Protocol I8G-MC-LMDA(b)

Single-Dose, Dose-Escalation Study with LY3303560 to Evaluate the Safety, Tolerability, and Pharmacokinetics in Healthy Subject and Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

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LY3303560

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1. Protocol Synopsis

Title of Study:
Single-Dose, Dose-Escalation Study with LY3303560 to Evaluate the Safety, Tolerability, and Pharmacokinetics in Healthy Subjects and Patients with Mild Cognitive Impairment due to Alzheimer's Disease (AD) or Mild to Moderate AD

Rationale:
Lilly is developing LY3303560, a humanized monoclonal antibody that targets aggregated tau, for the treatment of AD . It is believed that targeting aggregated tau will reduce tau propagation, and in so doing, may delay the progression of tau-related diseases like AD.

LY3303560 has not been administered to humans. This first-in-human study will investigate the safety, tolerability, and pharmacokinetics (PK) of LY3303560 in healthy subjects and patients with AD. Safety and tolerability evaluations will be conducted over a wide range of single doses and dose escalation will not proceed until safety data from previous doses have been reviewed. This study will aim to assess whether a maximum-tolerated dose (MTD) can be established or to demonstrate the tolerability of a dose greater than the expected therapeutic dose. The data generated in this study will be used to help design subsequent clinical studies. The inclusion of Japanese subjects in this study will facilitate the inclusion of Japanese patients in subsequent clinical trials.

Objectives/Endpoints:

Objectives	Endpoints
Primary The primary objective of this study is to assess the safety and tolerability following single doses of LY3303560 in healthy subjects and patients with Mild Cognitive Impairment due to Alzheimer's Disease (AD) or Mild to Moderate AD.	Safety and tolerability will be assessed by monitoring adverse events (AEs).
Secondary • To assess the serum pharmacokinetics (PK) of LY3303560 in healthy subjects, including those of Japanese origin, following single doses of LY3303560. • To assess the cerebrospinal fluid (CSF) PK of LY3303560 in patients with AD following single doses of LY3303560.	The primary parameters for analysis will be maximum drug concentration (C_{max}), area under the concentration versus time curve from time 0 to infinity (AUC0-∞), and AUC from time 0 to the last measurable concentration (AUC0-t_{last}) of LY3303560.
• To assess the effect of single doses of LY3303560 on the QTc interval in healthy subjects and patients with AD.	QT/QTc interval mean change from baseline

Summary of Study Design:
Study I8G-MC-LMDA is a Phase I, subject-/patient- and investigator-blind, placebo-controlled, randomized, single-ascending dose (SAD) study in healthy subjects and patients with mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) or mild to moderate AD. The study has been designed to assess the safety, tolerability, and PK of single intravenous (IV) and subcutaneous (SC) doses of LY3303560.

Treatment Arms and Duration:
For all cohorts (except Cohort 5), subjects or patients will receive either LY3303560 or placebo as an IV single dose; the planned doses are 7, 21, 70, 210, 700, 1400, 2800, and 5600 mg. In Cohort 5, it is intended that subjects will receive a single SC dose of 210 mg LY3303560, dependent on the observed safety profile from previous cohorts.

Number of Subject/Patients:
Cohorts 1 to 7, 10, and 11 (Healthy subjects): Up to 90 subjects may be enrolled so that approximately 70 subjects (8 subjects per cohort, except for Cohort 5 [n=6]), reach at least Day 29 of the study.

Cohorts 8 and 9 (Patients with AD): Up to 20 patients may be enrolled in order that 16 patients (8 patients per cohort) reach at least Day 29 of the study.

Subjects or patients who discontinue the study before completing the Day 29 assessment may be replaced at the discretion of the sponsor and investigator. Subjects or patients who discontinue after Day 29 may also be considered for replacement to ensure sufficient data are available for final data analysis.

Statistical Analysis:

Safety: Safety parameters that will be assessed include adverse events (AEs), safety laboratory parameters, vital signs, and electrocardiogram (ECG) parameters. The parameters will be listed and summarized using standard descriptive statistics for values at each time point as well as changes from baseline. Additional analyses may be performed if warranted upon review of the data.

For Cohorts 8 and 9, suicide-related thoughts and behaviors based on the Columbia Suicide Severity Rating Scale (C-SSRS) will be listed by patient. Only time points and patients that show ideation/behavior of suicide will be displayed, that is, all 'no's will not be displayed.

An assessment of potential QT prolongation will be performed using plots of PK data versus QTc values using Fridericia's formula (QtcF). The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

Analyses of (QTcF from ECG monitoring in a Phase 1 trial will be performed to judge the extent and/or risk of QT prolongation. Scatter plots will be created of QTcF versus LY concentration and change from baseline QTcF versus LY concentration.

Pharmacokinetic: PK parameter estimates for LY3303560 in serum and CSF will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be maximum drug concentration (C_{max}) and area under the concentration versus time curve from time 0 to infinity ($AUC_{0-\infty}$) of LY3303560. Other serum PK parameters such as half-life, clearance, and volume of distribution may be reported after IV

administration of LY3303560. Serum PK parameters such as bioavailability, apparent clearance, apparent volume of distribution and half-life may be reported after subcutaneous administration. The primary CSF PK parameters will be C_{max} and AUC, estimated by standard noncompartmental methods of analysis. A model-based approach may also be implemented using nonlinear mixed effects modeling (NONMEM) or other appropriate software to estimate serum and/or CSF PK parameters.

The serum PK parameters, C_{max} and AUC0-∞, for LY3303560 obtained for healthy subjects (IV only) will be evaluated to estimate the dose-exposure proportionality of LY3303560 using a linear-effect power model.

18F-AV-1451 Imaging Analyses (Cohorts 8 and 9): 18F-AV-1451 SUVR data will be summarized and/or plotted by region of interest as appropriate, further details will be given in the statistical analysis plan. Change from baseline of tau burden within regions of interested will be calculated, however, no formal analyses are planned to be conducted due to single dose nature of the study.

Additionally, the relationship between LY3303560 serum exposure and imaging endpoints may be explored graphically or by a modeling approach.

2. Schedule of Activities

Study Schedule Protocol I8G-MC-LMDA (Cohorts 1 to 7, 10, and 11, Healthy Subjects)

	Screen																		ED
Study Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	
Visit Window (days)										**±1**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Informed consent	X																		
Admit to CRU		X																	
Discharge from CRU						X													
LY3303560/placebo dosing[a]			X																
Prior/concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X
Preexisting conditions/AEs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X
Injection-site assessment (Cohort 5 only)			X	X	X	X	X	X	X	X	X	X	X	X					X
Physical examination	X	X							X			X		X		X			X
Neurological examination	X	X	0	24[j]		72[j]			X	X		X		X		X			
Alertness and attention assessments (Cohorts 10 and 11 only)		X	0			72[j]			X			X		X		X			X
Weight/height[b]	X		0									X	X	X		X			
Vitals (hours)[c,d]	X	X	0[e], 0.5[k], 3, 12	24	48	72	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X
12-lead electrocardiogram (hours)[d,f]	X	X	0[e], 0.5[k], 3, 12	24	48	72			144			X		X		X			X
Ethanol and urine drug screens	X	X																	
Clinical laboratory tests	X		0	24		72			X	X		X	X	X		X			X
Immunogenicity[g]			0						X	X		X		X		X[g]			X[g]
Stored serum for possible exploratory immune safety laboratory tests[h]	X															X			X
Magnetic Resonance Imaging	X									X						X			X
LY3303560 serum PK (hours)[i]			0[e], 0.5[k], 2, 4, 12	24	48	72	96	120	144	X	X	X	X	X	X	X	X[l]	X[l]	X
Plasma tau PD samples (hours)[i]		X	0[e],0.5[k], 2, 4, 12	24	48	72	96	120	144	X	X	X		X		X	X[l]	X[l]	
Plasma PD storage samples (hours)[i]		X	0, 2, 4, 12	24	48	72	96	120	144	X	X	X		X		X			
Serum PD storage samples (hours)[i]		X	0, 12		48		96		144										
Sample for genetic testing			X																
RNA testing (hours)			X						144										

Abbreviations: AE = adverse event; CRU = clinical research unit; ED = early discontinuation; PD = pharmacodynamics; PK = pharmacokinetics.

Time 0 is predose.

[a] Subjects in Cohorts 1 to 4, 6, 7, 10, and 11 will receive an IV single dose; subjects in Cohort 5 will receive a single SC dose.

[b] Height will be measured only at screening.

[c] Screening vital signs will be obtained in the sitting position (after at least 5 minutes sitting). For vital signs after study entry, subjects will rest in the supine position for at least 5 minutes and undergo supine blood pressure and pulse rate measurements. Subjects will sit for approximately 2 minutes then stand for approximately 2 minutes and undergo standing blood pressure and pulse rate measurements. If subjects are unable to stand, supine vital signs only will be recorded.

[d] The timing of the vital sign and ECG collections may be adjusted after review of these data or PK data.

[e] Performed predose (for ECG measurements, 4 sets of triplicate ECGs within 60 minutes).

[f] At screening and all timepoints post-Day 7, a single ECG will be obtained locally and stored at the investigational site. At all other time points, ECGs will be obtained in triplicate at approximately 1-minute intervals and will be transmitted and stored at the central ECG vendor. ECGs must be recorded before collecting any blood samples for safety evaluations, PK and PD, and close to the time of the blood draw.

[g] Up to 3 additional blood samples for immunogenicity evaluation per subject may be drawn during the study at the discretion of the investigator or sponsor.

[h] 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 stored serum 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.

[i] A maximum of 5 additional blood samples per subject may be drawn during the study at the discretion of the investigator or sponsor.

[j] To be conducted ± 1 hour.

[k] Performed at the end of the infusion.

[l] Cohorts 10 and 11 only.

Study Schedule Protocol I8G-MC-LMDA (Cohorts 8 and 9, Patients with AD)

	Screen																ED
Study Day	**-70 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	
Visit Window (days)										**±1**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	
Informed consent	X																
Admit to CRU[a]		X															
Discharge from CRU						X											
LY3303560/placebo IV dose			X														
Prior/concomitant medications	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
C-SSRS/SHSF[a,b]	X		X				X		X	X	X	X	X	X	X	X	X
Injection-site assessment			X	X	X	X	X	X	X	X	X	X	X	X			X
Physical examination	X	X							X			X		X		X	X
Neurological examination	X	X	0			72[n]			X	X		X		X		X	
Weight/height[c]	X		X									X	X	X		X	
Vitals (hours)[d,e]	X	X	0[f], 0.5[o], 3, 12	24, 36		72	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram (hours)[e,g]	X	X	0[f], 0.5[o], 3, 12	24, 36		72			X			X		X		X	X
Ethanol and urine drug screens	X	X															
Clinical laboratory tests	X		0	24		72			X	X		X	X	X		X	X
Immunogenicity[l]			0						X	X		X		X		X[l]	X[l]
Stored serum for possible exploratory immune safety laboratory tests[h]	X															X	X
Magnetic Resonance Imaging	X									X						X	X
LY3303560 serum PK (hours)[i]			0[f], 0.5[o], 2, 4, 12	24	48	72	96	120	144	X	X	X	X	X	X	X	X
Plasma tau PD samples (hours)[i]		X	0[f], 0.5[o], 2, 4, 12	24	48	72	96	120	144	X	X	X		X		X	
Plasma PD storage samples (hours)[i]		X	0, 2, 4, 12	24	48	72	96	120	144	X	X	X		X		X	
Serum PD storage samples (hours)		X	0, 12		48		96		144								
Sample for genetic testing			X														
RNA testing (hours)			X						144								

continued

Study Schedule Protocol I8G-MC-LMDA (Cohorts 8 and 9, Patients with AD) (concluded)

	Screen																ED
Study Day	**-42 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	
Visit Window (days)										**±1**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	
CSF sampling for PK and PD evaluations (hours)[m]			0[f], 2, 4, 12	24, 36													
Lumbar X-ray[j]	X																
Florbetapir PET scan	X																
18F-AV-1451 PET scan	X															X	
Cognitive scales[a,k]																	
MMSE	X															X	
FCSRT-IR	X															X	
CDR-SB	X															X	

Abbreviations: AE = adverse event; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CRU = clinical research unit; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; CRU = clinical research unit; ED = early discontinuation; FCSRT-IR = Free and Cued Selective Reminding Test with Immediate Recall; MMSE = Mini-Mental State Examination; IV = intravenous; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; SHSF = Self-Harm Supplemental Form.

Time 0 is predose.

[a] The caregiver/study informant is required to accompany the patient for the dosing day and for all days that the C-SSRS/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 any rating scales or questionnaires for that visit, such as the C-SSRS. The caregiver/study informant must accompany the patient to screening, baseline (Day -1), final study visit (Day 85 or ED), and cognitive outcome assessments (screening). If any caregiver/study informant familiar with the study cannot continue, 1 replacement will be allowed. More than 1 replacement may be allowed per investigator's discretion.

[b] The SHSF form will be completed at any visit, including baseline, when a suicidal or nonsuicidal self-injurious behavior is identified on the C-SSRS.

[c] Height will be measured only at screening.

[d] Screening vital signs will be obtained in the sitting position (after at least 5 minutes sitting). For Visits 1 to 3, vital signs will be taken in the supine position only. For all other vital signs after study entry, subjects will rest in the supine position for at least 5 minutes and undergo supine blood pressure and pulse rate measurements. Subjects will sit for approximately 2 minutes then stand for approximately 2 minutes and undergo standing blood pressure and pulse rate measurements. If subjects are unable to stand, supine vital signs only will be recorded.

