted to the central vendor for storage. For visit with no specified ECG timing ("X"), the ECG should be collected close to the PK collection and should be time matched with preadmission ECGs (Visit 4).

f If the investigator determines that suicide-related behaviors have occurred, the Lilly SHSF form will be used to collect additional information to allow for a more complete assessment of these behaviors.

g All analytes will be measured.

h If patient discontinues before the MRI, request that patient returns for this procedure even though all other interim study evaluations may be forgone.

i MRI must be performed before a LP. Cognitive tests must be performed before LP if done on the same day.

j The 18F-AV-1451 PET scan should be performed at least 24 hours apart from the florbetapir scan. Patients permanently discontinued from study treatment due to initiation of a prohibited medication known to significantly prolong the QT interval should not have an ED 18F-AV-1451 scan unless the scan can be performed prior to initiation of the prohibited medication. Patients who have continued on the study after introduction of a drug known to significantly prolong QT interval (with sponsor approval) need a minimum of 14 days or 5 half-lives, whichever is longer, without that drug prior to the 18F-AV-1451 scan.

l Inpatient stay is required until a minimum of 6 hours after the end of the infusion for observation. Patients will be assessed according to the Schedule of Events prior to being discharged. The 6-hour observation period at the site may be extended beyond 6 hours for safety or feasibility reasons (including an overnight stay), at the discretion of the investigator. In Part A, no more than 1 patient will be dosed on any 1 particular day across all sites. In Parts B and C, patients dosed on the same day at any 1 site should be dosed at least 1 hour apart and dose preparation should be based on the most recent body weight measurement taken per the Schedule of Activities.

m Performed predose and end of infusion, and 3 hours, 24 hours, and 72 hours after the start of infusion for vital signs and ECGs. For the preadmission ECG visit, time matched ECGs should approximately match the times planned on Day 1. Time matched ECGs can be taken at any day before the first dosing day, predose (at the time planned for the start of the dose on Day 1 visit), approximately at the end of infusion, and 3 hours after the start of infusion.

n For the baseline LP, it may be performed no closer than 24 hours before first dosing and be part of a Day -1 admission and dosing may not proceed until patient reports at least 12 hours after resolution of symptoms of post-LP headache, if present. For Part A only, predose CSF samples by single LP should be conducted at least 3 days before dosing, because a second CSF sample will be taken approximately 3 days after dosing with study drug. Local laboratory will process CSF for cells (RBCs and WBCs, where possible) and protein and glucose, the remainder will be sent to central laboratory. CSF will be analyzed for PK (post treatment sample only), Aβ, tau, protein, and cell count. Additional CSF will be collected for storage, as described in Section 10.3. LPs are required for all patients and can be performed up to 11 days before dosing. However, LPs are not required for Japanese patients who are added after the planned number of patients for a cohort has already been filled. LPs should be conducted at approximately the same time as plasma PK samples, if applicable. If there is no PK drawn, LPs should be conducted at approximately the same time of day.

o A pharmacogenetic sample will be obtained preadmission or before the first dosing. An additional sample may be taken postdose if required.

p Performed predose and 24 hours after the start of dose. If the subject is discharged prior to the 24-hour assessments, these should also be conducted prior to discharge.

q The numbers in the rows refer to scheduled hours postdose for sampling, measured from the start of the infusion. The “predose” collection indicates that the sample should be taken up to 30 minutes before the beginning of the infusion. The “end of infusion” collection indicates that the sample should be taken as close to the completion of the infusion as possible. On the day of dosing, postdose samples should be collected from a different arm than was used to administer study drug. If no specific time point is indicated (“X”), a single sample will be collected as close as possible to the dosing time on the previous infusion day.

r Predose and end of infusion samples should be collected. The “predose” collection indicates that the sample should be taken up to 30 minutes before the beginning of the infusion. The “end of infusion” collection indicates that the sample should be taken as close to the completion of the infusion as possible. Postdose samples should be collected from a different arm than was used to administer study drug.

s If the immunogenicity titer at the last scheduled assessment or discontinuation visit is positive, then additional safety assessments (concomitant medications, AEs, safety laboratory values, ECGs, vital signs) and samples for immunogenicity and PK should be taken every 12 weeks until the titer returns to baseline (comes within a single 2-fold dilution of the baseline titer), or up to 48 weeks after the last dose of LY3002813 if the antibody titer has not returned to baseline within 48 weeks after the last dose. In the case of a patient whose result is positive at baseline with a 1:10 titer and subsequently develops a treatment-emergent ADA response that increases to much higher titers, the antibody titer would need to decline to a titer of 1:20 or less to be considered a "return to baseline." In contrast, if the patient's result is "not detected" at baseline (in an assay with a 1:10 minimal required dilution), the titer would need to decline to either "detected" with a 1:10 titer or a result of "not detected" to be considered a "return to baseline."

t Stored serum samples for possible immune safety laboratory testing (including but not limited to β tryptase, total Immunoglobulin E, and immune complex testing) will be collected. In the event of a moderate or severe infusion reaction event, additional unscheduled samples should be collected approximately 60-120 minutes and 4-6 weeks after moderate or severe infusion reactions. Failure to collect these samples will not qualify as a protocol violation. Unscheduled samples may also be collected as needed.

u Performed predose and end of infusion and 2 hours after the end of infusion on dosing days.

v Performed predose and end of infusion.

w If a patient is deemed to be amyloid negative by florbetapir PET before completion of 18 months' dosing (SUVr <1.1 for 2 consecutive scans), the patient will receive placebo infusion for all subsequent visits, and continue the Part C visit schedule.

