I5T-MC-AACD Statistical Analysis Plan Version 1

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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1. Statistical Analysis Plan 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

(LY3002813)

This study is a patient-and investigator blind, randomized, placebo controlled single-dose followed by multiple dose, dose-escalation study in patients with mild cognitive impairment (MCI) due to Alzhiemr's disease (AD) or mild to moderate AD to assess the safety, tolerability and pharmacokinetics (PK) of IV LY3002813. The final portion of the study is an unblinded single subcutanuoes dose of LY3002813.

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Protocol I5T-MC-AACD
Phase IB

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

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Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to first patient visit when a patient receives study drug.

3. Study Objectives

3.1. Primary Objective

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

3.2. Secondary Objectives

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 Alheimer's disease (AD) or mild to moderate AD
- evaluate the immunogenicity of single and multiple doses of LY3002813.

3.3. Exploratory Objectives

The exploratory objectives are to:

- assess the relationship among dosing regimens, PK, and pharmacodynamic (PD) from florbetapir scan, immunogenicity, and immune safety
- evaluate changes in plasma, serum, and cerebrospinal fluid (CSF) biomarkers following 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 positron emission tomography (PET) scan
- evaluate genetic interactions with study treatment response or any adverse events (AEs).

3.4. Summary of Study Design

This study (Study I5T-MC-AACD [AACD]) will enroll patients with MCI due to AD, mild AD, or moderate AD with amyloid deposition confirmed by amyloid PET imaging using the 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 in multicountry sites including the United States and Japan. Up to 150 patients may be enrolled to ensure that approximately 72 patients (7 dosing cohorts of 8-12 patients) complete the study.

The study will be conducted in at least 7 cohorts (Figure AACD.3.1):

- Cohort 1: 10 mg/kg intravenous (IV) single dose
- Cohort 2: 20 mg/kg IV single dose

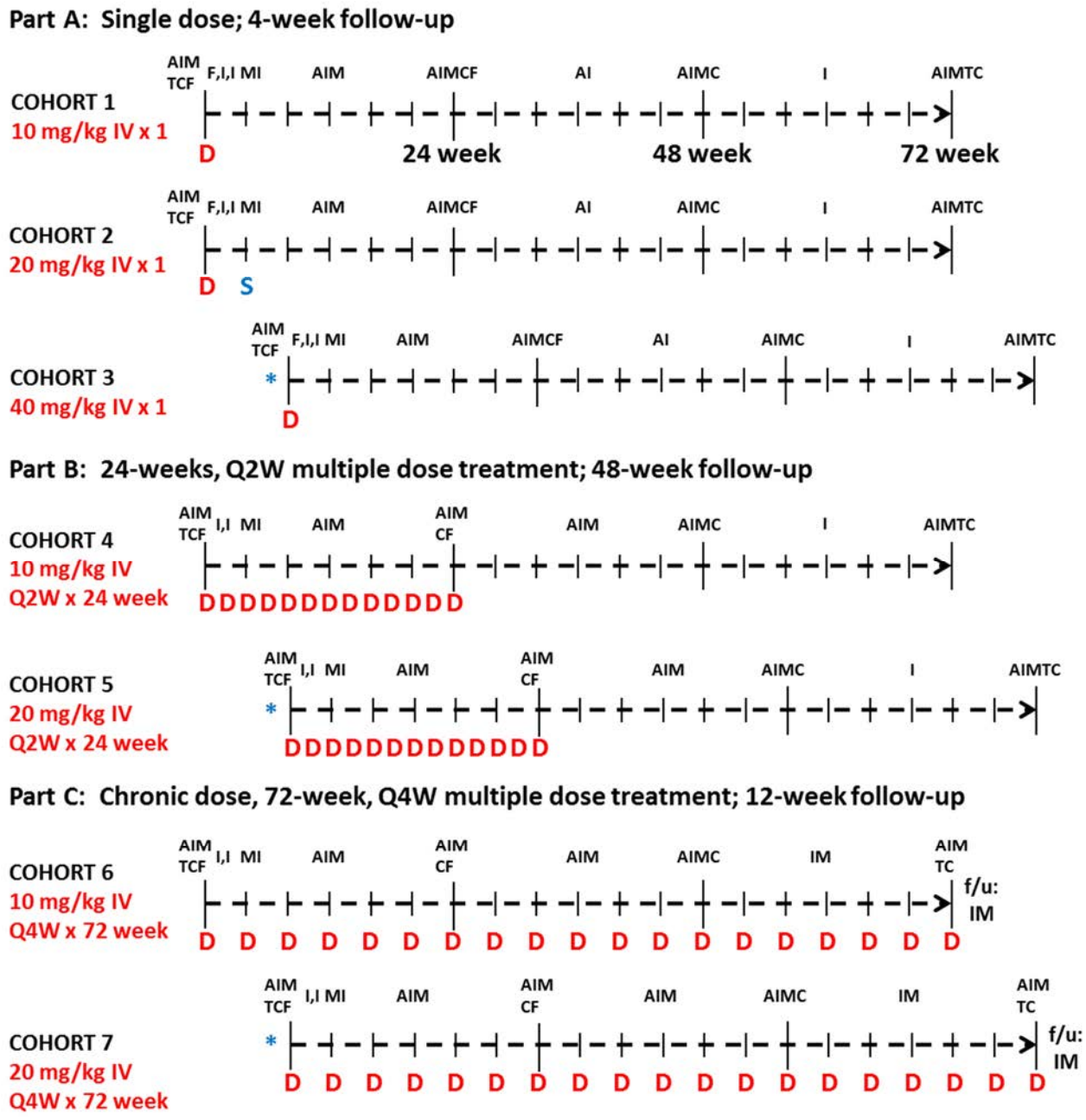
- Cohort 3: 40 mg/kg IV single dose (initiated after the 4-week safety review of Cohort 2)
- Cohort 4: 10 mg/kg IV every 2 weeks (Q2W) for 24 weeks
- Cohort 5: 20 mg/kg IV Q2W for 24 weeks (initiated after the 4-week safety review of Cohort 2; dosing interval may be modified based on single-dose PK of 20 mg/kg LY3002813)
- Cohort 6: 10 mg/kg IV every 4 weeks (Q4W) for up to 72 weeks
- Cohort 7: 20 mg/kg IV Q4W for up to 72 weeks (initiated after the 4-week safety review of Cohort 2)