[e] The timing of the vital sign and ECG collections may be adjusted after review of these data or PK data.

[f] Performed predose (for ECG measurements, 4 sets of triplicate ECGs within 60 minutes).

[g] At screening and all timepoints post-Day 7, a single ECG will be obtained locally and stored at the investigational site. At all other time points, ECGs will be obtained in triplicate at approximately 1-minute intervals and will be transmitted and stored at the central ECG vendor. ECGs must be recorded before collecting any blood samples for safety evaluations, PK and PD, and close to the time of the blood draw.

[h] 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 samples should be collected approximately 60 to 120 minutes and 4 to 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.

[i] A maximum of 5 additional blood samples per subject may be drawn during the study at the discretion of the investigator or sponsor.

[j] Patients may have a lumbar x-ray conducted at screening. If an x-ray was done within 12 months of screening, this may be used.

[k] Cognitive tests should be completed in the following order if done on the same day: (1) MMSE; (2) FCSRT-IR; (3) CDR-SB.

[l] Up to 3 additional blood samples for immunogenicity evaluation per subject may be drawn during the study at the discretion of the investigator or sponsor.

[m] The timing of the CSF sampling may be adjusted after review of serum PK data from previous cohorts.

[n] To be conducted ± 1 hour.

[o] Performed at the end of the infusion.

3. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by a progressive decline in cognitive function and ability to perform activities of daily living, and ultimately can lead to death due to complications of the disease. Pathologic hallmarks of AD identified at autopsy include the presence of neuritic amyloid-β (Aβ) plaques, neurofibrillary tangles (NFTs) (Hyman et al. 2012), and neuronal loss in brain regions important for cognition, such as the hippocampus and temporal cortex (Selkoe 1991).

Tau is an axonal microtubule binding protein that normally promotes microtubule assembly and stability. In AD and other tauopathies, hyperphosphorylated misfolded tau causes tau aggregation, tau seeding, NFT formation, microtubule destabilization, and neuronal toxicity. Over time, tau accumulates in the brains of patients with AD, and forms intraneuronal NFTs, with tau pathology spreading in sequence from transentorhinal, to limbic, then neocortical regions. The spread of tau pathology is highly correlated with neuronal loss, clinical symptoms and progression in AD and other neurodegenerative diseases such as progressive supranuclear palsy (PSP) (tauopathies).

LY3303560 is a humanized monoclonal antibody that binds to aggregated tau from patients with AD and other tauopathies, such as PSP. In preclinical in vitro and in vivo studies, LY3303560 reduces trans-cellular spread of tau seeds and tau pathology propagation. By binding to aggregated tau, LY3303560 is hypothesized to block or delay trans-cellular spread of aggregated tau, NFT formation and neuronal loss, and may have the potential to slow the progression of tau-related diseases.

3.1. Study Rationale

Lilly is developing LY3303560, a humanized monoclonal antibody that targets aggregated tau for the treatment of AD.

Prior to this study, LY3303560 had not been administered to humans. This first-in-human study will investigate the safety, tolerability, and pharmacokinetics (PK) of LY3303560 in healthy subjects and patients with AD. Safety and tolerability evaluations will be conducted over a wide range of single doses and dose escalation will not proceed until safety data from previous doses have been reviewed. This study will aim to assess whether a maximum-tolerated dose (MTD) can be established or to demonstrate the tolerability of a dose greater than the expected therapeutic dose. The data generated in this study will be used to help design subsequent clinical studies. The inclusion of Japanese subjects in this study will facilitate the inclusion of Japanese subjects in subsequent clinical trials.

3.2. Background

LY3303560 is a humanized monoclonal antibody engineered from the MC-1 antibody, which was identified among mouse monoclonal antibodies as the best antibody to target tau propagation in vitro and in vivo. LY3303560 binds preferentially to aggregated tau, with

minimal binding to monomeric tau by an enzyme-linked immunosorbent assay (ELISA) and Biacore measurements (>100-fold selectivity for aggregated tau over monomeric Tau).

In vitro, LY3303560 inhibits cell-based tau propagation, binds to brain sections derived from patients with AD or tauopathy, and does not interfere with the binding of the tau positron emission tomography (PET) tracer AV-1451 to neurofibrillary tangles. In vivo, LY3303560 inhibits tau propagation when co-injected with tau seeds in mice. The high affinity surrogate murine antibody (MC-1-3C9) reduced tau pathology following systemic dosing in 2 tau transgenic mouse models (JNPL3 and Tg4510).

3.2.1. Preliminary Data from Cohorts 1 through 7

As of 07 February 2017, the single-dose escalation up to 1400 mg has been completed (Cohorts 1 to 7). A single subcutaneous (SC) cohort of 210 mg has also been completed (Cohort 5). No serious adverse events (SAEs) have been reported, and no subject has withdrawn from the study because of an adverse event (AE). A total of 27 AEs have been reported by a total of 16 subjects, irrespective of causality. The most common AEs reported were headache (4), upper respiratory infection (2), contact dermatitis (2), back pain (2), and influenza (2). A total of 7 AEs were deemed related to study drug by the investigator: headache (2) and hot flashes, feeling swollen, upper respiratory infection, vomiting, and cloudy mind (1 each). There have been no infusion reactions reported to date, and there have been no clinically significant findings in magnetic resonance imaging (MRI) scans. In addition, there have been no clinically significant changes in vital signs, electrocardiograms (ECGs), neurological examinations, and safety laboratory tests.

Preliminary PK data following single intravenous (IV) doses indicated that the exposure of LY3303560 was approximately linear up to 1400 mg. The observed clearance was approximately 180 mL/day, with a half-life of 2 to 3 weeks. A relative bioavailability of approximately 60% was calculated based on PK data from the 210-mg SC cohort. The observed PK profile of LY3303560 is consistent with the PK properties of an immunoglobulin (Ig) G antibody.

3.3. Benefit/Risk Assessment

The nonclinical safety information for LY3303560 detailed in the Investigator's Brochure (IB) adequately supports the transition from preclinical status to a clinical, single-dose study. On the basis of the nonclinical data, LY3303560 is not considered to be a high-risk compound. This protocol reflects the fact that LY3303560 had not been administered to humans prior to this study, and to mitigate this risk, the study has been designed to be conducted in accordance with principles outlined in the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products. It is intended that sentinel dosing will be conducted for the first dose cohort to minimize risk to subjects. Sentinel dosing will also be conducted for Cohorts 10 and 11 (2800 and 5600 mg), the additional cohorts introduced in Amendment (b). Based on preliminary PK data from Cohorts 1 to 7, the mean exposure of LY3303560 at a dose of 5600 mg in Cohort 11 is predicted to approximate the no-observed-adverse-effect level (NOAEL) exposure observed in the monkey (see Section 5.5).

Accordingly, in addition to review of safety data, the PK data from the 2800-mg dose will be analyzed and the projected exposure of 5600 mg will be reviewed prior to dose escalation. In addition, for Cohorts 10 and 11, alertness and attention assessments will be administered to assess potential central nervous system (CNS) effects.

Risks around immunogenicity and infusion reactions are considered to be monitorable and manageable at the planned dose range of 7 to 5600 mg for LY3303560 in healthy subjects and patients with AD.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of LY3303560 is to be found in the IB.

4. Objectives and Endpoints

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

Table LMDA.1. Objectives and Endpoints

Objectives	Endpoints
Primary The primary objective of this study is to assess the safety and tolerability following single doses of LY3303560 in healthy subjects and patients with Mild Cognitive Impairment due to Alzheimer's Disease (AD) or Mild to Moderate AD.	Safety and tolerability will be assessed by monitoring adverse events.
Secondary	
• To assess the serum pharmacokinetics (PK) of LY3303560 in healthy subjects, including those of Japanese origin, following single doses of LY3303560.	The primary parameters for analysis will be maximum drug concentration (C_{max}), area under the concentration versus time curve from time 0 to infinity (AUC 0-∞), and AUC from time 0 to the last measurable concentration (AUC0-t_{last}) of LY3303560.
• To assess the cerebrospinal fluid (CSF) PK of LY3303560 in patients with AD following single doses of LY3303560.	
• To assess the effect of single doses of LY3303560 on the QTc interval in healthy subjects and patients with AD	QT/QTc interval mean change from baseline
Exploratory Objectives • To evaluate changes in plasma, serum and CSF biomarkers following single doses of LY3303560 (Cohorts 8 and 9).	Plasma and serum biomarkers, including tau, and neurogranin will be assessed if suitable assays are available. CSF biomarkers, including tau, p-tau, Aβ, neurogranin will be assessed if suitable assays are available.
• To evaluate the effects of single doses of LY3303560 on cognitive function (Cohorts 8 and 9).	MMSE, FCSRT-IR, CDR-SB
• To evaluate changes in MRI measures.	Presence of amyloid related imaging abnormalities (ARIA)-E (vasogenic edema) and ARIA-H (microhemorrhage). Exploratory analyses of brain volume changes may also be performed.
• To evaluate the immunogenicity of single doses of LY3303560	Treatment-emergent anti-LY3303560 antibody titers.

5. Study Design

5.1. Overall Design

This is a Phase I, subject-/patient- and investigator-blind, placebo-controlled, randomized, parallel, single-ascending dose (SAD) study in healthy subjects and patients with mild cognitive impairment (MCI) due to AD or mild to moderate AD. The study has been designed to assess the safety, tolerability, and PK of single IV and SC doses of LY3303560. The planned doses to be explored are 7, 21, 70, 210, 700, 1400, 2800, and 5600 mg.

Cohorts 1 to 7, 10, and 11 will consist of healthy subjects. The planned number of subjects per cohort will be 8 (6:2, LY3303560:placebo), except for Cohort 5 (6 subjects on LY3303560). For each IV cohort, the intention is to enroll 4 subjects of Japanese origin (first generation) and 4 subjects of non-Japanese origin, but enrollment to a cohort will not be contingent upon fulfilling these requirements. The minimum requirement is to enroll 4 Japanese subjects to at least 3 of the IV cohorts, including the highest dose level cohort (a minimum of 12 Japanese subjects in total). However, if enrollment of Japanese subjects is slower than anticipated, cohorts may complete enrollment with non-Japanese subjects and proceed to dose escalation without waiting for the desired number of Japanese subjects to be enrolled. If 4 subjects of Japanese origin are not included in a cohort initially, additional subjects may subsequently be enrolled to achieve a maximum of 4 subjects of Japanese origin, if agreed between the sponsor and investigator. Although not required, it is preferred that the non-Japanese subjects are not Asian. The randomization will be such that the placebo assignments for the cohorts enrolling Japanese and non-Japanese subjects will be balanced between these 2 populations. Cohorts 8 and 9 will consist of patients with MCI due to AD or mild to moderate AD. The number of patients (LY3303560:placebo) in each cohort will be 6:2 patients.

Subjects/patients will be admitted to the clinical research unit (CRU) on Day -1 and eligibility will be confirmed. Safety will be monitored by AEs, ECGs, vital signs (blood pressure and heart rate), physical examinations, neurological examinations, and safety laboratory tests; and additionally for Cohorts 10 and 11, the Bond and Lader, and the Digit Span Forward and Backward test. The Columbia Suicide Severity Rating Scale (C-SSRS) will be assessed in Cohorts 8 and 9. Subjects/patients will remain resident in the CRU and safety will be monitored daily until discharge from the CRU on Day 4 at the earliest, then at regular intervals thereafter (see the Schedule of Activities in Section 2). In addition, each subject/patient will have 1 baseline MRI scan prior to dosing with LY3303560 or placebo, then approximately 2 weeks and 3 months after dosing, primarily for the assessment of any potential imaging abnormalities. In Cohorts 8 and 9, cerebrospinal fluid (CSF) will be obtained by an indwelling lumbar catheter prior to dosing with LY3303560 or placebo, and up to 48 hours after dosing with LY3303560 or placebo to measure CSF levels of LY3303560 and tau related pharmacodynamic (PD) biomarkers.

For all cohorts (except Cohort 5), subjects or patients will receive either LY3303560 or placebo as an IV single dose; in Cohort 5, it is intended that subjects will receive a single SC dose of 210 mg LY3303560, dependent on the observed safety profile from previous cohorts.