x May increase window ±28 days and the 18F-AV-1451 PET scan should be done before dosing. The 18F-AV-1451 PET scan may be performed after dosing following discussion with the Lilly clinical pharmacologist/CRP if there is a manufacturing issue on the day of the scheduled Visit 4 18F-AV-1451 PET scan and the scan needs to be rescheduled. Patients who have continued on the study after introduction of a drug known to significantly prolong QT interval (with sponsor approval) need a minimum of 14 days or 5 half-lives, whichever is longer, without that drug prior to the 18F-AV-1451 scan. The scan is performed after the patient qualifies based on the results of the florbetapir PET scan.

y Coagulation test results should be reviewed before each LP. Concomitant medications should be reviewed to ensure that no changes to anticoagulation or antiplatelet therapy have occurred since the last coagulation test.

z This LP is only needed if an LP was not performed during Visit 18 for Part B and Visit 13 for Part C.

Attachment 2. Protocol AACD Clinical Laboratory Tests

Laboratory Tests at Screening (Performed at Local Laboratory)

Hematology	Clinical chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate[d]
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Glucose (random)
Leukocytes (WBC)	Blood urea nitrogen
Cell morphology (absolute or relative % counts)	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase
Eosinophils	Aspartate aminotransferase (SGOT)
Basophils	Alanine aminotransferase (SGPT)
Platelets	Creatinine
Urinalysis	Ethanol testing[b,c]
Specific gravity	Urine drug screen[c]
pH	Hepatitis B surface antigen
Protein	Hepatitis C antibody
Glucose	HIV
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Microscopic examination of sediment[a]	
Coagulation	
Prothrombin time/international normalized ratio	
Activated partial thromboplastin time	

Abbreviations: HIV = human immunodeficiency virus; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = glutamic-pyruvic transaminase; WBC = white blood cells.

[a] Test only if dipstick result is abnormal.

[b] At site discretion this may be a serum, breath, or urine sample.

[c] Urine drug screen and ethanol level may be repeated before admission to the site.

[d] May not be collected in Japan.

Laboratory Tests during Study (Performed at Central/Local Laboratory)

Hematology[a]	Clinical chemistry[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)[a]	Bicarbonate[e]
Mean cell volume	Uric acid
Mean cell hemoglobin	Chloride
Mean cell hemoglobin concentration	Calcium
Leukocytes (WBC)	Glucose
Cell morphology (absolute or relative % counts)	Blood urea nitrogen
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Total bilirubin
Eosinophils	Alkaline phosphatase
Basophils	Aspartate aminotransferase (SGOT)
Platelets	Alanine aminotransferase (SGPT)
Urinalysis[a]	Creatinine
Specific gravity	Total cholesterol
pH	Low-density lipoprotein cholesterol
Protein	High-density lipoprotein cholesterol
Glucose	Triglycerides
Ketones	Ethanol testing[c,d]
Bilirubin	Urine drug screen[c,d]
Urobilinogen	Anti-LY antibodies/immunogenicity[h]
Blood	Cerebrospinal fluid[e]
Nitrite	Glucose[d]
Microscopic examination of sediment[b]	Total protein[d]
Coagulation[d]	Blood (visual inspection)[f]
Prothrombin time/international normalized ratio[d]	WBC[d]
Activated partial thromboplastin time[d]	Exploratory immune safety laboratory tests[g]

Abbreviations: LY = LY3002813; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = glutamic-pyruvic transaminase; WBC = white blood cells.

a Results will be validated by the central laboratory at the time of initial testing.

b Test only if dipstick result is abnormal.

c May be done, as needed, at the discretion of the investigator. Ethanol testing may be done with serum, breath, or urine sample.

d Performed at local laboratory. Results will be validated by local laboratory at the time of initial testing.

e May not be collected in Japan.

f Performed at time of collection.

g If testing ordered, will be performed at central laboratory.

h Results will be validated by the central laboratory.

Attachment 3. Protocol AACD Blood Sampling Summary

These tables summarize the maximum number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I5T-MC-AACD Sampling Summary Part A (Cohorts 1 and 2)

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	26	1	26
Clinical laboratory tests[a]	12	9	108
Coagulation tests	6	1	6
Drug assays[b]	4	17 (+3)	68 (12)
Blood discard for cannula patency	3	15	45
Immunogenicity assessments[a]	10	10	100
Pharmacogenetic sample[c]	11	1 (+1)	11 (11)
Nonpharmacogenetic/biomarker samples	21	2	42
Blood sample for exploratory immune safety[a]	14	2	28
Total			434 (457)
Total for clinical purposes (rounded to the nearest 10 mL)			440 (460)

[a] Additional samples may be drawn if needed for safety purposes.

[b] A maximum of 3 blood samples per patient may be drawn at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor.

[c] An additional sample may be taken postdose if required.

Protocol I5T-MC-AACD Sampling Summary Part A (Cohort 3)

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	26	1	26
Clinical laboratory tests[a]	12	9	108
Coagulation tests	6	1	6
Drug assays[b]	4	13 (+3)	52 (12)
Blood discard for cannula patency	3	11	33
Immunogenicity assessments[a]	10	6	60
Pharmacogenetic sample[c]	11	1 (+1)	11 (11)
Nonpharmacogenetic/biomarker samples	21	2	42
Blood sample for exploratory immune safety[a]	14	2	28
Total			366 (389)
Total for clinical purposes (rounded to nearest 10 mL)			370 (390)

[a] Additional samples may be drawn if needed for safety purposes.
[b] A maximum of 3 blood samples per patient may be drawn at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor.
[c] An additional sample may be taken postdose if required.