Cohorts 1, 2, 4, and 6 may be initiated in parallel. Cohorts 3, 5, and 7 can only be initiated after a review of safety data from a minimum of 4 patients on LY3002813 and 1 patient on placebo completing the 4-week safety review in Cohort 2. Each cohort will contain 6 to 9 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 I5T-MC-AACC (AACC).

The primary target engagement outcome is the reduction of cerebral amyloid as measured by quantitative amyloid PET imaging (SUVr) assessed at baseline and 12 weeks, 24 weeks, 36 weeks, 48 weeks, and 72 weeks after starting treatment. The early postbaseline scans aim to assess the time course of amyloid reduction; the later scans aim 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, 2, and 3, a cerebrospinal fluid (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 to 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 magnetic resonance imaging (MRIs) beginning at baseline and following according to the study schedule for assessment of amyloid-related imaging abnormalities, adverse events (AEs), electrocardiograms (ECGs), vital signs (blood pressure, heart rate), physical examinations, neurological examinations, and safety laboratory tests of blood (including immunogenicity) with approximately a 12-week follow-up safety visit after the final dose.



Abbreviations: 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

***** - cohorts may be initiated after 4-week safety review of Cohort 2. In addition, for Cohort 5, confirmation that at least 2 patients have been dosed safely for at least 2 doses each in Cohort 4, will be required before commencing this cohort

f/u – 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 if titers are increasing.

Figure AACD.3.1. Study Design.

4. A Priori Statistical Methods

4.1. Determination of Sample Size

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

In order to maintain a constant accrual rate, the randomization ratio will be 6:2 in Cohorts 1, 2, and 3; randomization will progress with a 9:3 ratio in Cohorts 4 to 7. It is intended that at least 2 Japanese patients will be enrolled in each dose cohort for Cohorts 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. If the number of recruited Japanese patients per cohort is fewer than 3, then the randomization will continue. Japanese patients will continue to enroll with a 2:1 randomization ratio with the cohort. Details on the randomization plan will be described in the interactive web response system (IWRS).

This ratio is based on the enrolment rate of Study AACC.