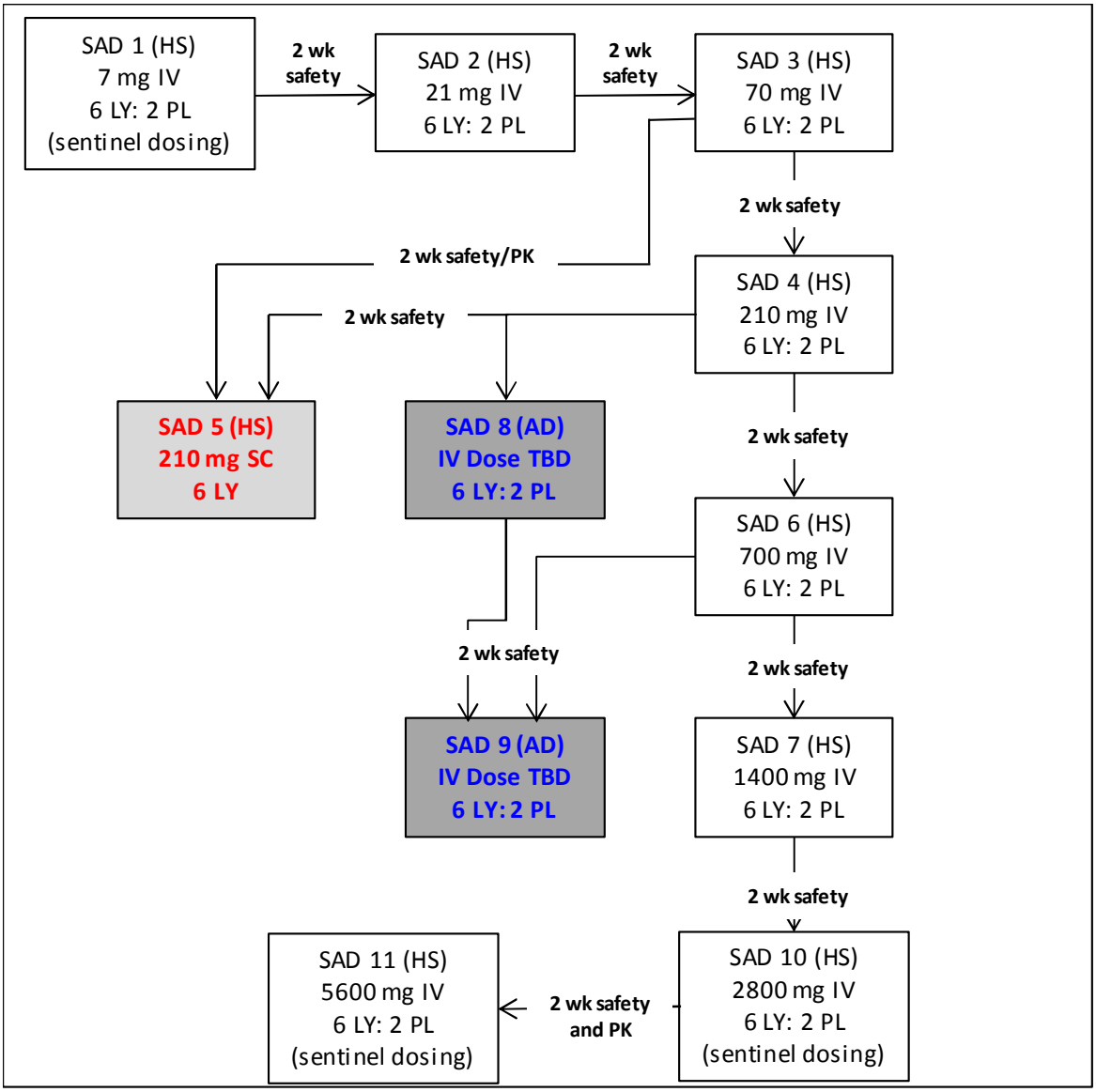
Subjects/patients will be followed for up to 12-weeks after dosing to evaluate single-dose safety and PK. Dose escalation to the next dose cohort will be triggered by a review of safety data from a minimum of 5 subjects (4 on LY3303560 and 1 on placebo) completing the 2-week safety evaluation procedures (see Section 7.4.1). This process is repeated until the final cohort of the dose escalation is complete. Patients in Cohorts 8 and 9 will not be dosed until equal or greater doses have been found to be well tolerated in healthy subjects (Cohorts 1 to 7). The doses selected for Cohorts 8 and 9 (intended to be 210 and 700 mg, respectively) are predicted to be within the efficacious dose range. The actual doses administered in Cohorts 8 and 9 will depend on observed safety and PK data from Cohorts 1 to 7, but the maximum dose will not exceed 1400 mg. These patient cohorts should confirm whether the safety and PK of LY3303560 is similar between patients with AD and healthy subjects, and support the dose range for future studies in patients with AD.

Sentinel dosing will be performed for Cohorts 1, 10, and 11. Two subjects will be dosed initially (1 assigned to LY3303560 and 1 to placebo) and followed to 48 hours postdose before the remaining subjects in that cohort are dosed. The remaining 6 subjects may be dosed on the same day, at appropriate intervals. If there are no issues with the first cohort, subjects in Cohorts 2 to 9 may be dosed on the same day at appropriate intervals, or on separate days, as practical, however, the timing of dosing will be staggered such that subjects will not be dosed simultaneously.

The highest dose may be adjusted based on emerging data, but it is intended that the magnitude of the escalation between dose levels will not exceed a half-log interval (approximately 3-fold) and a maximum dose of 5600 mg LY3303560 will not be exceeded. All subjects in a particular cohort must have been dosed and safety data for 2 weeks after dosing must be reviewed from at least 4 subjects on LY3303560 and 1 subject on placebo, prior to dose escalation. Additionally, PK data from Cohort 10 will be reviewed prior to escalation to Cohort 11. If criteria for stopping rules are not met (see Section 7.4.1), then the next dose cohort will be enrolled with next planned dose increases until 5600 mg or stopping criteria are met. If a termination dose is reached, a dose reduction of at least one-half of the termination dose may be tested in one of the remaining dose cohorts, if deemed appropriate.

The PK data for LY3303560 obtained during the study may be used to assist in dose escalation decisions, but such data are not required for dose escalation, except for dose escalation from Cohorts 10 and 11. If the PK data reveal that the current sampling schedule does not allow for an adequate characterization of the PK profile, the blood sampling schedule for subsequent dose administrations may be adjusted. A maximum of 5 additional PK samples per subject may be allowed if indicated by emerging data. See Section 10.3.7 for further information about PK reviews.

Figure LMDA.1 illustrates the study design.



Abbreviations: AD = patients with Alzheimer's disease; HS = healthy subjects; IV = intravenous; LY = LY3303560; PK = pharmacokinetics; PL = placebo; SAD = single-ascending dose; SC = subcutaneous.

Figure LMDA.1. Illustration of study design for Protocol I8G-MC-LMDA.

5.2. Number of Participants

For Cohorts 1 to 7, 10, and 11, up to 90 healthy subjects may be enrolled so that approximately 70 subjects (8 subjects per cohort, except for Cohort 5 [n=6]) reach at least Day 29 of the study.

For Cohorts 8 and 9, up to 20 patients with AD may be enrolled so that approximately 16 patients (8 patients in each cohort) reach at least Day 29 of the study.

Subjects or patients who discontinue the study before completing the Day 29 assessment may be replaced at the discretion of the sponsor and investigator. Subjects or patients who discontinue

after Day 29 may also be considered for replacement to ensure sufficient data are available for final data analysis. The ethnicity of the replacement subject (Japanese or non-Japanese) should match the ethnicity of the discontinued subject, where possible.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject/patient.

5.4. Scientific Rationale for Study Design

This study will be conducted to investigate the safety, tolerability, and PK of a single IV administration of LY3303560 in healthy subjects and patients with AD. Sentinel dosing will be implemented for the first cohort, where only 1 subject is dosed with LY3303560 in parallel with 1 subject dosed with placebo and these 2 subjects are observed for at least 48 hours before any other subjects are dosed. The remaining subjects may be dosed on the same day, at appropriate intervals. Also a minimum 4-day in-patient stay after dosing with study drug provides further risk management.

Given planned doses for Cohorts 10 and 11 will approximate the NOAEL exposure in monkeys, sentinel dosing will also be conducted in these cohorts. In addition, the Bond and Lader, and Digit Span Forward and Backward test will be measured in these cohorts to assess potential CNS effects.

Due to the anticipated long half-life of LY3303560, separate groups of subjects will be randomized to each dose cohort in a parallel design rather than using a crossover study design within subjects. Two subjects per cohort will be administered an IV infusion of placebo to allow for a blinded, placebo-controlled assessment of effects.

Cohort 5 (SC dose) will allow for a determination of SC exposure relative to IV, and to assess safety. It is intended that the dose administered in Cohort 5 will be 210 mg LY3303560, but the actual dose will be dependent on the observed safety and PK profile of previously administered doses. However, the dose will not exceed 700 mg or the highest well-tolerated dose in the prior ascending IV cohorts.

Magnetic resonance imaging is commonly used to detect amyloid related imaging abnormalities (ARIAs) which have been associated with anti-amyloid therapy. Both ARIA-E (vasogenic oedema) and ARIA-H (microhaemorrhage) have been reported after administration of several amyloid antibodies. While there is no evidence for imaging abnormalities with tau target therapies from the preclinical data for LY3303560 or from other tau therapeutics in the literature, MRI scans will be taken predose and then approximately 2 weeks and 3 months after dosing with LY3303560, in order to assess the potential for LY3303560 induced tau related imaging changes, including, but not restricted to, vasogenic oedema and microhaemorrhage, in both healthy subjects and patients with AD.

It is intended that this study will support further development of LY3303560 in Japanese patients, therefore, it is planned that healthy Japanese subjects may be enrolled in each cohort. If

the recruitment of Japanese subjects becomes limiting for a particular cohort, then cohorts may complete enrollment with non-Japanese subjects and proceed to dose escalation without waiting for the desired number of Japanese subjects to be enrolled. Japanese subjects may subsequently be enrolled to fulfill the desired number of Japanese subjects at the discretion of the sponsor and investigator. It is preferred that non-Japanese subjects be non-Asian.

5.5. Justification for Dose

The proposed dose range is 7 to 5600 mg LY3303560. The doses were selected based upon the analysis of nonclinical PK, efficacy and toxicology data from studies conducted in Tg4510 tau transgenic mice expressing human four-repeat tau with the P301L mutation that is linked to hereditary tauopathy and cynomolgus monkeys.

A mechanistic PK/PD model was used to predict a clinically relevant LY3303560 dose range by estimating the steady-state reduction in aggregated tau in CSF at various doses. The CSF was used as a surrogate matrix to understand the disposition of aggregated tau in the CNS. Model predictions suggested a clinical dose of 10.5 mg LY3303560 administered every 4 weeks (Q4W) and 385 mg LY3303560 Q4W will decrease CSF aggregated tau by approximately 20% and 90%, respectively. However, an update to the PK/PD model based on recent nonclinical findings in monkey suggest that the predicted clinical dose of LY3303560 may be higher than what was previously predicted. As such, the maximum dose to be evaluated in this study has been increased from 1400 to 5600 mg. A dose of 10.5 mg (20% decrease in CSF aggregated tau) is defined as the minimally anticipated biological effect level (MABEL). Therefore, a starting dose of 7 mg LY3303560 (approximately 0.1 mg/kg for a 70-kg person) is below the MABEL and thus considered an appropriate starting dose.

The safety of LY3303560 was assessed in 5-week and 6-month toxicology studies in cynomolgus monkeys which included evaluation of safety pharmacology and toxicokinetics. The cynomolgus monkey is an appropriate large animal species to evaluate the safety of LY3303560 with respect to monomeric tau. The administration of LY3303560 in monkeys up to a maximum dose of 200 mg/kg/week (bolus IV) for 5 weeks or 6 months resulted in no compound-related adverse findings. It is anticipated that the mean exposure resulting from doses of LY3303560 to be administered in Cohorts 10 and 11 will approximate the mean exposure in monkeys dosed 200 mg/kg LY3303560 (the NOAEL), see Table LMDA.2. The safety and PK data from doses up to 1400 mg LY3303560 also support dosing in Cohorts 10 and 11. The safety of LY3303560 was also assessed in 5-week and 6-month toxicology studies in a Tg4510 mouse model. The Tg4510 transgenic mouse is an appropriate species to evaluate the safety of LY3303560 with respect to binding aggregated tau and small tau fibrils. The administration of LY3303560 to Tg4510 mice up to a maximum SC dose of 200 mg/kg resulted in no compound-related adverse findings.

Table LMDA.2. Margin of Safety for Subcutaneous/Intravenous Administration of LY3303560 Based on Administered Dose and Predicted Exposure

	Dose	Dose Multiple[a] (Starting dose/ Maximum dose)	AUC0-168hr (µg•day/mL)	Exposure Multiple[a] (Starting dose/ Maximum dose)
Human[b]				
Starting Dose	7 mg (0.1 mg/kg)	–	36.1[c]	–
Maximum Dose	5600 mg (80 mg/kg)	–	35,400	–
Tg4510 mouse NOAEL[d]	200 mg/kg	2000/2.5	15,458[e]	428/0.4
Monkey NOAEL[f]	200 mg/kg	2000/2.5	47,083[e]	1304/1.3

Abbreviations: $AUC_{0\text{-}168hr}$ = area under the serum concentration time curve from time zero through 168 hours postdose; NOAEL = no-observed-adverse-effect level.

a Dose multiple is the dose in animals divided by the dose in humans based on mg/kg basis. Exposure multiple is the calculated AUC in animals divided by the predicted AUC in humans.

b Clinical dose assumes a 70 kg subject; 7 mg = 0.1 mg/kg, 5600 mg = 80 mg/kg.

c Observed data from Study LMDA (preliminary).

d NOAEL determined in a 6-month repeat dose toxicity study (Study 8326195).

e AUC is mean of male and female.

f NOAEL determined in a 6-month repeat dose toxicity study (Study 8326196).

Overall, the proposed starting dose of 7 mg LY3303560 is considered appropriate as it is below the calculated MABEL. The projected mean exposure at the highest planned dose of 5600 mg is expected to approximate the NOAEL exposure observed in the 6-month toxicology study in cynomolgus monkeys. Prior to dosing Cohort 11 (5600 mg), LY3303560 PK data from Cohort 10 (2800 mg) will be reviewed and the exposure for Cohort 11 (5600 mg) will be predicted. The dose to be administered in Cohort 11 may be adjusted if necessary to ensure the projected mean exposure does not exceed the mean monkey NOAEL exposure of 47,083 µg•day/mL.