Protocol I5T-MC-AACD Sampling Summary Part B (Cohorts 4 and 5)

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	26	1	26
Clinical laboratory tests[a]	12	14	168
Coagulation tests	6	2	12
Drug assays[b]	4	40 (+3)	160 (12)
Blood discard for cannula patency	3	20	60
Immunogenicity assessments[a]	10	10	100
Pharmacogenetic sample[c]	11	1 (+1)	11 (11)
Nonpharmacogenetic/biomarker samples	21	5	105
Blood sample for exploratory immune safety[a]	14	4	56
Total			698 (721)
Total for clinical purposes (rounded to nearest 10 mL)			700 (730)

[a] Additional samples may be drawn if needed for safety purposes.
[b] A maximum of 3 blood samples per patient may be drawn at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor.
[c] An additional sample may be taken postdose if required.

Protocol I5T-MC-AACD Sampling Summary Part C (Cohorts 6 and 7)

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	26	1	26
Clinical laboratory tests[a]	12	21	252
Coagulation tests	6	2	12
Drug assays[b]	4	36 (+3)	144 (12)
Blood discard for cannula patency	3	25	75
Immunogenicity assessments[a]	10	12	120
Pharmacogenetic sample[c]	11	1 (+1)	11 (11)
Nonpharmacogenetic/biomarker samples	21	7	147
Blood sample for exploratory immune safety[a]	14	6	84
Total			871 (894)
Total for clinical purposes (rounded to nearest 10 mL)			880 (900)

[a] Additional samples may be drawn if needed for safety purposes.

[b] A maximum of 3 blood samples per patient may be drawn at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor.

[c] An additional sample may be taken postdose if required.

Attachment 4. Protocol AACD Blinding/Unblinding Plan

Levels of unblinding are indicated in the table below. This table provides general guidance as to who will be allowed access to randomization codes at various steps of the trial. The information elsewhere in the protocol will always take precedence over this table. For interim analysis, appropriate interim analysis team members, including a statistician, a programmer, and a data manager, will be identified and agreed upon between Lilly and the TPO.

Randomization data are kept strictly confidential and are accessible only by authorized personnel until unblinding of the trial as described below. All measures possible must be taken to maintain the blind, which means that access to the randomization code must be restricted to authorized personnel as described in the protocol and summarized in the table below.

If there is a need for unblinding of select people from Lilly and/or the TPO who are not in direct contact with the site, the detailed process, including formation of the unblinded team, creating restricted access electronic folders, and measures taken to guard against inappropriate dissemination of treatment codes (for example, by maintaining no contact with the study team until team is unblinded), will be described in the unblinding plan or another appropriate document and approval sought from Lilly and Covance team statisticians.

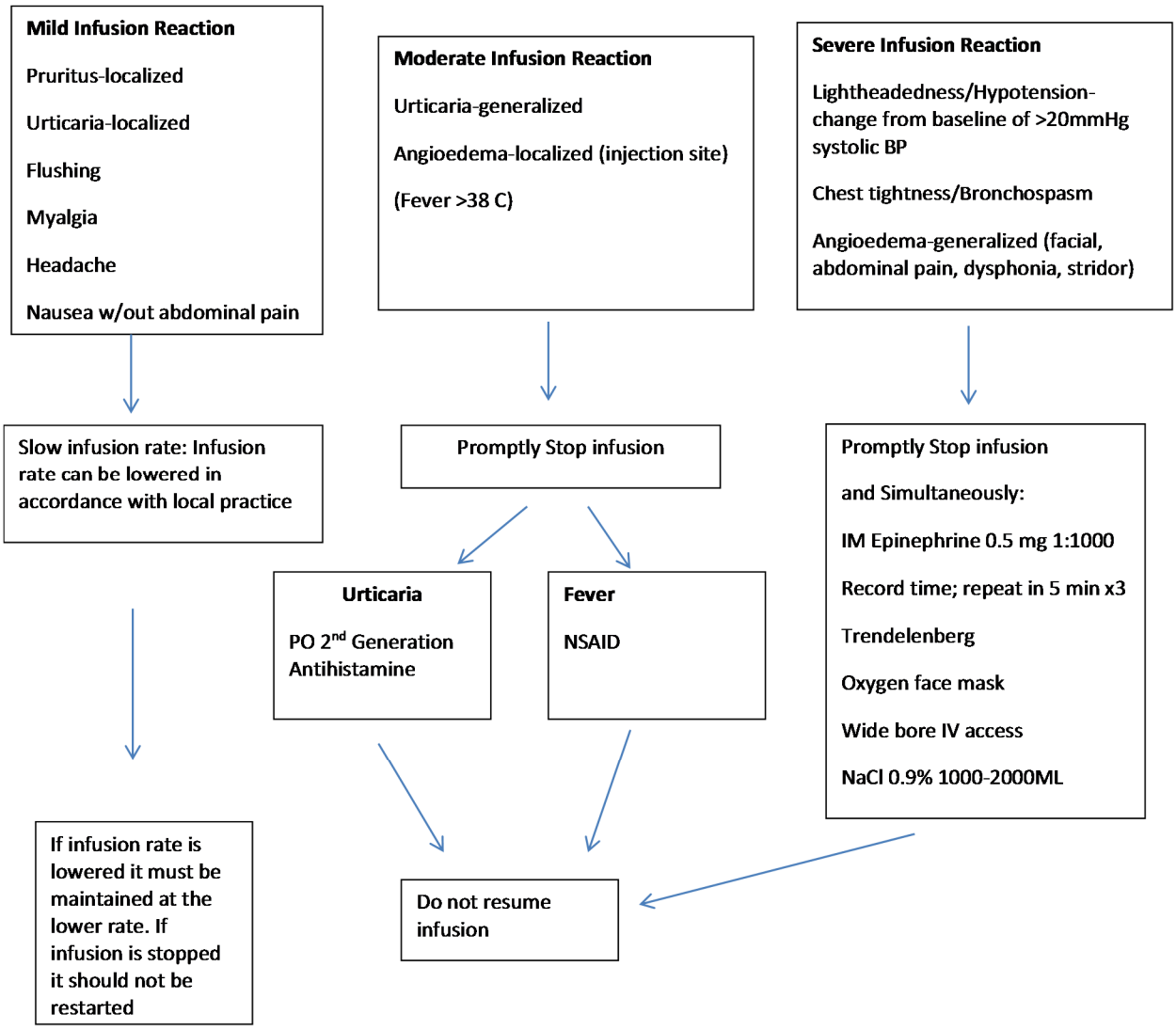
Study I5T-MC-AACD Blinding and Unblinding Plan