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

4.2. Data Analysis Plans

4.2.1. General Considerations

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

Pharmacokinetic/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 pharmacokinetic analysis purposes to avoid issues with posthoc analyses and incomplete disclosures of analyses.

4.2.2. 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.

For all Screening entries, compute a summary count table to enumerate the reasons for screen failure according to criteria as defined by the following inclusion and exclusion evaluations. Essentially, summarize visits 1,2, and 3.

At Visit 1, patients will undergo the screening tests outlined in the Study Schedule in Protocol 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 lumbar puncture (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 clinical research unit (CRU) on Day -1 (the day before the first dosing day).

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 ot 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: Free and Cued Selective Reminding Test with Immediate Recall (FCSRT-IR): *≤24 for free recall* **or** *≤46 for total 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) Clinical Dementia Rating (CDR)=0.5 to 2 and memory box score ≥0.5

d) Mini–Mental State Examination (MMSE) score 16 to 30

e) positive florbetapir scan (central read)

f) Geriatric Depression Scale (GDS; Sheikh and Yesavage 1986) score <6 (on the staff-administered short form)

[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 a caregiver/study informant who provides a separate written informed consent to participate. The caregiver/study informant is required to accompany the patient for signing consent, all dosing days and for all days that the Columbia Suicide Severity Rating Scale (C-SSRS)/Self-Harm Follow-Up (SHSF) and cognitive and functional scales are administered. If the caregiver/study informant is not able to accompany the patient in person because of an unavoidable circumstance, he/she must be available by telephone to answer questions regarding AEs and concomitant medications, and to answer the questions for the caregiver portions of the C-SSRS/SHSF. If any caregiver/study informant familiar with the study cannot continue, 1 replacement is allowed. More than 1 replacement may be allowed per investigator's discretion. The replacement(s) will also need to sign a separate written informed consent on the first visit he/she accompanies the patient to participate. The caregiver(s)/study informant(s) must be in frequent contact with the patient (defined as at least 10 hours per week), willing to accompany the patient to the office and/or be available by telephone at designated times, and willing to monitor administration of prescribed medications.

[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

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 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 posttreatment hypersensitivity reactions (including but not limited to erythema multiforme major, linear IgA 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 corrected QT interval ≥470 msec for male patients or ≥480 msec for female patients.

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

[19] show evidence of suicidal ideation as assessed by the C-SSRS

[20] show evidence of significant active neuropsychiatric disease; depression as assessed by medical history, examination, or GDS

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

[22] show evidence of syphilis and/or are positive for syphilis test

[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 CRU (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) 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

[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 catheter insertion

[34] show abnormalities in lumbar spine previously known or determined by screening lumbar x-ray (if conducted)

[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

[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.

4.2.3. Study Participant Characteristics

The patient's age, sex, race (Non-Japanese and Japanese), weight, height, smoking habits, APOE4 status, MMSE baseline value, FCSRT-IV total score, CDR-Sum of Boxes score, ADAS-Cog (14), NTB total score, and ADL24, number of ARIA-E , ARIA-M and/or other demographic characteristics will be summarize in baseline table for all IV dose group and subset by Part A Single IV doses, Part B Multiple doses (Q2W dosing), and Part C Chronic doses (Q4W dosing). The placebo-groups will be combined within the 3 study Parts (A,B, and C). In addition, a baseline table will be constructed for all Japanese patients and a similar baseline summary table will constructed for all non-Japanese patients. A complete patient listing of the baseline characteristics will be constructed for each IV dose group.

4.2.4. Pharmacokinetic Analyses

4.2.4.1. Pharmacokinetic Parameter Estimation

The analysis methodology of PK parameter estimates for LY3002813 are documented in a separate PK analysis plan.

4.2.5. Pharmacodynamic Analyses

Pharmacodynamic and cognition measures as function of visit or time relative to first IV dose will be summarized and/or plotted as appropriate. As there will not be sufficient information to make informative comparisons on 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. The following sections provide details of the specific pharmacodynamic measure or cognitive measure.