6. Study Population

Eligibility of healthy subjects and patients for study enrollment will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, ECG, clinical imaging tests, and, for patients, the research disease diagnostic criteria. Additionally for patients, a cognitive examination will be performed.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days before enrollment for Cohorts 1 to 7, 10, and 11 (healthy subjects). Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Screening may occur up to 70 days before enrollment for Cohorts 8 and 9 (patients with AD). Patients who are not enrolled within 70 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility and exceptions to the 70-day screening window may be granted as follows:

- free and cued selective reminding test with immediate recall (FCSRT-IR), Mini Mental State Examination (MMSE), and Clinical Dementia Rating (CDR): 90 days
- florbetapir imaging: 120 days

Patients should only proceed to the next screening test when the patient passes the prior screening test. The screening tests are to occur in the following order:

1. all screening tests except MRI and PET scans
2. MRI
3. florbetapir PET

Japanese healthy subjects will be recruited at a site outside of Japan and, for the purpose of analysis, should be first generation Japanese (defined as the subject, the subject's biological parents, and all of the subject's biological grandparents are of exclusive Japanese descent and were born in Japan).

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

6.1. Inclusion Criteria

Subjects/patients are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

[1a] For Cohorts 1 to 7, 10, and 11, are overtly healthy, as determined by medical history and physical examination

[1b] For Cohorts 8 and 9, have mild cognitive impairment due to AD or mild-to-moderate AD based on National Institute of Aging and Alzheimer's Association diagnostic criteria (Albert et al. 2011; McKhann et al. 2011):

- gradual and progressive change in memory function reported by patients or informants over more than 6 months
- objective evidence of significantly impaired episodic memory characteristic of hippocampal dysfunction on testing:
  - FCSRT-IR: ≤22 for free recall or ≤42 for total recall
  - CDR of 0.5 to 2, global score
  - MMSE of 16 to 30
- positive florbetapir PET scan

[2a] male subjects/patients:

agree to use an effective method of contraception and will not donate sperm during the study and for approximately 6 months following the last dose of investigational product (IP)

At least one effective method of contraception will be used (for example, condoms with spermicide, oral contraceptives, intrauterine device (IUD), male sterilization, etc.). The subject 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 [i.e., 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 due to the high failure rate when these barrier methods are combined.

[2b] female subjects/patients:

women not of child-bearing potential may participate, and include those who are:

a) Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
b) Postmenopausal – postmenopausal is defined as women at least 50 years of age with an intact uterus who have not taken hormones or oral contraceptives within 1 year, who have had either cessation of menses for at least 1 year, or 6 to 12 months of spontaneous amenorrhea with follicle-stimulating hormone >40 mIU/mL.

[3] are at least 30 years old at the time of screening for Cohorts 1 to 7, 10, and 11. For Cohorts 8 and 9, are at least 50 years old at the time of screening

[4] have a body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, at screening

[5] have clinical laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator

[6] have venous access sufficient to allow for blood sampling and administration of IP for IV administration as per the protocol

[7] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures and research unit policies

[8] for healthy subjects (Cohorts 1 to 7, 10, and 11): are able and willing to give signed informed consent. For Cohorts 8 and 9, patients not capable of providing consent must provide assent; informed consent must be provided by a legally authorized representative

[9] for patients with AD (Cohorts 8 and 9): have adequate vision and hearing for neuropsychological testing in the opinion of the investigator

[10] for patients with AD (Cohorts 8 and 9): have a reliable caregiver/study informant who provides a separate written informed consent to participate. The caregiver/study informant is required to accompany the patient for screening, all dosing days and for all days that the C-SSRS/Self-Harm Supplemental Form (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 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 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

Note: The caregiver(s)/study informant(s) 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. Participants living in an assisted-living facility may be included if regular contact with a caregiver who accompanies the patient is maintained. If it is known that the caregiver could change and the 2 caregivers are available (in the same location), both should be advised of the study procedures and may attend the visits with the patient. In addition, both will have to sign an informed consent form (ICF) (see Appendix 3)

6.2. Exclusion Criteria

Subjects/patients will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

[11] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling. For Cohorts 8 and 9, have caregivers who are investigator site personnel directly affiliated with this study

[12] are Lilly employees or employees of third-party organizations (TPOs) involved with the study who require exclusion of their employees, or have caregivers (Cohorts 8 and 9) who are Lilly employees or employees of TPOs involved in study who require exclusion of their employees

[13] are currently enrolled in a clinical trial involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.

[14] have participated, within the last 30 days, in a clinical trial involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed

[15] have previously completed or withdrawn from this study

[16] have known allergies to LY3303560, related compounds or any components of the formulation, or history of significant atopy

[17] have significant allergies to humanized monoclonal antibodies, diphenhydramine, epinephrine, or methylprednisone

[18] have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)

[19] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[20] have persistent abnormal blood pressure as determined by the investigator

[21] have a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data

[22] show evidence of significant active neuropsychiatric disease

[23] regularly use known drugs of abuse and/or show positive findings on urinary drug screening

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

[25] show evidence of hepatitis C and/or positive hepatitis C antibody

[26] show evidence of hepatitis B and/or positive hepatitis B surface antigen

[27] are women who are lactating

[28] for healthy subjects (Cohorts 1 to 7, 10, and 11): have used or intend to use over-the-counter or prescription medication (including herbal medications) within 7 days prior to dosing or during the study with the exception of vitamins and mineral supplements (not providing >100% of the recommended dietary allowance); thyroid replacement and/or estrogen hormone replacement; and occasional paracetamol/acetaminophen. If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the sponsor.

[29] have donated blood of more than 500 mL within the last month before dosing

[30] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (males over 65 and females), or are unwilling to stop alcohol consumption 48 hours before dosing until 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)

[31] have received treatment with biologic agents (such as monoclonal antibodies, including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.

[32] have an increased risk of seizures as evidenced by a history of head trauma with loss of consciousness within the last 5 years or ≥1 seizure (except childhood febrile seizure); prior electroencephalogram with epileptiform activity; stroke; surgery to the cerebral cortex; or history within the last 5 years of a serious infectious disease affecting the brain (including neurosyphilis, meningitis, or encephalitis)

[33] have any contraindications for MRI studies, including claustrophobia, the presence of metal (ferromagnetic) implants/cardiac pacemaker, or contraindication for gadolinium contrast

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

Additional criteria for patients with AD (Cohorts 8 and 9):

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

[36] 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 lumbar puncture

[37] MRI demonstrating presence of macrohemorrhage or >4 microhemorrhages or pathology inconsistent with AD or clinically significant finding that may impact patient's ability to safely participate in the study

[38] have received acetylcholinesterase inhibitors (AChEIs), memantine, and/or other AD therapy for less than 4 weeks or have less than 4 weeks of stable therapy on these treatments by time of randomization (Note: If a patient has recently stopped AChEIs and/or memantine, he or she must have discontinued treatment at least 4 weeks before time of randomization) or has received medications that affect the CNS, except treatments for AD, for less than 4 weeks; that is, doses of chronic medications that affect the CNS should be stable for at least 4 weeks before randomization. Any intended concomitant or concurrent medication use will be evaluated by the investigator in consultation with the Lilly clinical pharmacologist

[39] have criteria that would preclude a lumbar puncture, such as allergy to all local anesthetics (such as lidocaine); have a local infection at the site of the lumbar puncture; have <100 GI/L (100,000/mm3) platelets or clinically significant coagulation abnormality or significant active bleeding; or treatment with an anticoagulant or treatment with >2 antiplatelet agents

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

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

[42] have current serious or unstable illnesses including hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with the analyses of safety and efficacy in this study

[43] have 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 postresection

[44] any prior exposure to or participation in clinical trials of active or passive immune therapies directed against tau Aβ protein

[45] have had a ventriculperitoneal shunt within the last year

[46] have had gamma globulin (IgG) therapy within the last year

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Subjects/patients should fast for at least 4 hours prior to study drug administration and are required to remain recumbent for approximately 2 hours (unless otherwise required for procedures) after study drug administration and remain sedentary in a bed or chair for the subsequent 2 hours for observation. Subjects/patients are permitted to have a meal approximately 2 hours following dosing. While resident in the CRU, a standardized diet will be provided. When outpatient, a subject's/patient's typical diet may be consumed at all other meal times during the study.

6.3.2. Caffeine, Alcohol, and Tobacco

Consumption of caffeine- and xanthine-containing products is allowed, provided that the subject's/patient's consumption has been consistent for the past 30 days.

Subjects/patients will not be permitted to consume alcohol from 48 hours before CRU admission to leaving the CRU. Subjects/patients will not exceed their habitual alcohol consumption during the study. When not resident in the CRU, male subjects/patients should be advised to limit alcohol consumption to no more than 21 units per week and males older than 65 years and female subjects/patients to no more than 14 units per week, and all subjects/patients should be advised to limit alcohol consumption to no more than 3 units in a day.

Subjects/patients will not be permitted to smoke from 48 hours before visiting the CRU until discharge from the CRU.

6.3.3. Activity

On CSF sampling days in Cohorts 8 and 9, movement will be restricted during the procedure and for an appropriate time after removal of the lumbar catheter, as determined by the investigator (see Section 9.5.1). Patients will be monitored following removal of the lumbar catheter until discharge from the CRU on Day 4. Dosing cannot proceed if dural puncture headache is present after insertion of the catheter.

6.4. Screen Failures

Healthy subjects who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

Patients with AD who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times. The interval between rescreening should be at least 1 week. Each time rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of LY3303560 and placebo, over a planned dose range of 7 to 5600 mg. Table LMDA.3 shows the treatment regimens.

For all cohorts except Cohorts 5, 7, 10, and 11, the IP will be administered as a slow IV infusion over at least 30 minutes. Every attempt should be made to complete the infusion within 60 minutes. The infusion time for Cohorts 7 and 10 should be at least 60 minutes, and for Cohort 11, at least 90 minutes.

For Cohort 5, the planned 210 mg dose of IP will be administered SC as two 1.4 mL injections of 105 mg each.

The minimum time for close observation in the CRU following dosing is 4 hours. The site must have resuscitation equipment, emergency drugs, and appropriately trained staff available during dosing and for at least 24 hours after dosing.

All IP provided to the investigator will be stored in a secure location, and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the IPs will be fully documented and verified by a second person. Detailed records of the amounts of IP received, dispensed and remaining at the end of the study will be maintained. Detailed instructions for the preparation and handling of LY3303560 will be provided by the sponsor in a pharmacy manual.

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

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

Table LMDA.3. Treatments Administered

Treatment Name	LY3303560	Placebo
Dosage Formulation	lyophilized powder in vial	liquid in vial
Unit dose strength(s)/Dosage Level(s)	each vial can deliver 90 mg LY3303560	0.9% normal saline
Route of Administration	intravenous infusion or subcutaneous injection	intravenous infusion or subcutaneous injection
Dosing instructions	single administration	single administration

The investigator or designee is responsible for:

- explaining the correct use of the IPs to the subject/patient/patient's caregiver,

- verifying that instructions are followed properly,
- maintaining accurate records of IP 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 investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

7.1.1. Packaging and Labeling

Investigational product will be manufactured in accordance with good manufacturing practices and will be labeled according to applicable local regulatory requirements.

7.2. Method of Treatment Assignment

Treatment assignment will be determined according to a randomization schedule.

7.2.1. Selection and Timing of Doses

The actual time of all dose administrations will be recorded in the subject's/patient's CRF. For IV infusions, the actual duration time of the infusion will be recorded in the CRF. If the infusion is terminated, this should be recorded in the CRF.

7.3. Blinding

This is a subject-/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.

Randomization tables for allocation of LY3303560 and placebo will be prepared by the Lilly statistician and provided to the study site pharmacists or pharmacy staff involved in dose preparation. Blinding will be maintained throughout the conduct of the trial until all data are cleaned to an acceptable level of quality and locked. The details are included in the Blinding/Unblinding Plan.

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject/patient's treatment assignment is warranted for medical management of the event. Subject/patient's 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 clinical research physician (CRP) prior to unblinding a study subject/patient's treatment assignment unless this could delay emergency treatment of the patient. If a study subject/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.

7.4. Dose Modification

7.4.1. Dose Decision/Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the MTD is determined or the highest planned dose has been administered. The highest dose level that is tolerated will be designated as the MTD.

Safety data will be the primary criteria for the dose escalation. In addition, if available at the time of dose escalation decision, PK (C_{max}, AUC, and total clearance [CL]) results will be used as supporting data for dose escalation, but such data are not required, aside from dose escalation from Cohort 10 to 11 (see below). No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly clinical pharmacologist/CRP.

Safety data collected up to 2 weeks after dosing will be evaluated from at least 4 subjects on LY3303560 and 1 subject on placebo prior to each dose escalation. The safety data reviewed will include: AEs, MRI, neurological monitoring, safety laboratories, ECGs and vital signs.

Safety data, in particular AEs and adverse laboratory abnormalities, will be independently assessed by the investigator, and will be considered related to the IP unless there is clear evidence that the event is not related. After review of these data, an agreement on the appropriate dose escalation will be made by the investigator and sponsor for the next cohort. The magnitude of the dose escalation may be reduced following data review, but subsequent escalations cannot be increased by more than approximately 3-fold (a half-log increment).

At a minimum, safety data from Cohort 4 (210 mg IV LY3303560) will be reviewed prior to starting Cohorts 5 and 8. For Cohort 5, PK data from up to Cohort 3 (70 mg LY3303560) will also be reviewed prior to dosing this cohort. Cohort 9 will only be initiated after review of safety data from Cohorts 6 (700 mg LY3303560) and 8.

For dose escalation from Cohort 10 to 11, LY3303560 PK data from Cohort 10 will be analyzed and the exposure at 5600 mg LY3303560 re-projected based on the observed PK at 2800 mg LY3303560. The PK projection will be reviewed before escalation to Cohort 11 and the dose to be administered in Cohort 11 may be adjusted if necessary to ensure the projected mean exposure does not exceed the mean monkey NOAEL exposure of 47,083 μg•day/mL.