	Study Timelines				
Study Team Member	**Screening**	**Randomization**	**Treatment Phase**	**Follow-Up**	**Database Lock**
General					
Drug supply	NA	U	U	U	U
Randomization statisticians	NA	U	U	U	U
ECG reader	NA	U	U	U	U
Bioanalysis lab/sample analysis	NA	U	U	U	U
Clinical site					
Pharmacist	NA	U	U	U	U
Dosing nurse	NA	B	B	B	B
Patient	NA	B	B	B	B
CP/investigator	NA	B	B	B	U
Study monitor	NA	U	U	U	U
Covance Early Clinical Biometrics					
Project integration	NA	U	U	U	U
Data management	NA	U	U	U	U
Programming	NA	U	U	U	U
Statistician	NA	U	U	U	U
Medical writing	NA	U	U	U	U
Pharmacokinetic scientist/associate	NA	U	U	U	U
Lilly					
CPM	NA	U	U	U	U
CPA/CPC	NA	U	U	U	U
DSA	NA	U	U	U	U
SDTM core team	NA	U	U	U	U
Statistician	NA	U	U	U	U
Medical writing	NA	U	U	U	U
CP	NA	U	U	U	U
CRP	NA	U	U	U	U
Pharmacokinetic scientist/associate	NA	U	U	U	U
Pharmacovigilance personnel	NA	U	U	U	U

Abbreviations: B = blinded; CP = clinical pharmacologist; CPA/CPC = clinical pharmacology associate/clinical pharmacology consultant; CPM = clinical project manager; CRP = clinical research physician; DSA = data sciences associate; ECG = electrocardiogram; lab = laboratory; NA = not applicable; SDTM = study data tabulation model; U = unblinded.

Attachment 5. Protocol AACD Management of Infusion Reactions

Infusion Reaction Management Flowchart



Abbreviations: BP = blood pressure; IM = intramuscular; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = by mouth.
Continue supportive care in accordance with the symptoms/signs (Section 9.5.1.2).
Source: Adapted from Lichtenstein et al. 2015.

Attachment 6. Protocol Amendment I5T-MC-AACD(f) Summary
A Single- and Multiple-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Intravenous Doses of LY3002813 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

Overview

Protocol I5T-MC-AACD "A Single- and Multiple-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Intravenous Doses of LY3002813 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease" has been amended. The new protocol is indicated by Amendment (f) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- The cohort description in Section 7 has been updated to clarify that the patient numbers in each cohort are planned enrollment numbers, rather than a minimum required number of patients to complete the study.
- The duration of the follow-up period after administration of a single dose of 40 mg/kg LY3002813 has been reduced from 18 months to 6 months. The reduced follow-up period is attributable to emerging amyloid PET data in Cohorts 1 and 2 that indicate that follow-up PET scans up to 6 months will be sufficient to evaluate the effect of a single dose of 40 mg/kg LY3002813 on amyloid burden assessed using florbetapir PET. However, if the immunogenicity titer at the last scheduled assessment or discontinuation visit is positive, then additional safety assessments remain the same (see Section 10.4.1).
- Section 9.2.3 (18F-AV-1451 Dosage and Administration) has been amended to allow previously conducted 18F-AV-1451 PET scans to be used as the baseline scan.
- Minor editorial changes and formatting corrections were made but not necessarily documented below.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