4.2.5.1. Primary Objective of Amyvid PET Imaging Statistical Analyses

Statistical assessment of the composite SUVr change from baseline will be analyzed by a mixed model repeated measure (MMRM). The response measurements are (1) SUVr change from baseline and (2) the percent change from baseline. Baseline is defined as the pre-dose SUVr obtained at screening visit 3 or prior to randomization. The change from baseline are computed from the SUVr obtained from the scheduled study visits at weeks 12, 24, 36, and 48. Patients have the option to have a PET image taken at early discontinuation. In those case, SUVr value will be mapped to the closest scheduled study visit at weeks 12, 24, 36, or 48. The planned analyses is an MMRM using an appriopriate 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 IV doses 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 individual brain regions of SUVr if needed. A table of the LSmeans per dose group with associated p-value contrast to placebo will be constructed. A graphical summary of the LSmeans and a mean confidence interval on the y-axis and the study visit on the x-axis for each IV dose-group. Given the small sample size of n=6 patients per IV dose group, simplification of the mixed-effects model might be considered if the model fails to converge or other model fit diagnostics.

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. This analysis may be omitted if access to appropriate software such as SAS version 9.4 is not available.

Summary tables for SUVr values across the PET scan study visits for each IV dose group will include the n, mean, median, SD, minimum, maximum values. In addition, the number of patients within each IV dose group and study visit with post-dose composite SUVr values less than 1.2.

In addition to Amyvid PET scan SUVr analysis, an exploratory analysis of 18F-AV-1451 PET scan SUVr results will be conducted using an analysis of covariance (ANCOVA) model. The

18F-AV-1451 PET scans will be obtained from each randomized patient at pre-dose Visit 4 and at Visit 17 approximately 72 weeks post-dose. The change in SUVr as the response variable and the IV dose group as the explanatory factor with the baseline SUVr as a covariate. The primary contrast will be the mean change in SUVr of each IV dose group relative to placebo. A summary table of the LSmean results and contrast p-value will be generated. In addition, a graphical display of the LSmean and confidence interval on the y-axis and the IV dose-groups and placebo along the x-axis.

Magnetic resonance imaging changes in volume over the course of the study will be explored, and exploratory evaluation of whole brain and anatomically localized structural changes will be summarized (including, but not limited to, whole brain, ventricle, and hippocampus). Magnetic resonance imaging volumetric assesssments will be obtained at baseline, 24 weeks, 48 weeks, and 72 weeks as applicable. An MMRM will be constructed by fitting treatment and study visit as fixed effects. Response variables are brain structural changes of whole brain, ventricle, and hippocampal volumes.

Additionally, the relationship between LY3002813 serum exposure and imaging endpoints may be explored graphically or by additional exploratory analyzes.

4.2.5.2. Assessment of Cognitive and Functional Measurements

Statistical assessment of the total cognitive measurement change from baseline will be analyzed by an MMRM. The response measurements are (1) change from baseline and (2) the percent change from baseline for ADAS-Cog (14), ADL, MMSE, FCSRT-IR total, CDR-Sum of Boxes, and NTB. Baseline for each measurement is defined as the pre-dose measurement obtained at screening Visit 3 or prior to randomization. The change from baseline and percent change are computed from the total cognitive measurment obtained from the scheduled study visits at weeks 24, 48, and 72. Patients have the option to have the cognitive measures assessed taken at early discontinuation. For early discontinuations, cognitive value will be mapped to the nearest scheduled study visit at week 24, 48, or 72. The planned analyses is an MMRM using an appriopriate 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 IV doses and placebo for change from baseline or percent. A table of the LSmeans per dose group with associated p-value contrast to placebo will be constructed. A graphical summary of the LSmeans and a mean confidence interval on the y-axis and the study visit on the x-axis for each IV dose-group. Given the small sample size of n=6 patients per IV dose group, simplification of the mixed-effects model might be considered.

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. This analysis may be omitted if access to appropriate software such as SAS version 9.4 is not available.

4.2.5.3. 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 concentrations. Using an ANCOVA model, IV dosing regimen will be a fixed effect with the baseline concentration as a covariate in the model. These analyses are considered exploratory in order to estimate mean change and the variance of the change following IV single, multiple and chronic doses of LY3002813. A logarithmic transformation may be used to ensure valid statistical estimation properties.

In addition to these analyses, correlation analyses between changes in CSF biomarkers ($A\beta_{1-40}$, $A\beta_{1-42}$, total tau, phospho-tau), or imaging endpoints (MRI measures, or SUVr from florbetapir scans) with posthoc serum AUC estimates derived from the PK model (or an alternative measure of exposure if deemed appropriate) may be completed. For SUVr, this will be conducted for the individual regions (if collected) and the total SUVr. Additionally, CSF and/or serum LY3002813 exposures may be related to CSF biomarkers, as appropriate.