If any of the following scenarios occur, dosing at the current level and further dose escalation will be discontinued:

1) Two or more subjects experience a SAE (aside from a SAE occurring during the infusion/SC delivery, see below) or clinically significant event (CSE) that is considered related to LY3303560 administration. 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 subject, or

2) Two or more subjects 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.

3) After the introduction of premedication in accordance with the protocol, 2 or more subjects develop (according to Common Terminology Criteria for Adverse Events) ≥Grade 2 acute AEs related to the infusion, during or within 2 hours of completing the infusion, that do not resolve with a reduced infusion rate and supportive care.

4) If an SAE occurs during the infusion or SC delivery of the study drug, irrespective of causality, the drug is discontinued immediately. No re-dosing or completion of dosing is considered for that subject. If the infusion SAE is considered related to LY3303560 then the remaining cohort is not dosed.

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

In the event of an SAE that is related to the IP, other than precautionary in-patient observation, dosing will be suspended, for that cohort and higher cohorts, pending notification of the ethical review board (ERB) and appropriate regulatory authorities. Dosing will only resume, per protocol, after the ERB, investigator, and sponsor agree on the appropriateness of further dosing.

7.4.2. Special Treatment Considerations

7.4.2.1. Premedication for Infusions

Premedication for the infusions is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigator(s). If infusion reactions are observed, but review of the data suggests that dose escalation may continue, administration of acetaminophen, 500 to 1000 mg and/or an antihistamine may be administered orally 30 to 60 minutes prior to the start of infusion for subsequent subjects.

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

Any premedications given will be documented as a concomitant therapy (see Section 7.7).

7.4.2.2. 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 IP 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 IP for that subject 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 Appendix 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 IgE, and immune complex testing) will be collected at time points indicated in the Schedule of Activities (Section 2).

Additionally, stored serum samples for possible immune safety laboratory testing (including but not limited to β tryptase, total IgE, and immune complex testing) should also be collected approximately 60 to 120 minutes and 4 to 6 weeks after moderate or severe infusion reactions. Unscheduled samples may also be collected as needed.

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

7.5. Preparation/Handling/Storage/Accountability

Only participants enrolled in the study may receive IP and only authorized site staff may supply or administer study treatment. All study treatments should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

7.6. Treatment Compliance

The IP will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Prohibited medications are summarized in the inclusion and exclusion criteria (Section 6). Use of vitamins/mineral supplements (not providing more than 100% of the RDA), thyroid replacement, and/or estrogen hormone replacement is allowed. Occasional paracetamol/acetaminophen use without prior consultation with a Lilly clinical pharmacologist will be allowed. Patients with AD on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. Additional drugs for subjects/patients should be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

If the need for concomitant medication arises, inclusion or continuation of the subject/patient may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist or CRP. Any additional medication used during the course of the study must be documented.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Subjects/patients will be discontinued from the IP in the following circumstances:

- AE
    - if a CSE occurs, the IP 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 wellbeing of the subject/patient
    - a clinically significant systemic hypersensitivity reaction occurs following administration of the IP (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
    - symptomatic or asymptomatic cerebral vasogenic edema or cerebral microhemorrhage

Subjects/patients who discontinue the study early should complete all remaining scheduled visits if feasible or, at a minimum, the early termination procedures as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Subject/Patients

The criteria for enrollment must be followed explicitly. If the Sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist to allow the inadvertently enrolled patient to continue in the study without continued treatment with IP.

8.2. Discontinuation from the Study

Subjects/patients will be discontinued in the following circumstances:

- Enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)

- Investigator Decision
    - the investigator decides that the subject/patient should be discontinued from the study
    - if the subject/patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- Subject/Patient Decision
    - the subject/patient, or designee, for example, parents, legal guardian or caregiver (for patients with AD), requests to be withdrawn from the study

Subjects/patients who discontinue the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Patients/Subjects Lost to Follow-up

A subject/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 subjects/patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

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

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

Appendix 4 provides a summary of the number and volume of invasive samples, for all sampling, during the study.

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

Investigators must document their review of each laboratory safety report.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects/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 subject/patient.

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

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

After the ICF is signed, study site personnel will record, via CRF, the occurrence and nature of each subject's/patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

A "reasonable possibility" means that there is a cause and effect relationship between the IP, study device and/or study procedure and the AE.

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

If a subject's/patient's IP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF.

9.2.1. Serious Adverse Events

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

- 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
- events considered significant by the investigator based upon appropriate medical judgment

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.

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

Lilly collects product complaints on IPs 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.

Subjects/patients should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP [or drug delivery system] so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3303560 is considered any dose higher than the dose assigned through randomization.

Refer to the IB for LY3303560.

9.4. Safety

9.4.1. Laboratory Tests

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

9.4.2. Vital Signs

For each subject/patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Screening vital signs will be obtained in the sitting position (after at least 5 minutes sitting). In Cohorts 8 and 9 (patients with AD), for Visits 1 to 3, vital signs will be measured in the supine position only. For all other vital signs after study entry, subjects will rest in the supine position for at least 5 minutes and undergo supine blood pressure and pulse rate measurements. Subjects will sit for approximately 2 minutes then stand for approximately 2 minutes and undergo standing blood pressure and pulse rate measurements. If subjects are unable to stand, supine vital signs only will be recorded. If the subject is unable to stand or sit, omission of the standing or sitting vital signs will not be considered a protocol violation.

Subjects/patients who are unable to stand for 2 minutes because of adverse symptoms should be placed immediately in a supine position with their legs elevated above the level of their chest. An unscheduled measurement of blood pressure and pulse rate should be obtained as soon as possible without causing delay in the resumption of recumbency.

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.

9.4.3. Electrocardiograms

For each subject/patient, ECGs should be collected according to the Schedule of Activities (Section 2).

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject/patient receives the first dose of the IP, should be reported to Lilly, or its designee, as an AE via the CRF. Any clinically significant findings that do not result in a diagnosis should be commented on and appropriately documented. If a clinically significant change is seen, additional ECGs may be added at appropriate intervals to follow return to baseline. Any new clinically significant findings should be reported as an AE.

Electrocardiograms must be recorded before collecting any blood for safety or PK tests. Subjects/patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms 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 screening ECGs recorded should be stored at the investigational site.

At screening and at all timepoints post-Day 7, a single ECG will be obtained and does not need to be transmitted to the ECG vendor. The screening ECG will be interpreted by the investigator or qualified designee at the site to determine whether the subject/patient meets entry criteria.

At all other timepoints, ECGs will be obtained in triplicate at approximately 1-minute intervals at each ECG time point and will be transmitted and stored at the central ECG vendor. Electrocardiograms 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 after enrollment, the investigator will assess the subject/patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the subject/patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject/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.

Digital ECGs will be electronically transmitted to and stored at the centralized 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).

9.4.4. Other Tests

9.4.4.1. Neurological Examinations

A directed neurological examination will be performed by a physician, nurse practitioner, or physician's assistant at the time points specified in the Schedule of Activities (Section 2). 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 LMDA.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 LMDA.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 to 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			

9.4.4.2. Alertness and Attention Assessments (Cohorts 10 and 11)

The Bond and Lader Visual Analog Scale (VAS), and Digit Span Forward and Backward Test will be performed according to the Schedule of Activities (Section 2).

9.4.4.2.1. Bond and Lader VAS

The Bond and Lader VAS (Bond et al. 1974) consists of 16 mood self-rating 100-mm lines between 2 opposite adjectives. The subject has to indicate on the line how he or she is feeling at the time of evaluation. The response is scored by measuring the distance in millimeters between the left end of the line and the subject's mark. This questionnaire derives 3 factors that assess self-rated alertness, self-rated calmness, and self-rated contentment. Approximately 5 minutes is needed to complete the questionnaire. Subjects will complete a training session for the VAS as indicated in the Schedule of Activities (Section 2). This test will be completed approximately 5 minutes before all other assessments at the same time point.

9.4.4.2.2. Digit Span Forward and Backward Test

The Digit Span Forward and Backward subtest (Wechsler 2009) of the Wechsler Adult Intelligence Scale-IV (Wechsler 2008) is a brief test of attention. Digit Span is a series of orally

presented number sequences that the examinee repeats verbatim for Digits Forward and in reverse for Digits Backward (Wechsler 2009).

9.4.4.3. Magnetic Resonance Imaging

The MRI scans will be obtained at time points indicated in the Schedule of Activities (Section 2).

Magnetic resonance imaging safety monitoring will include sequences appropriate for detecting vasogenic edema (ARIA-E) and microhemorrhage (ARIA-H). A 1.5T scanner is preferred but a 3T scanner may be used if a 1.5T scanner is not available. Patients in Cohorts 8 and 9 with >4 microhemorrhages in their screening MRI will be excluded from the study. 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 MRI using T_2*-weighted gradient-echo sequence. Additional fluid attenuation inversion recovery (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.

9.4.4.4. Injection-Site Assessments (Cohort 5)

Injection sites will be observed and evaluated for injection-site reactions after SC dose administration, as specified in the Schedule of Activities (Section 2). If an injection-site reaction is present, it will be fully characterized (including erythema, induration, pain, itching, etc.) and will be closely monitored until resolution.

Investigational site staff will be provided with separate instructions/training in how to consistently evaluate injection-site reactions and their severity. Photographs of injection-site reactions will be taken in a standardized fashion for record-keeping purposes; however, the photographs will not be used to evaluate injection-site reaction severity.

9.4.4.5. Columbia Suicide Severity Rating Scale (Cohorts 8 and 9)

By industry guidance regarding suicidality (US Food and Drug Administration; 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 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. There is cognitive impairment in this population and inability of the caregiver/informant to have direct knowledge of the patient's thoughts; therefore, Lilly will assess the investigator's confidence in the responses to the child C-SSRS with a rater question in the CRF.

The child version of the C-SSRS should be administered to the patient with the caregiver/study informant present or available by phone. Responses from both the caregiver/study informant and patient should be considered when administering the scale. The response from the caregiver/study informant 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.

If the investigator determines that suicide-related behaviors have occurred, a Lilly SHSF will be used to collect additional information to allow for a more complete assessment of these behaviors. Patients with any clinically significant changes as determined by the investigator will be referred to a mental health professional.

9.4.4.6. Imaging (Cohorts 8 and 9)

A florbetapir scan will be performed at screening. At the florbetapir PET scanning visit, patients will receive a single IV administration of approximately 370 MBq (10 mCi) of florbetapir F 18, followed 50 minutes later by a 20 minute continuous imaging session. The injection of the imaging agent will be followed by a saline flush according to the injection procedure described in the imaging operations manual. The image should be reviewed immediately following the acquisition session. If the image is not interpretable because of technical artifact (scanner failure, patient motion), the patient can be rescanned. However, in order to maximize image quality, it is strongly recommended that this second imaging session begin as soon as possible, ideally within 80 minutes of the florbetapir administration.

A total of two ^{18}F-AV-1451 PET scans will be performed, approximately 12 weeks apart. At each ^{18}F-AV-1451 PET imaging visit, patients will receive a single IV administration of approximately 370 MBq (10 mCi) of ^{18}F-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.

9.4.4.6.1. Radiation Doses Associated with PET Imaging

The estimated exposure to ionizing radiation per patient enrolled in this study (effective dose) is summarized in Table LMDA.5. This includes contributions from florbetapir and 18-AV-1451 scans, along with low-dose CT scans required for attenuation correction. The injected doses for florbetapir and ^{18}F-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 the screening florbetapir PET scan, 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.

Table LMDA.5. 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	Total Effective Dose (mSv)
Florbetapir scan	10	370	7.43	1	7.43
^{18}F-AV-1451 scan	10	370	9.1	2	18.2
Totals				3	25.63

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.

9.4.5. 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

If a study subject/patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated total bilirubin ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure subject/patient safety and compliance with regulatory guidance, the investigator is to consult with the Lilly designated CRP regarding collection of specific recommended clinical information and follow-up laboratory tests.

The levels of tau protein in plasma have been shown to be associated with AD, age, BMI, diabetes, hypertension, atrial fibrillation, and head injuries (traumatic brain injury, sports related concussion) (Zetterberg et al. 2013; Shahim et al. 2014), therefore patients should be monitored for any changes or occurrences of these variables during the study as they may impact the assessment of one of the PD biomarkers, plasma tau.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the personnel included in the Blinding/Unblinding Plan.

9.4.6. Immunogenicity Assessments

As detailed in the Schedule of Activities (Section 2), blood samples for immunogenicity testing will be collected for both healthy subjects and patients with AD to determine antibody production against the LY3303560. 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 anti-drug antibodies in the presence of LY3303560. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the LY3303560.

Samples will be retained for a maximum of 15 years after the last subject/patient visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY3303560. Any samples remaining after 15 years will be destroyed.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), blood samples of approximately 3 mL each will be collected to determine the serum concentrations of LY3303560. A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Time points for PK sampling may be modified based on any available interim PK results obtained during the study. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

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

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

9.5.1. Cerebrospinal Fluid Sampling (Cohorts 8 and 9)

A lumbar x-ray may be conducted to rule out potential contraindication to a lumbar puncture, such as significant osteoarthritic disease and bone overgrowth. If an x-ray was conducted within 12 months of screening, this may be used.

A licensed anesthesiologist or other specially trained physician will insert a flexible, indwelling subarachnoid lumbar catheter designed for serial sampling of CSF. Serial CSF samples will be collected from each patient at times specified in the Schedule of Activities (Section 2).