2. Synopsis

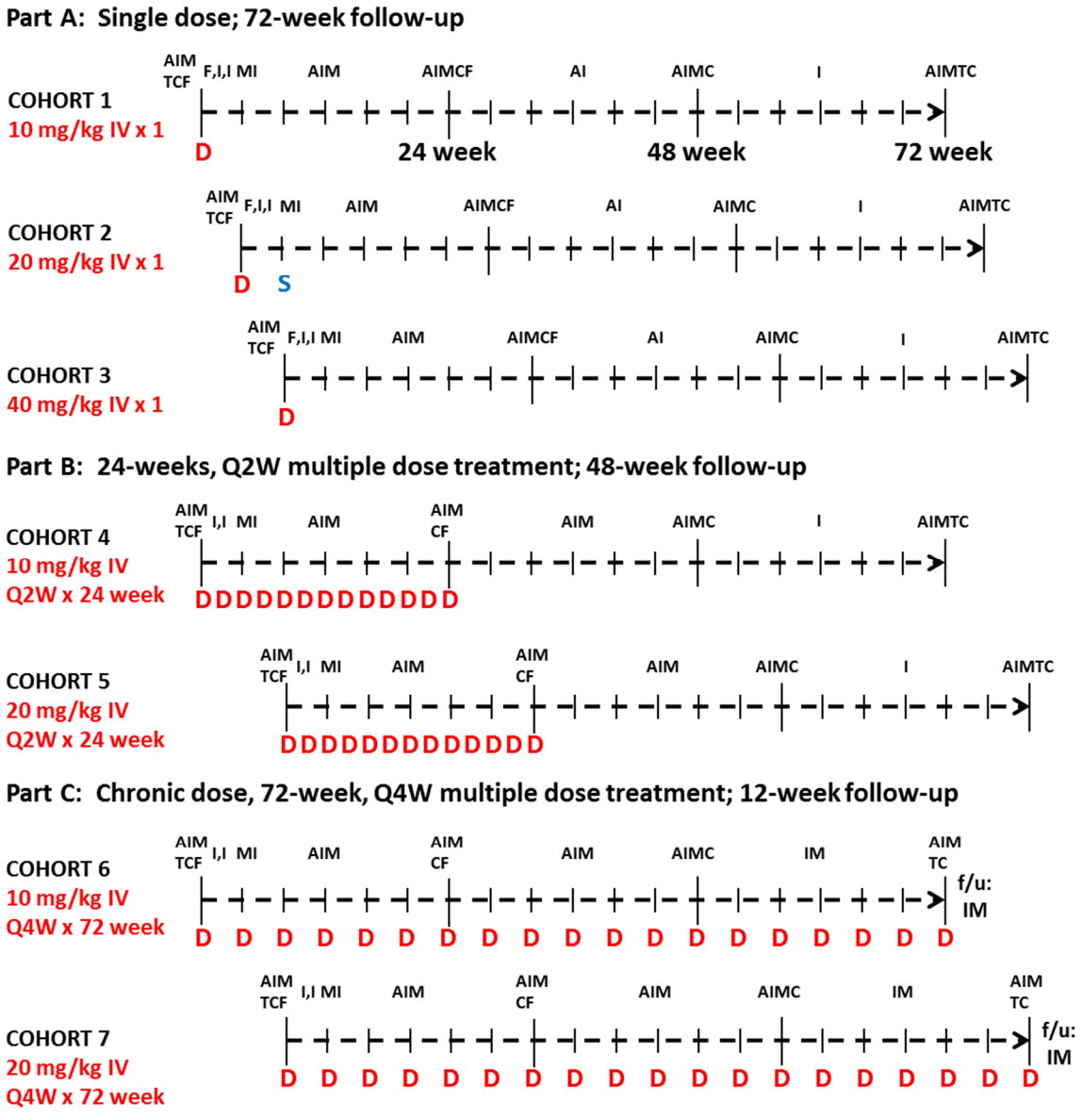
Number of Planned Patients: Up to 150 patients may be enrolled so ~~to ensure~~ that approximately ~~a minimum of~~ 72 patients complete the study (7 dosing cohorts of 8 to 12 ~~. Eight~~ patients) ~~each in Cohorts 1, 2, and 3. Twelve patients each in Cohorts 4, 5, 6, and 7~~.	**Phase of Development:** 1b
Length of Study: Part A (Cohorts 1, 2, and 3): screening—approximately 6 weeks; single intravenous (IV) LY3002813 or placebo treatment; 72-week (for Cohorts 1 and 2) and 24-week (for Cohort 3) follow-up. Part B (Cohorts 4 and 5): screening—approximately 6 weeks; multiple dose IV LY3002813 or placebo treatment every 2 weeks (Q2W) for 24 weeks; 48-week follow-up after dosing. Part C (Cohorts 6 and 7): screening—approximately 6 weeks; multiple dose IV LY3002813 or placebo treatment every 4 weeks (Q4W) for 72 weeks; 12 weeks follow-up after dosing.	
Study Design: This is a 3-part, patient- and investigator-blind, randomized within cohort, placebo-controlled, parallel-group, single- and multiple-dose study in patients with MCI due to AD or mild to moderate AD to assess the safety, tolerability, PK, and PD of single and multiple IV doses of LY3002813. The study will be conducted in at least 7 cohorts. • Cohort 1: 10 mg/kg IV single dose • Cohort 2: 20 mg/kg IV single dose • Cohort 3: 40 mg/kg IV single dose • Cohort 4: 10 mg/kg IV Q2W for 24 weeks • Cohort 5: 20 mg/kg IV Q2W for 24 weeks • Cohort 6: 10 mg/kg IV Q4W for up to 72 weeks • Cohort 7: 20 mg/kg IV Q4W for up to 72 weeks Each cohort will contain ~~a minimum of~~ approximately 6 (single dose) or 9 (multiple dose) patients treated with LY3002813 and 2 to 3 patients treated with placebo so that the study can detect target engagement and antidrug antibody (ADA) frequency relative to those observed in Study I5T-MC-AACC.	
Planned Duration of Treatment: Part A (Cohorts 1, 2, and 3): single dose of LY3002813 or placebo followed by 72 weeks (for Cohorts 1 and 2) and 24 weeks (for Cohort 3) follow-up for each dose level Part B (Cohorts 4 and 5): 13 doses of LY3002813 or placebo administered Q2W for 24 weeks followed by 48-weeks follow-up Part C (Cohorts 6 and 7): 19 doses of LY3002813 or placebo administered Q4W for 72 weeks followed by 12-weeks follow-up	