4.2.5.4. 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 if there is mean change following doses of LY3002813. If required, a logarithmic transformation may be considered.

4.2.6. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory correlational analyzes may be conducted to describe the relationship between exposure and changes in the florbetapir SUVr; MRI of whole brain,ventricle, and hippocampus volumes; CSF concentrations of abeta, tau and ptau; maximum ADA levels; and number AEs related to infusion reactions. It is intended that these analyses will be descriptive graphs 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.

4.2.7. Safety Analyses

4.2.7.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed. At a minimum, all safety data will be summarized using descriptive methodology.

The incidence of symptoms for each IV dose 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.

4.2.7.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety clinical 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 IV dose will be constructed to assess the MRI measurement pre- and postdose for changes and additions of vasogenic edema and microhemorrhages (ARIA-E and ARIA-H)

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 may not be displayed).

Exploratory analyses of Fridericia's corrected QT interval (QTcF) 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 QTcF 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.

4.2.7.3. Evaluation of Immunogenicity (for Large Molecules)

As part of the secondary study objective, Antibody drug formation will be summarized over time for each IV dose group. An MMRM will be done fitting IV 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. The relationship between the presence, absence or level of ADAs and number of IV drug infusion reation AEs, PK estimates of exposure, PD measurements of amyloid SUVr. These associations may be assessed using simple pairwise correlations and pairwise graphical relationship. These relationships may also be described using a modeling approach, if appropriate.

4.3. Planned Interim Analyses

There are 3 planned interim reviews of PK data. The first interim review will occur after a minimum of 4 patients on LY3002813 in Cohort 2 complete Visit 10 (Day 29). The second interim PK data review is planned to occur after a minimum of 4 patients on LY3002813 in Cohort 3 (40 mg/kg IV single dose) complete Visit 8 (Day 85). The third interim PK data review is planned to occur after a minimum of 4 patients on LY3002813 in Cohort 4 and also in Cohort 5 (for a total of 8 patients) have completed Visit 16 (Day 141). Additional interim PK data reviews may also be conducted to summarize data for internal decision making and/or supporting subsequent clinical studies/regulatory agency/Investigator's Brochure (IB) annual updates, as required.

There are 2 planned interim reviews of AEs, clinical laboratory data, vital signs and imaging SUVr data. All available ADA titers will be included. These two planned interim review require study data tabulation model (SDTM) datasets for all safety data, ADA titer data and the amyloid

imaging SUVr values along with all available cognitive measurements. Descriptive summaries of all safety, ADA, PD imaging and cognitive measures will be computed by each IV dose group and placebo. Given the small sample sizes, more advance statistical evaluations will be conducted if appropriate.

1. The first review will occur after a minimum of 4 patients on LY3002813 in Cohort 3 (40 mg/kg IV single dose) complete Visit 13 (Day 169).
2. The second interim data review is planned to occur after a minimum of 4 patients on LY3002813 in Cohort 4 and also in Cohort 5 (for a total of 8 patients) have completed Visit 18 (Day 169). The second interim data review should coincide with the third PK data review. Associations between drug exposure and safety data, ADA titers and PD imaging SUVr will be assessed using simple graphical and pair-wise correlations.

As PD data accrues, there will be periodic reviews of PD data by the Lilly study team. Notably PD reivews will occur after a minimum of 4 patients on LY3002813 complete each scheduled florbetapir scan within 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.

4.4. Clinical Trial Registry Analysis Plan and DSUR

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs will be summarized: by treatment group, by MedDRA PT.
- An AE is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following will be provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).

- Adverse event reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

The following reports will be included the DSUR:

[1] Estimated cumulative subject exposure,

[2] Cumulative exposure to investigational drug by demographic characteristics for ongoing unblinded clinical trials and completed clinical trials,

[3] Exposure information for ongoing clinical trials and clinical trials that completed during the reporting period

[4] Listingof subjects who died during the DSUR period,

[5] Disconinuations due to an AE during the DSUR Period.

5. Unblinding Plan

Unblinding is described in the I5T-MC-AACD protocol under Attachment 4.

6. References

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