At each designated time point, CSF will be collected (5 mL at the -4-hour predose time point when sample is collected for safety [red blood cell (RBC) count, glucose, and protein], PK, and PD biomarkers; 4 mL at the -2-hour predose time point when sample is collected for PK/PD

biomarkers only; 4 mL at 0-hour time point when sample is collected for safety, and PK/PD biomarkers; 4 mL at each postdose time point when sample is collected for measurement of PK/PD biomarkers). Because 4 to 5 mL cannot be collected instantaneously, 8 to 10 minutes is needed to collect 4 to 5 mL at a rate of 0.5 mL/min. Postdose CSF collections are therefore started as close to the designated time as possible.

The residual volume "dead space" that remains in the sterilized tubing needs to be withdrawn and separately retained prior to subsequent samples being collected using the same rate of 0.5 mL/min. The tubing set-up used by the site retains approximately 1.7 mL of fluid. Therefore, before each collection period, 2 mL over a 4-minute period needs to be collected and stored. These samples may be stored and used for assay validation or exploratory work.

Patients who cannot complete the entire CSF sampling period but who complete CSF collections for a minimum of 24 hours postdose will not be replaced.

The safety of draining 6 mL of CSF in a given hour has been documented (Jhee and Zarotsky 2003). This volume is considerably less than the normal rate of CSF production, which is approximately 20 to 24 mL/hour (White et al. 1969; Baker et al. 1999). Removal of up to 12 mL/hour is tolerated based on previous clinical experience; therefore, no more than 12 mL of CSF will be taken during a given hour including that withdrawn from the "dead space".

Red blood cell counts will be measured in CSF at catheter placement and at least once before dosing with study drug and may be measured at other times as deemed necessary by the investigator. Red blood cell counts are to be measured using a clinical laboratory method available to the study site. In addition, each CSF sample collected will be visually inspected for evidence of gross blood contamination. The results of CSF RBC counts are to be documented in the CRF. Grossly evident blood by visual inspection will be reported as positive and documented in the CRF. Any sample that shows visual or laboratory evidence of blood contamination may be excluded from the PD and statistical analyses if the level of contamination is estimated to be sufficient to produce misleading results. This calculation will be based on the number of RBCs present in the samples, the estimated amount of blood/plasma that would correlate to that number of RBCs, and the estimated concentration of LY3303560 that would potentially be from blood contamination given the C_{max} of the drug at that dose.

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

9.5.2. Bioanalysis

Plasma and CSF samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of LY3303560 will be assayed using a validated ELISA. Analyses of samples collected from placebo-treated subjects and patients are not planned.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last subject or patient visit for the study.

9.6. Exploratory Pharmacodynamics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 10 mL will be collected for measurement of plasma tau concentrations if a suitable assay exists. A maximum of 5 additional time points per subject/patient may be drawn during the study at the discretion of the investigator or sponsor. These additional samples may be drawn to measure LY3303560, tau or exploratory PD biomarker concentrations. Cerebrospinal fluid samples for exploratory PD will be collected as described in Section 9.5.1.

Plasma concentrations of tau and CSF concentrations of tau, p-tau, neurogranin, and Aβ1-42 will be determined using validated immunoassay methods if a suitable assay exists. The samples will be identified by the subject/patient number and stored for a maximum of 15 years after the last subject/patient visit for the study at a facility selected by the sponsor. Plasma and CSF samples collected for PD measurements will have aliquots stored for future exploratory biomarker work for a maximum of 15 years after last subject/patient visit for the study. Any sample remaining after this period will be destroyed. Research will be limited to investigation of the safety and PD of LY3303560, biomarkers relevant to neurodegenerative diseases, the mechanism of action of LY3303560. Time points for PD samples may be modified based on any available interim results obtained during the study. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

On the day of dosing, PD samples should be collected from the arm that did not receive the IV infusion of study drug.

The sample(s) will be stored for up to a maximum of 15 years after the last subject/patient visit for the study at a facility selected by the sponsor.

9.6.1. Exploratory Cognitive and Functional Scales (Cohorts 8 and 9)

The test of cognitive function, MMSE, Clinical Dementia Rating - Sum of Boxes (CDR-SB), and FCSRT-IR will be performed during the study at the times specified in the Schedule of Activities (Section 2). 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 LY3303560 in this small patient population and single dose nature of the study. Cognitive and functional tests that are performed on the same day should be done in a specific order. Cognitive and functional tests should be completed in this order: 1) FCSRT-IR, 2) CDR, and 3) MMSE.

9.6.1.1. 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).

9.6.1.2. 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.

9.6.1.3. 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.

9.7. Genetics

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

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be tested for the apolipoprotein E (APOE) genotype (ε2, ε3, ε4) to determine whether these genetic variants are potentially associated with a pharmacological response to LY3303560. Apolipoprotein E genotype has been demonstrated even in small sample sizes to be associated with vasogenic edema complications. 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 LY3303560, 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.

In the event of an unexpected AE or the observation of unusual pharmacological response, the pharmacogenetic samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3303560. 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 IPs.

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

Samples will be retained for a maximum of 15 years after the last subject/patient visit, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3303560 or after LY3303560 is commercially available.

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

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, blood ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Serum, plasma, CSF, whole RNA samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3303560, pathways associated with AD, mechanism of action of LY3303560, and/or research method, or for validating diagnostic tools or assay(s) related to neurodegenerative diseases.

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

Samples will be retained for a maximum of 15 years after the last subject/patient visit, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3303560 or after LY3303560 is commercially available.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The sample size is customary for Phase 1 studies evaluating safety, PK, and/or PD parameters, and 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.

Up to 90 healthy subjects may be enrolled to ensure that approximately 70 subjects (8 subjects per cohort, except for Cohort 5 [n=6]) reach at least Day 29 of the study.

For each of the IV healthy subject cohorts, the intention is to include 4 Japanese subjects and 4 non-Japanese subjects (preferred non-Asian) to support the development of LY3303560 in Japan. The target minimum requirement is to include 4 Japanese subjects in at least 3 of these cohorts (12 Japanese subjects total), including the highest dose level cohort. It is not anticipated that there will be differences in LY3303560 exposure/safety/PD response between Japanese and non-Japanese subjects, therefore the enrollment is not contingent upon fulfilling this requirement. If 4 Japanese subjects are not included in a cohort initially, the cohort will complete with non-Japanese subjects and additional Japanese subjects may subsequently be enrolled to achieve the intended 4 Japanese subjects, at the discretion of the sponsor.

Up to 20 patients with AD may be enrolled to ensure that 16 patients (8 patients in each cohort) complete Cohorts 8 and 9.

See Section 5.2 for replacement of subjects/patients.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of healthy subject and patient disposition will be provided at the end of the study.

All patients/healthy subjects 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.

10.2.2. Study Participant Characteristics

The patient's/healthy subject's age, sex, race, weight, height, APOE4 status 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.

10.3. Statistical Analyses

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

Pharmacokinetic and PD analyses will be conducted on the full analysis set. This set includes all data from all randomized healthy subjects and patients receiving a dose of the IP according to the

treatment the subjects/patients actually received. Safety analyses will be conducted for all enrolled patients/healthy subjects, whether or not they completed all protocol requirements.

Summary statistics, data tabulations, and data graphs by ethnicity (Japanese and non-Japanese, and combined) 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 (SAP).

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All IP and protocol procedure AEs will be listed, and 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 IP as perceived by the investigator. Symptoms reported to occur prior to 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 IP-related SAEs will be reported.

10.3.1.2. 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 for values at each time point as well as changes from baseline. Outliers will also be identified and listed where appropriate. Additional analyses may be performed if warranted upon review of the data. All planned safety analyses will be detailed in the SAP.

Magnetic resonance imaging changes in volume over the course of the study will be explored and exploratory evaluation of vMRI changes for whole brain, ventricle, whole brain boundary shift integral and hippocampus will be summarized; further analyses may be conducted and will be outlined in the SAP. A shift table for each dose group will be constructed to assess the MRI measurement predose and postdose for changes and additions of ARIA-E and ARIA-H.

For Cohorts 8 and 9, 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, that is, all ‘no’s will not be displayed.

An assessment of potential prolongation will be performed using plots of PK data versus QTc values. The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

Analyses of QTc using QTcF from ECG monitoring in a Phase 1 trial will be performed to judge the extent and/or risk of QT prolongation. Scatter plots will be created of QTcF versus LY3303560 concentration and change from baseline QTcF versus LY3303560 concentration.

Placebo data will be included in the plot with concentration imputed to zero. The reference line of 450, 480, and 500 ms will be used for the QTcF versus concentration plot; while 10, 30 and 60 ms for QTcF change from baseline versus concentration plot. Analysis will be performed to assess the mean change in QTcF as a function of plasma drug concentration. The average of the triplicate QTcF measurements will be computed at each of the scheduled time points, and baseline will be the mean of the triplicate measurements collected prior to dosing at time 0 in each treatment period.

A mixed-effect model may be fitted to the QTcF change from baseline, with log-transformed plasma-drug concentration and dose included as fixed effects. Separate analysis may be conducted for healthy subjects and patients with AD as required.

For Cohorts 10 and 11, results from the Bond and Lader VAS, and Digit Span Forward and Backward tests will be summarized by parameter and time point, including change from baseline.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

It is intended that PK parameter estimates for LY3303560 in serum and CSF will be calculated by standard noncompartmental methods of analysis. The primary serum and CSF parameters for analysis will be maximum drug concentration (C_{max}), area under the concentration versus time curve from time 0 to infinity ($AUC_{0-\infty}$) and AUC from time 0 to the last measurable concentration ($AUC0\text{-}t_{last}$) of LY3303560. Other serum PK parameters, such as half-life, clearance, and volume of distribution may be reported after IV administration of LY3303560. Serum PK parameters such as bioavailability, apparent clearance, apparent volume of distribution and half-life may be reported after SC administration.

A model-based approach may also be implemented using nonlinear mixed effects modeling (NONMEM) or other appropriate software to estimate serum and/or CSF PK parameters.

Exploratory analyses of the effect of dose, route of administration, concentration or demographic factors, including healthy subjects versus patients, on the PK parameters may be conducted, and modeling analyses may be performed for characterization purposes. Exploratory analyses relating LY3303560 serum exposure versus LY3303560 CSF concentrations may be conducted.

10.3.2.2. Pharmacokinetic Statistical Inference

The serum PK parameters, C_{max} and $AUC_{0-\infty}$ or $AUC0\text{-}t_{last}$, for LY3303560 obtained for healthy subjects (IV only) will be evaluated to estimate the dose-exposure proportionality of LY3303560 using a linear-effects power model (Smith et al. 2000). In this model, log-transformed dose will be the independent variable, and subject will be a random effect. Both C_{max} and AUC will be log-transformed prior to analysis. The least-square means for each treatment together with the treatment differences and associated 90% confidence intervals (CIs) will be estimated from the model. These estimates will be back-transformed to present geometric means, the ratios of geometric means, and the corresponding 90% CIs. Dose-exposure analysis will be conducted using the healthy subject IV cohorts (Cohorts 1, 2, 3, 4, 6, 7, 10, and

11). Exploratory analyses of Japanese and non-Japanese subjects may be conducted. Additional dose-exposure analyses may be conducted using patient data.

10.3.3. Exploratory Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

For the healthy subjects, plasma tau will be summarized and/or illustrated graphically by time and dose/formulation.

For the patient cohorts (Cohorts 8 and 9), the concentration of the CSF biomarkers, including tau, p-tau, Aβ, and neurograinin, will be summarized and/or illustrated graphically based on availability of data. The mean change in concentration of the biomarkers from predose will be evaluated.

10.3.3.2. Pharmacodynamic Statistical Inference

No statistical analysis of PD parameters are planned.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses (Cohorts 8 and 9)

Model-based approaches may be used to characterize the relationship between changes in CSF biomarkers and exposure of LY3303560.

10.3.5. 18F-AV-1451 Imaging and Cognition Analyses (Cohorts 8 and 9)

Cognition endpoints collected at screening and Day 85 may be summarized and correlated with imaging and CSF endpoints. The data are collected to provide information on cognition changes in a 2 to 3 month timeframe will not be used to assess efficacy of the molecule.

Amyloid status at baseline will be summarized and may be used as a factor in plots of other endpoints.

18F-AV-1451 SUVR data will be summarized and/or plotted by region of interest as appropriate, further details will be given in the statistical analysis plan. Change from baseline of tau burden within regions of interested will be calculated, however, no formal analyses is planned to be conducted due to single dose nature of the study.

Additionally, the relationship between LY3303560 serum exposure and imaging endpoints may be explored graphically or by a modeling approach.

10.3.6. Evaluation of Immunogenicity

Antibody formation will be listed and summarized as well as presented graphically over time by subject/patient and treatment. If trends following the dosing of LY3303560 are observed, then a mixed effect model will be used, fitting dose and day and the interaction between day and dose as a fixed effects and the dependent variable as the log transformed change from baseline in antibody formulation following dosing of LY3303560. If a neutralization assay is performed,

the frequency of neutralizing antibodies will be determined. The relationship between the presence (or absence) of antidrug antibodies and clinical parameters (e.g., AEs and changes in blood pressure) may be assessed. Likewise, the relationship between the presence of antidrug antibodies and the PK parameters and PD response to LY3303560 may be assessed.

10.3.7. Interim Analyses

Select individuals may gain access to unblinded data, prior to the interim or final database lock, in order to initiate the final population PK/PD model development processes for interim or final analyses. The individuals and unblinded data are as specified in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

Safety and/or PK interim access to data (IAD) is scheduled to occur throughout the study. The purpose of these IAD reviews is to examine the safety data and guide dose selections. The investigator and the Lilly study team will make the determination regarding dose escalation based on their review of the safety and tolerability data, along with PK data, as applicable.