7.1. Summary of Study Design

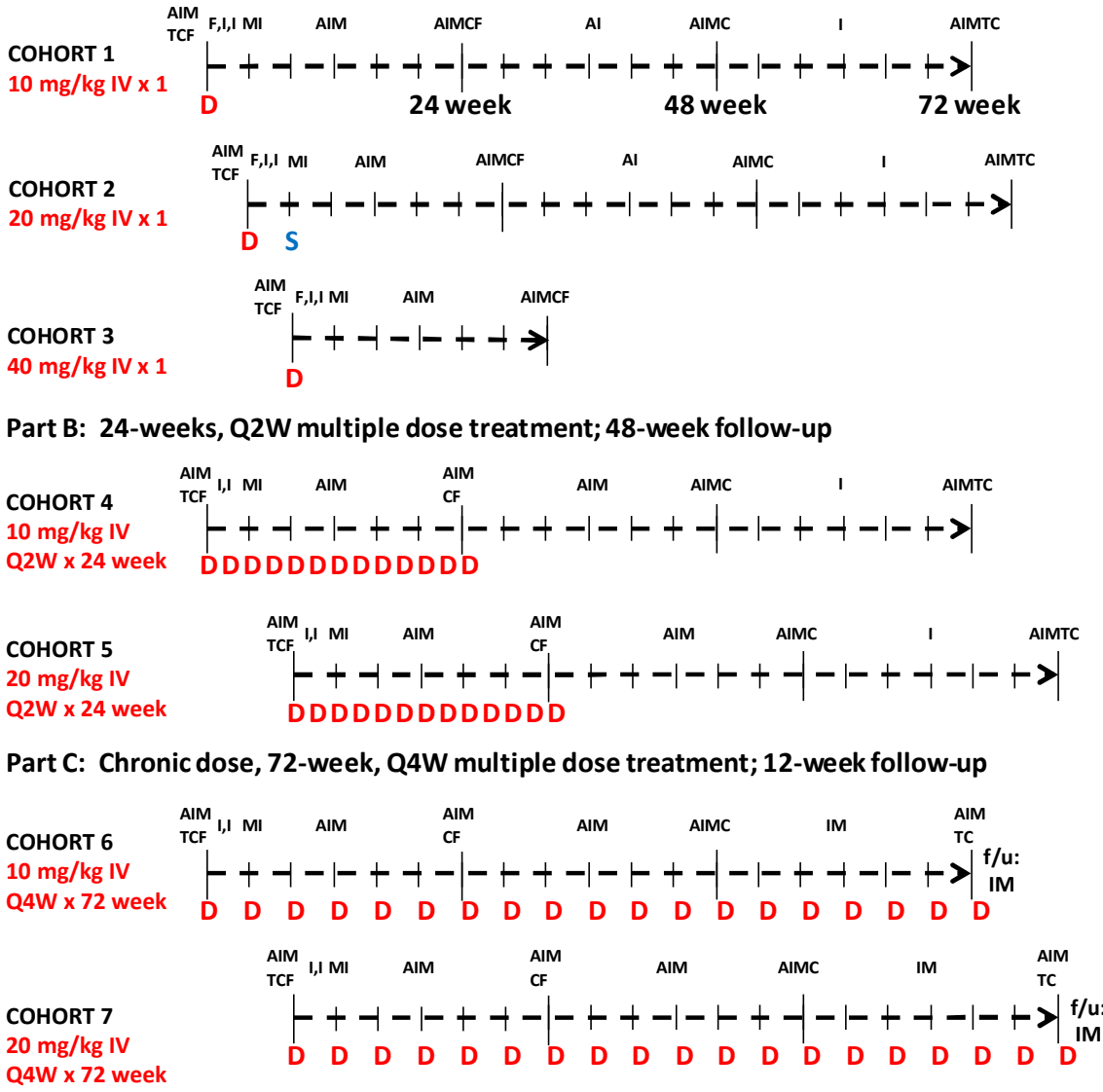
[…]

This study (Study AACD) will enroll patients with MCI due to AD, mild AD, or moderate AD with amyloid deposition confirmed by florbetapir PET imaging using National Institute on Aging-Alzheimer's Association (NIAAA) work group consensus guidelines (Albert et al. 2011; McKhann et al. 2011). This study will be conducted at sites in in multiple countries, including the United States and Japan. Up to 150 patients may be enrolled ~~to ensure~~ so that approximately 72 patients (7 dosing cohorts of 8 to 12 patients) complete the study.

Previous diagram:



Revised diagram:



Cohort 2 will only be initiated after review of safety data from Cohort 1. Thereafter, Cohort 3 will be initiated after review of safety data from Cohort 2. Cohorts 4 and 5 will be initiated after review of safety and PK data from their respective single-dose cohorts. An additional requirement for Cohort 5 is confirmation that at least 2 patients have received at least 3 doses each of LY3002813 safely in Cohort 4. Cohort 6 and Cohort 7 may proceed in parallel with Cohorts 4 and 5, respectively. In addition, Cohort 7 will only be initiated after confirmation that at least 2 patients have received at least 2 doses each of LY3002813 safely in Cohort 6. Safety/PK reviews will occur after a minimum of 4 patients receiving LY3002813 and 1 patient

receiving placebo have been dosed. For Cohorts 1 to 3, no more than 1 patient will be dosed on any one particular day. For Cohorts 4 to 7, patients dosed on the same day at any one site should not be dosed simultaneously but should be separated by at least 1 hour. Each cohort will contain ~~a minimum of~~ approximately 6 (single dose) or 9 (multiple dose) patients treated with LY3002813 and 2 to 3 patients treated with placebo so that the study can detect target engagement and ADA frequency relative to those observed in Study AACC.