An interim review of safety and PK data is planned after healthy subjects in Cohort 3 complete the 28-day postdose PK blood draw. Additional interim PK data reviews may be performed as required during study conduct. The PK data obtained during the study may be used to assist in dose-escalation decisions, but such data are not required for dose escalation.

11. References

Albert MS, Dekosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270-279.

Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geracioti TD Jr. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. *Am J Psychiatry.* 1999;156(4):585-588.

Bond AJ, James DC, Lader MH. Physiological and psychological measures in anxious patients. *Psychol Med*. 1974;4(4):364-373.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.

Grober E, Buschke H. Genuine memory deficits in dementia. *Dev Neuropsychol*. 1987;3:13-36.

Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ. National Institute on Aging – Alzheimer's Association guidelines on neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement*. 2012;8(1):1-13.

Jhee SS, Zarotsky V. Safety and tolerability of serial cerebrospinal fluid (CSF) collections during pharmacokinetic/pharmacodynamic studies: 5 years experience. *Clin Res Reg Affairs.* 2003;20(3):357-363.

Lichtenstein L, Ron Y, Kivity S, Ben-Horin S, Israeli E, Fraser GM, Dotan I, Chowers Y, Confino-Cohen R, Weiss B. Infliximab-related infusion reactions: systematic review. *J Crohns Colitis*. 2015;9(9):806-815.

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-269.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164(7):1035-1043.

Selkoe DJ. The molecular pathology of Alzheimer's disease. *Neuron*. 1991;6(4):487-498.

Shahim P, Tegner Y, Wilson DH, Randall J, Skillback T, Pazooki D, Kallberg B, Blennow K, Zetterberg H: Blood biomarkers for brain injury in concussed professional ice hockey players. *JAMA neurology*. 2014;71:684-692.

Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. *Pharm Res.* 2000;17(10):1278-1283.

Wechsler D. WAIS-IV administration and scoring manual. 4th ed. San Antonio, TX: Pearson; 2008.

Wechsler D. Wechsler Memory Scale (WMS–IV) technical and interpretive manual. 4th ed. San Antonio, TX: Pearson; 2009.

White RJ, Dakters JG, Yashon D, Albin MS. Temporary control of cerebrospinal fluid volume and pressure by means of an externalized valve-drainage system. *J Neurosurg*. 1969;30(3):264-269.

Zetterberg H, Wilson D, Andreasson U, Minthon L, Blennow K, Randall J, Hansson O. Plasma tau levels in Alzheimer's disease. *Alzheimers Res Ther*. 2013;5(2):9.

Appendix 1. Abbreviations and Definitions

Term	Definition
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An 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.
ARIA	amyloid related imaging abnormality
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-microhemorrhage
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
AUC	area under the concentration versus time curve
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject/patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject/patient are not. A double-blind study is one in which neither the subject/patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BMI	body mass index
CDR-SB	Clinical Dementia Rating-Sum of boxes
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Total clearance
C_{max}	maximum drug concentration
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.

compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRF	Case report form
CRP	Clinical Research Physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CSE	clinically significant event
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
enroll	The act of assigning a subject/patient to a treatment. Subjects/patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Subjects/patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board
FCSRT-IR	free and cued selective reminding test with immediate recall
FDA	Food and Drug Administration
GCP	good clinical practice
HIV	human immunodeficiency virus
IAD	interim access to data
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IgG	gamma globulin

informed consent	A process by which a subject/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 subject's/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 (IP)	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
Legal Representative	An individual 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.
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
NFT	neurofibrillary tangles
Non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical trial, but is provided to subjects and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
NONMEM	nonlinear mixed effects modeling
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic
QTcF	Fridericia's corrected QT
RBC	Red blood cell
RNA	ribonucleic acid

SAD	single-ascending dose
SAE	serious adverse event
SC	subcutaneous
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.
SHSF	Self-Harm Supplemental Form
SUSARs	suspected unexpected serious adverse reactions
TPO	third-party organizations
VAS	Visual Analog Scale

Appendix 2. Clinical Laboratory Tests

Laboratory Tests[a]

Hematology
- Hemoglobin
- Hematocrit
- Erythrocyte count (red blood cell [RBC])
- Mean cell volume (MCV)
- Mean cell hemoglobin (MCH)
- Mean cell hemoglobin concentration (MCHC)
- Leukocytes (white blood cell [WBC])
- Cell morphology (absolute or relative % counts):
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Platelets

Urinalysis
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Microscopic examination of sediment

Coagulation (Cohorts 8 and 9)[b,g]
- Prothrombin time (PT)
- International normalized ratio (INR)
- Partial thromboplastin time (PTT)

Clinical Chemistry
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Phosphorous
- Magnesium
- Glucose (random)
- Blood urea nitrogen (BUN)
- Uric acid
- Total cholesterol[b]
- Total protein
- Creatinine
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
- Gammaglutamyl transferase[b]
- Total bilirubin
- Albumin

Pregnancy test[c]

Follicle-stimulating hormone[b,d]

Ethanol testing[e]

Urine drug screen[e]

Viral serology[b,f]
- Hepatitis B surface antigen
- Hepatitis C antibody
- Human immunodeficiency virus (HIV)

a Safety laboratory tests performed at screening will be validated by the local laboratory. All other safety laboratory tests performed during the study will be validated by the central laboratory at the time of initial testing.

b Performed only at screening.

c Per the investigator's discretion, females only. To be completed by the clinical research unit. A serum pregnancy test will be performed at screening; a urine pregnancy test will be performed prior to PET scans (Cohorts 8 and 9) and dosing.

d To be done for women only when needed to confirm postmenopausal status.

e To be completed by clinical research unit at each clinical research unit admission.

f Each of these tests will be completed unless results have been obtained from the subjects/patients within the last 6 months.

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

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

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

Ethical Review

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). Lilly or its representatives must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

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

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

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) applicable ICH GCP Guidelines
3) applicable laws and regulations

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

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.

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

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.

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.
- provide 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 subject/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.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Study and Site Closure

Discontinuation of Study Sites

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

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.

Appendix 4. Blood Sampling Summary

This table summarizes the approximate 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.

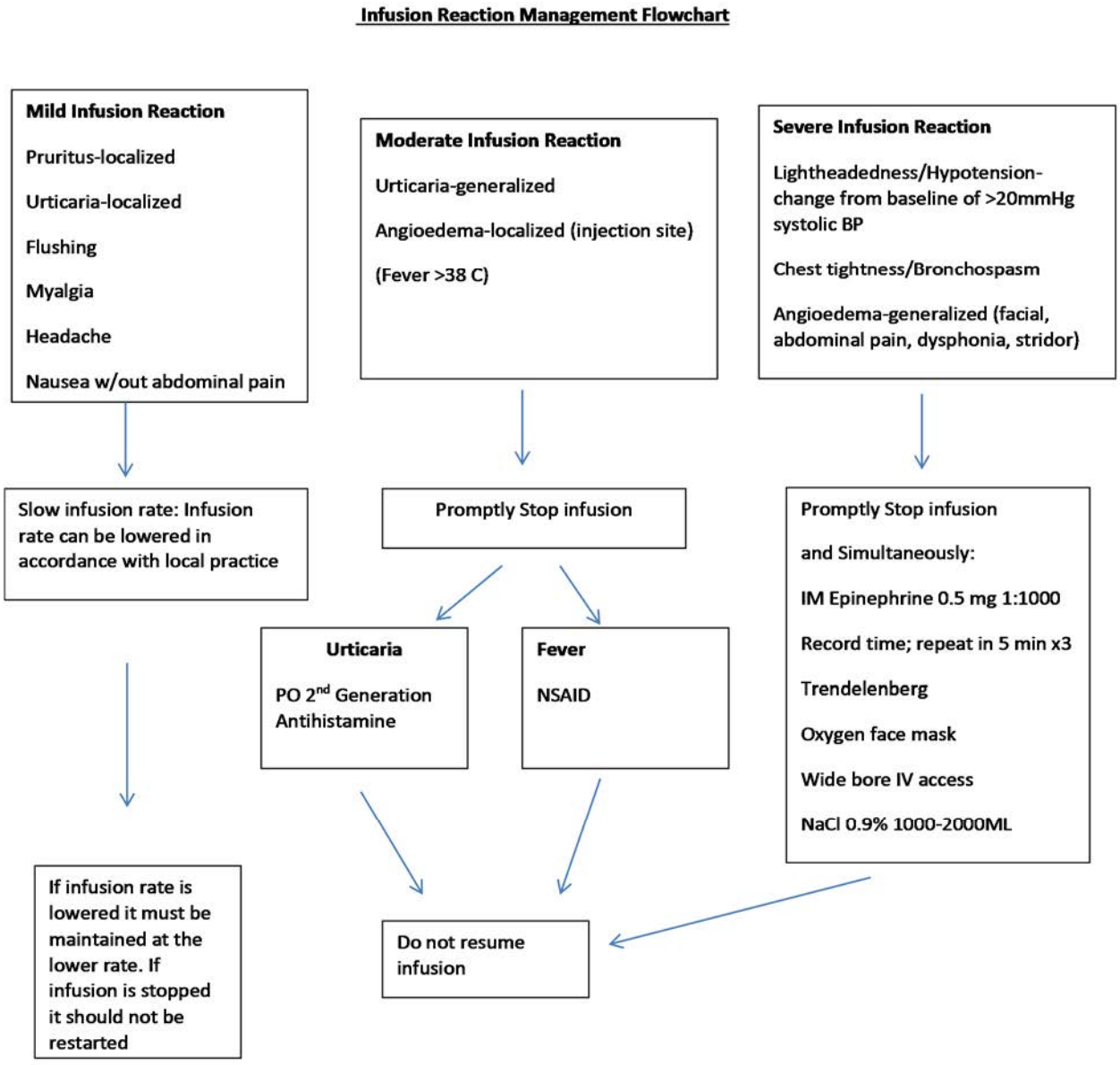
Protocol I8G-MC-LMDA Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	25	1	25
Clinical laboratory tests[a]	12	10	120
LY3303560 serum PK[b]	3	21 (+5)	63 (+15)
Blood discard for cannula patency	1	7	7
Plasma tau PD samples[b]	0.5	19 (+5)	9.5 (+2.5)
Plasma PD samples for storage[b]	10	16 (+5)	160 (+50)
Serum PD samples for storage[b]	2	6 (+5)	12 (+10)
Immunogenicity	7.5	7	52.5
Stored serum sample for possible exploratory immune safety	14	3	42
Sample for genetic testing	10	1	10
RNA testing	10	2	20
Total			521 (598.5)
Total for clinical purposes [rounded up to nearest 10 mL]			530 (600)

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

b A maximum of 5 additional time points per subject may be drawn during the study at the discretion of the investigator or sponsor. These additional samples may be drawn to measure LY3303560, tau or exploratory PD biomarker concentrations.

Appendix 5. Management of Infusion Reactions



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 7.4.2.2).

Source: Adapted from Lichtenstein et al. 2015

Appendix 6. Protocol Amendment I8G-MC-LMDA(b) Summary [Single-Dose, Dose-Escalation Study with LY3303560 to Evaluate the Safety, Tolerability, and Pharmacokinetics in Healthy Subjects and Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease]

Overview

Protocol I8G-MC-LMDA [Single-Dose, Dose-Escalation Study with LY3303560 to Evaluate the Safety, Tolerability, and Pharmacokinetics in Healthy Subjects and 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 (b) 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 single dose escalation in Study LMDA will be extended from the current maximum achieved dose of 1400 to 5600 mg. Higher doses of LY3303560 will be administered to healthy volunteers as 2 single dose cohorts of 2800 and 5600 mg. The mechanistic PK/PD model, which was used to predict an efficacious dose of 385-mg LY3303560 by estimating the steady-state reduction in aggregated tau in CSF, was updated based on recent nonclinical findings in monkey. The updated model now suggests that the predicted clinical dose of LY3303560 may be higher than what was previously predicted. The administration of higher doses of LY3303560 is also supported by preliminary safety and PK data from the preceding single-dose cohorts. LY3303560 is well tolerated when administered as a single dose up to 1400 mg. There were no dose-limiting AEs and no clinically significant changes in MRIs, ECGs, vital signs, neurological examinations, and safety laboratory tests. The PK of LY3303560 following single oral doses was approximately linear up to 1400 mg, supporting continued increasing exposure with LY3303560 dosing. The projected mean exposure at the highest dose of 5600 mg is expected to approximate the mean exposure observed in the 6-month toxicology studies in cynomolgus monkeys.
- The Bond and Lader, and Digit Span Forward and Backward tests have been added as additional safety measures in Cohorts 10 and 11 in order to assess potential CNS effects when high doses of LY3303560 are administered.
- Per request from the CRU, the screening visit window in Cohorts 8 and 9 has been increased from 42 to 70 days to allow greater flexibility for the patients.
- In Cohorts 8 and 9, per request from the CRU, the time point for the Visit 3 CSF sampling, vital signs, and ECG measurements has been amended from 48 to 36 hours.

- In Cohorts 8 and 9, orthostatic vital signs will not be measured during the first 36 hours; Sections 2 (Schedule of Activities) and 9.4.2 (Vital Signs) have been updated to clarify this. This is due to the feasibility of measuring orthostatic vital signs when the patient is in a supine position during serial CSF sampling.
- Appendix 5 (Management of Infusion Reactions) has been amended to correct an error in the flow diagram for the management of infusion reactions.
- 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.