7.1.3. Part A: Single Dose Cohorts (Cohorts 1 through 3)

Safety, PK, and PD will be assessed in Cohorts 1 through 3 after single doses of LY3002813 or placebo. The planned doses are 10, 20, and 40 mg/kg IV for Cohorts 1, 2, and 3, respectively; with ~~a minimum of~~ 8 patients (6 LY3002813; 2 placebo) ~~completing~~ planned to be enrolled in each cohort. Dose escalation will only occur after the safety from the preceding cohort has been established in at least 4 patients receiving LY3002813 and 1 receiving placebo. Safety data will be collected at least 1 week after dosing for dose escalation to Cohort 2 and at least 4 weeks after dosing for dose escalation to Cohort 3. Enrollment in Cohorts 2 and 3 will only commence once enrollment into the preceding cohort has completed. Safety, PK, and PD will be assessed at regular intervals for approximately 72 weeks (in Cohorts 1 and 2) or 24 weeks (in Cohort 3) after starting the dosing with study drug (Attachment 1).

7.1.4. Part B: 24-Week Q2W Multple Dose Cohorts (Cohorts 4 through 5)

Safety, PK, and PD will be assessed in Cohorts 4 and 5, during and after multiple doses of LY3002813 or placebo have been administered Q2W for 24 weeks. The planned doses are 10 and 20 mg/kg IV with ~~a minimum of~~ 12 patients (9 LY3002813; 3 placebo) planned to be enrolled in ~~completing~~ each cohort. Cohort 4 (10 mg/kg IV Q2W for 24 weeks) will be initiated after review of the safety (at least 1 week after dosing) and PK data (complete Day 29 visit) from at least 4 patients receiving LY3002813 and 1 receiving placebo in Cohort 1. Cohort 5 (20 mg/kg IV Q2W for 24 weeks) will only be initiated after review of the safety and PK data (at least 4 weeks after dosing) from Cohort 2 in at least 4 patients receiving LY3002813 and 1 receiving placebo, and after confirmation that at least 2 patients have been dosed safely with LY3002813 at least 3 times each in Cohort 4. Safety and PD will be assessed at regular intervals for approximately 48 weeks after completion of 24 weeks of dosing with LY3002813 (Attachment 1).

7.1.5. Part C: Chronic, 72-Week Q4W Multiple Dose Cohorts (Cohorts 6 and 7)

Safety, PK, and PD will be assessed in Cohorts 6 and 7 during and after multiple doses of LY3002813 or placebo have been administered Q4W for up to 72 weeks, or when the LY3002813-induced reduction in amyloid measured by florbetapir reaches the maximum reduction (defined as SUVr <1.1 for 2 consecutive scans) (Joshi et al. 2015). The planned doses

are 10 and 20 mg/kg IV with ~~a minimum of~~ 12 patients (9 LY3002813; 3 placebo) planned to be enrolled in ~~completing~~ each cohort. Cohort 6 (10 mg/kg IV Q4W) and Cohort 7 (20 mg/kg IV Q4W) may proceed, in parallel with Cohorts 4 and 5, respectively. In addition, Cohort 7 will only be initiated after confirmation that at least 2 patients have received at least 2 doses each of LY3002813 safely in Cohort 6. The maximum dose of 20 mg/kg will not be exceeded. If a patient is deemed to be amyloid negative by florbetapir PET before completion of 18 months' dosing (SUVr <1.1 for 2 consecutive scans), the patient will receive placebo infusion for all subsequent visits and continue the Part C visit schedule, including assessment of sustained amyloid reduction at the scheduled PET scan assessments. Safety, PK, and PD will be assessed for all patients at regular intervals for approximately 12 weeks after completion of 72 weeks of dosing with LY3002813 (Attachment 1).

7.1.7. Study Design for Japanese Patients

Sites in Japan will participate in this study to recruit Japanese patients.

At least 2 Japanese patients should be enrolled in each dose cohort for Cohorts 1, 2, 4, and 6. Assuming that the cohorts will be dosed based on safety reviews, it is intended that at least 3 Japanese patients will be enrolled in each dose cohort for Cohorts 3, 5, and 7; however, recruitment to a cohort will not be contingent upon fulfilling these requirements. At least 17 Japanese patients should be enrolled in the study when all cohorts are dosed. Japanese patient enrollment into cohorts should ensure sufficient exposures at applicable doses to support future studies (for example, at least 6 Japanese patients overall exposed to LY3002813, and at least 2 Japanese patients per cohort exposed to LY3002813 at the highest doses to be used in future studies). For the purpose of safety evaluation in Japanese patients during the study, Japanese patients at sites in Japan and up to third-generation Japanese patients at sites outside of Japan will be included. The definition of up-to-third-generation Japanese is defined in Section 8.1.

9.2.3. 18F-AV-1451 Dosage and Administration

A total of two 18F-AV-1451 PET scans will be performed approximately 72 weeks apart, except for Cohort 3 where scans will be approximately 24 hours apart. During this study, patients will receive a single IV administration of approximately 240 MBq (6.5 mCi) of 18F-AV-1451. At approximately 75 minutes following injection, a continuous 30 minute brain scan (6 acquisitions, each of 5 minutes in duration) will be performed.

Previously conducted 18F-AV-1451 PET scans can be used as baseline measurements, if the sponsor approves. During these previous scans, patients might receive a single IV administration of approximately 240 MBq (6.5 mCi) or 370 MBq (10.0 mCi) of 18F-AV-1451. For each patient, the baseline data originally collected for previous Lilly and Avid Radiopharmaceuticals studies can only be entered/sent for Study AACD after the patient signs the ICF agreeing to participate in this study.

9.2.4. Radiation Doses Associated with PET Imaging

[…]

In a previously conducted and accepted 18F-AV-1451 scan, the patient might have been administered with 370 MBq (10.0 mCi) rather than 240 MBq (6.5 mCi) of 18F-AV-1451. In this case, the patient would be exposed to an additional 2.9 mSv of ionizing radiation.

10.5.2. Imaging

A total of two 18F-AV-1451 PET scans will be performed, approximately 72 weeks apart, except for Cohort 3 where scans will be approximately 24 weeks apart. 18F-AV-1451 PET scan should be performed at least 24 hours apart from the florbetapir scan (for further details on florbetapir imaging see Section 9). The change in grey matter SUVr will be compared to total dose exposure. Additional approaches for tau PET quantitation may be applied based on emerging data.

MRI changes in brain volume over the course of the study will be explored. Over an approximate span of 72 weeks, except for Cohort 3, which will be 24 weeks, screening MRI and up to 8 post-baseline MRIs will be performed, mostly for safety monitoring (ie, occurring 4 weeks after the first dose, every 12 weeks starting from the first dose, and up to 12 weeks after the last dose). However, additional MRI scans are included for exploratory evaluation of brain structural changes (including, but not limited to, whole brain, ventricle, and hippocampal volumes), white matter and tissue microstructure changes, and functional connectivity in brain networks at baseline, 24 weeks, 48 weeks, and 72 weeks as applicable.

11.1. Determination of Sample Size

Up to approximately 150 patients may be enrolled ~~to ensure~~so that approximately 72 patients complete the study. Cohorts 1, 2, and 3 are each planned to have ~~a minimum of~~approximately 8 patients (6 LY3002813; 2 placebo) complete the study. Cohorts 4 and 5 are each planned to have ~~a minimum of~~approximately 12 patients (9 LY3002813; 3 placebo) complete the study. Also, Cohorts 6 and 7 are each planned to have ~~a minimum of~~approximately 12 patients (9 LY3002813; 3 placebo) complete the study.

Attachment 1. Protocol AACD Study Schedule

New Schedule of Activities for Cohort 3:

Schedule of Activities, Protocol I5T-MC-AACD, Part A: Cohort 3 (Single Dose), Visit 4 through Visit 13

Procedure											
Visit No.:	**V4[a]**	**V5[b]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**ED**
Day Relative to First Dose	**-4**	**1**	**4**	**6**	**8**	**15**	**29**	**57**	**85**	**169**	
Week			**1**	**1**	**1**	**2**	**4**	**8**	**12**	**24**	
Tolerance Interval for Visit (days)	**±4***	**0**	**0**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±7**	
Entry and Administrative/Every Visit											
Body weight	X						X		X	X	X
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Preexisting conditions/AEs		X	X	X	X	X	X	X	X	X	X
Study medication administered[l]		X									
Cognitive Assessments											
ADAS-Cog	X									X	X
ADCS-MCI-ADL24	X									X	X
NTB	X									X	X
CDR										X	X
FCSRT-IR										X	X
MMSE										X	X
Safety Assessment											
Vital signs	X	X[m]	72h	X	X	X	X	X	X	X	X
C-SSRS[d]/SHSF[f]	X	X				X	X	X	X	X	X
Physical/neurological examination		X[p]				X	X	X	X	X	X
12-lead digital ECG[e]	X[m]	X[m]	72h	X	X	X	X	X	X	X	X
Imaging											
MRI[h,i]							X		X	X	X
Florbetapir PET scan									X	X	X
18F-AV-1451 PET scan	X[x]									X[j]	X[j]
Laboratory Assessments											
LP[n]	X		X								
ABI tempus tube/blood RNA	X				X						
Pharmacogenetic sample[o]	X										
Clinical chemistry, electrolytes, hematology, urinalysis[g]		X	X	X	X	X	X	X	X	X	X
Coagulation tests (at local laboratory, prior to LP, except the V6 LP)[y]	X										
Serum LY3002813 PK[q]		predose, end of infusion, 3, 24, 48h	72h	X	X	X	X	X	X	X	X
Plasma Aβ	X		X								
Serum for immunogenicity[s]	X				X	X	X		X	X	X
Aliquoted plasma (EDTA) and serum for storage	X				X						
Stored serum for possible exploratory immune safety laboratory tests[t]	X								X		X

Attachment 3. Protocol AACD Blood Sampling Summary

New blood sampling table for Cohort 3:

Protocol I5T-MC-AACD Sampling Summary Part A (Cohort 3)

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	26	1	26
Clinical laboratory tests[a]	12	9	108
Coagulation tests	6	1	6
Drug assays[b]	4	13 (+3)	52 (12)
Blood discard for cannula patency	3	11	33
Immunogenicity assessments[a]	10	6	60
Pharmacogenetic sample[c]	11	1 (+1)	11 (11)
Nonpharmacogenetic/biomarker samples	21	2	42
Blood sample for exploratory immune safety	14	2	28
Total			366 (389)
Total for clinical purposes (rounded to the nearest 10 mL)			370 (390)

[a] Additional samples may be drawn if needed for safety purposes.

[b] A maximum of 3 blood samples per patient may be drawn at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor.

[c] An additional sample may be taken postdose if required.

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