1. Synopsis

Treatment Arms and Duration:

For all cohorts (except Cohort 5), subjects or patients will receive either LY3303560 or placebo as an IV single dose; the planned doses are 7, 21, 70, 210, 700, ~~and~~ 1400 ~~mg~~, 2800, and 5600 mg. In Cohort 5, it is intended that subjects will receive a single SC dose of 210 mg LY3303560, dependent on the observed safety profile from previous cohorts.

Number of Subject/Patients:

Cohorts 1 to 7, 10, and 11 (Healthy subjects): Up to ~~70~~90 subjects may be enrolled so that approximately ~~54~~70 subjects (8 subjects per cohort, except for Cohort 5 [n=6]), reach at least Day 29 of the study.

2. Schedule of Activities

Study Schedule Protocol I8G-MC-LMDA (Cohorts 1 to 7, 10, and 11, Healthy Subjects)

	Screen																		ED
Study Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	
Visit Window (days)										**±1**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Prior/concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X
Preexisting conditions/AEs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X
Alertness and attention assessments (Cohorts 10 and 11 only)		X	0			72[j]			X			X		X		X			X
Vitals (hours)[c,d]	X	X	0[e], 0.5[k], 3, 12	24	48	72	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X
LY3303560 serum PK (hours)[i]			0[e], 0.5[k], 2, 4, 12	24	48	72	96	120	144	X	X	X	X	X	X	X	X[l]	X[l]	X
Plasma tau PD samples (hours)[i]		X	0[e],0.5[k], 2, 4, 12	24	48	72	96	120	144	X	X	X		X		X	X[l]	X[l]	

[a] Subjects in Cohorts 1 to 4, ~~and~~ 6, 7, 10, and 11 will receive an IV single dose; subjects in Cohort 5 will receive a single SC dose.

[l] Cohorts 10 and 11 only.

Study Schedule Protocol I8G-MC-LMDA (Cohorts 8 and 9, Patients with AD)

	Screen																ED
Study Day	**~~42~~ 70 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	
Visit Window (days)										**±1**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	
Vitals (hours)[d,e]	X	X	0[f], 0.5[o], 3, 12	24, 36	~~48~~	72	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram (hours)[e,g]	X	X	0[f], 0.5[o], 3, 12	24, 36	~~48~~	72			X			X		X		X	X
CSF sampling for PK and PD evaluations (hours)[m]			0[f], 2, 4, 12	24, 36	~~48~~												

d Screening vital signs will be obtained in the sitting position (after at least 5 minutes sitting). For Visits 1 to 3, vital signs will be taken in the supine position only. For all other vital signs after study entry, subjects will rest in the supine position for at least 5 minutes and undergo supine blood pressure and pulse rate measurements. Subjects will sit for approximately 2 minutes then stand for approximately 2 minutes and undergo standing blood pressure and pulse rate measurements. If subjects are unable to stand, supine vital signs only will be recorded.

3.1. Study Rationale

[…]

Prior to this study, LY3303560 ~~has~~ had not been administered to humans. This first-in-human study will investigate the safety, tolerability, and pharmacokinetics (PK) of LY3303560 in healthy subjects and patients with AD. Safety and tolerability evaluations will be conducted over a wide range of single doses and dose escalation will not proceed until safety data from previous doses have been reviewed. This study will aim to assess whether a maximum-tolerated dose (MTD) can be established or to demonstrate the tolerability of a dose greater than the expected therapeutic dose. The data generated in this study will be used to help design subsequent clinical studies. The inclusion of Japanese subjects in this study will facilitate the inclusion of Japanese subjects in subsequent clinical trials.

3.2. Background

3.2.1. Preliminary Data from Cohorts 1 through 7

As of 07 February 2017, the single-dose escalation up to 1400 mg has been completed (Cohorts 1 to 7). A single subcutaneous (SC) cohort of 210 mg has also been completed (Cohort 5). No serious adverse events (SAEs) have been reported, and no subject has withdrawn from the study because of an adverse event (AE). A total of 27 AEs have been reported by a total of 16 subjects, irrespective of causality. The most common AEs reported were headache (4), upper respiratory infection (2), contact dermatitis (2), back pain (2), and influenza (2). A total of 7 AEs were deemed related to study drug by the investigator: headache (2) and hot flashes, feeling swollen, upper respiratory infection, vomiting, and cloudy mind (1 each). There have been no infusion reactions reported to date, and there have been no clinically significant findings in magnetic resonance imaging (MRI) scans. In addition, there have been no clinically significant changes in vital signs, electrocardiograms (ECGs), neurological examinations, and safety laboratory tests.

Preliminary PK data following single intravenous (IV) doses indicated that the exposure of LY3303560 was approximately linear up to 1400 mg. The observed clearance was approximately 180 mL/day, with a half-life of 2 to 3 weeks. A relative bioavailability of approximately 60% was calculated based on PK data from the 210-mg SC cohort. The observed PK profile of LY3303560 is consistent with the PK properties of an immunoglobulin (Ig) G antibody.

3.3. Benefit/Risk Assessment

The nonclinical safety information for LY3303560 detailed in the Investigator's Brochure (IB) adequately supports the transition from preclinical status to a clinical, single-dose study. On the basis of the nonclinical data, LY3303560 is not considered to be a high-risk compound. This protocol reflects the fact that LY3303560 had~~s~~ not been administered to humans prior to this

studystarting Study LMDApreviously, and to mitigate this risk, the study has been designed to be conducted in accordance with principles outlined in the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products. It is intended that sentinel dosing will be conducted for the first dose cohort to minimize risk to subjects. Sentinel dosing will also be conducted for Cohorts 10 and 11 (2800 and 5600 mg), the additional cohorts introduced in Amendment (b). Based on preliminary PK data from Cohorts 1 to 7, the mean exposure of LY3303560 at a dose of 5600 mg in Cohort 11 is predicted to approximate the no-observed-adverse-effect level (NOAEL) exposure observed in the monkey (see Section 5.5). Accordingly, in addition to review of safety data, the PK data from the 2800 mg dose will be analyzed and the projected exposure of 5600 mg will be reviewed prior to dose escalation. In addition, for Cohorts 10 and 11, alertness and attention assessments will be administered to assess potential central nervous system (CNS) effects.

Risks around immunogenicity and infusion reactions are considered to be monitorable and manageable at the planned dose range of 7 to 14005600 mg for LY3303560 in healthy subjects and patients with AD.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3303560 areis to be found in the IB.

5. Study Design

5.1. Overall Design

This is a Phase I, subject-/patient- and investigator-blind, placebo-controlled, randomized, parallel, single-ascending dose (SAD) study in healthy subjects and patients with mild cognitive impairment (MCI) due to AD or mild to moderate AD. The study has been designed to assess the safety, tolerability, and PK of single intravenous (IV) and subcutaneous (SC) doses of LY3303560. The planned doses to be explored are 7, 21, 70, 210, 700, and 1400, 2800, and 5600 mg.

Cohorts 1 to 7, 10, and 11 will consist of healthy subjects. The planned number of subjects per cohort will be 8 (6:2, LY3303560: placebo), except for Cohort 5 (6 subjects on LY3303560). For each IV cohort, the intention is to enroll 4 subjects of Japanese origin (first generation) and 4 subjects of non-Japanese origin, but enrollment to a cohort will not be contingent upon fulfilling these requirements. The minimum requirement is to enroll 4 Japanese subjects to at least 3 of the IV cohorts, including the highest dose level cohort (a minimum of 12 Japanese subjects in total). However, if enrollment of Japanese subjects is slower than anticipated, cohorts may complete enrollment with non-Japanese subjects and proceed to dose escalation without waiting for the desired number of Japanese subjects to be enrolled. If 4 subjects of Japanese origin are not included in a cohort initially, additional subjects may subsequently be enrolled to achieve a maximum of 4 subjects of Japanese origin, if agreed between the sponsor and investigator. Although not required, it is preferred that the non-Japanese subjects are not Asian. The randomization will be such that the placebo assignments for the cohorts enrolling Japanese and non-Japanese subjects will be balanced between these 2 populations. Cohorts 8 and 9 will

consist of patients with MCI due to AD or mild to moderate AD. The number of patients (LY3303560: placebo) in each cohort will be 6:2 patients.

Subjects/patients will be admitted to the clinical research unit (CRU) on Day -1 and eligibility will be confirmed. Safety will be monitored by AEs, ~~electrocardiograms (~~ECGs~~)~~, vital signs (blood pressure and heart rate), physical examinations, neurological examinations and safety laboratory tests; and additionally for Cohorts 10 and 11, the Bond and Lader, and the Digit Span Forward and Backward test. ~~Cohorts 8 and 9~~The Columbia Suicide Severity Rating Scale (C-SSRS) will be assessed in Cohorts 8 and 9. Subjects/patients will remain resident in the CRU and safety will be monitored daily until discharge from the CRU on Day 4 at the earliest, then at regular intervals thereafter (see the Schedule of Activities in Section 2). In addition, each subject/patient will have 1 baseline ~~magnetic resonance imaging (~~MRI~~)~~ scan prior to dosing with LY3303560 or placebo, then approximately 2 weeks and 3 months after dosing, primarily for the assessment of any potential imaging abnormalities. In Cohorts 8 and 9, cerebrospinal fluid (CSF) will be obtained by an indwelling lumbar catheter prior to dosing with LY3303560 or placebo, and up to 48 hours after dosing with LY3303560 or placebo to measure CSF levels of LY3303560 and tau related pharmacodynamic (PD) biomarkers.

[…]

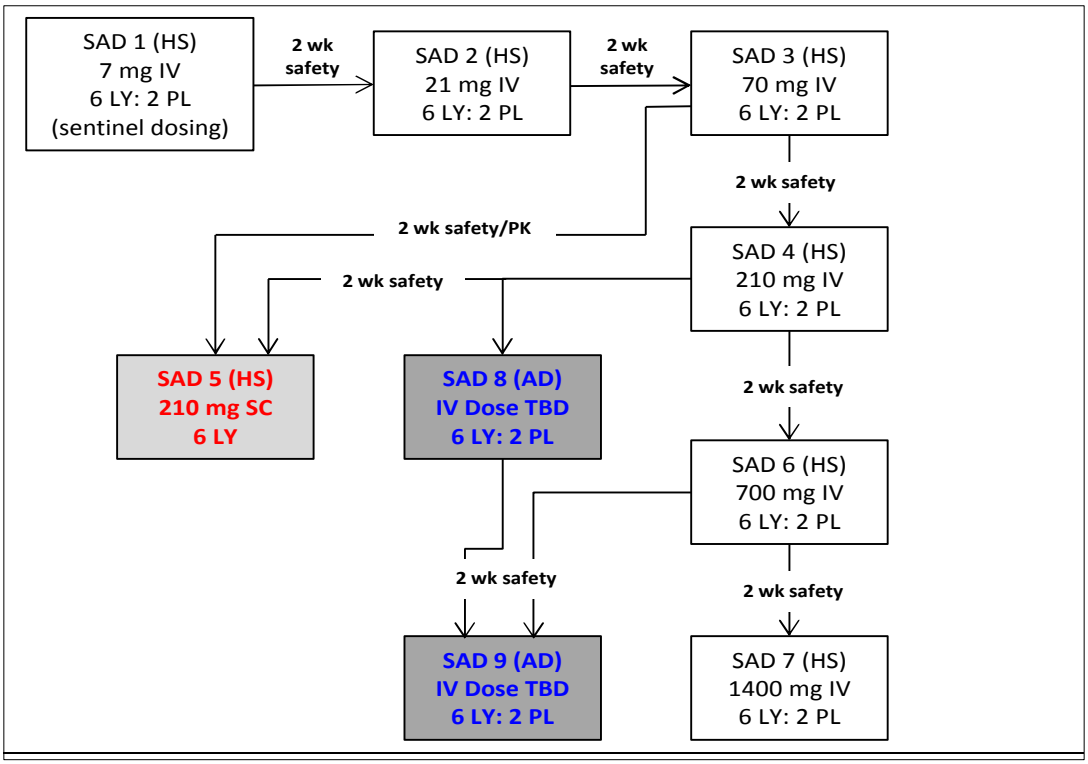
Sentinel dosing will be performed for Cohorts 1, 10, and 11. Two subjects will be dosed initially (1 assigned to LY3303560 and 1 to placebo) and followed to 48 hours postdose before the remaining subjects in that cohort are dosed. The remaining 6 subjects may be dosed on the same day, at appropriate intervals. If there are no issues with the first cohort, subjects in ~~subsequent c~~Cohorts ~~1~~2 to 9 may be dosed on the same day at appropriate intervals, or on separate days, as practical, however, the timing of dosing will be staggered such that subjects will not be dosed simultaneously.

The highest dose may be adjusted based on emerging data, but it is intended that the magnitude of the escalation between dose levels will not exceed a half-log interval (approximately 3-fold) and a maximum dose of ~~1400~~ 5600 mg LY3303560 will not be exceeded. All subjects in a particular cohort must have been dosed and safety data for 2 weeks after dosing must be reviewed from at least 4 subjects on LY3303560 and 1 subject on placebo, prior to dose escalation. Additionally, PK data from Cohort 10 will be reviewed prior to escalation to Cohort 11. If criteria for stopping rules are not met (see Section7.4.1), then the next dose cohort will be enrolled with next planned dose increases until ~~1400~~ 5600 mg or stopping criteria are met. If a termination dose is reached, a dose reduction of at least one-half of the termination dose may be tested in one of the remaining dose cohorts, if deemed appropriate.

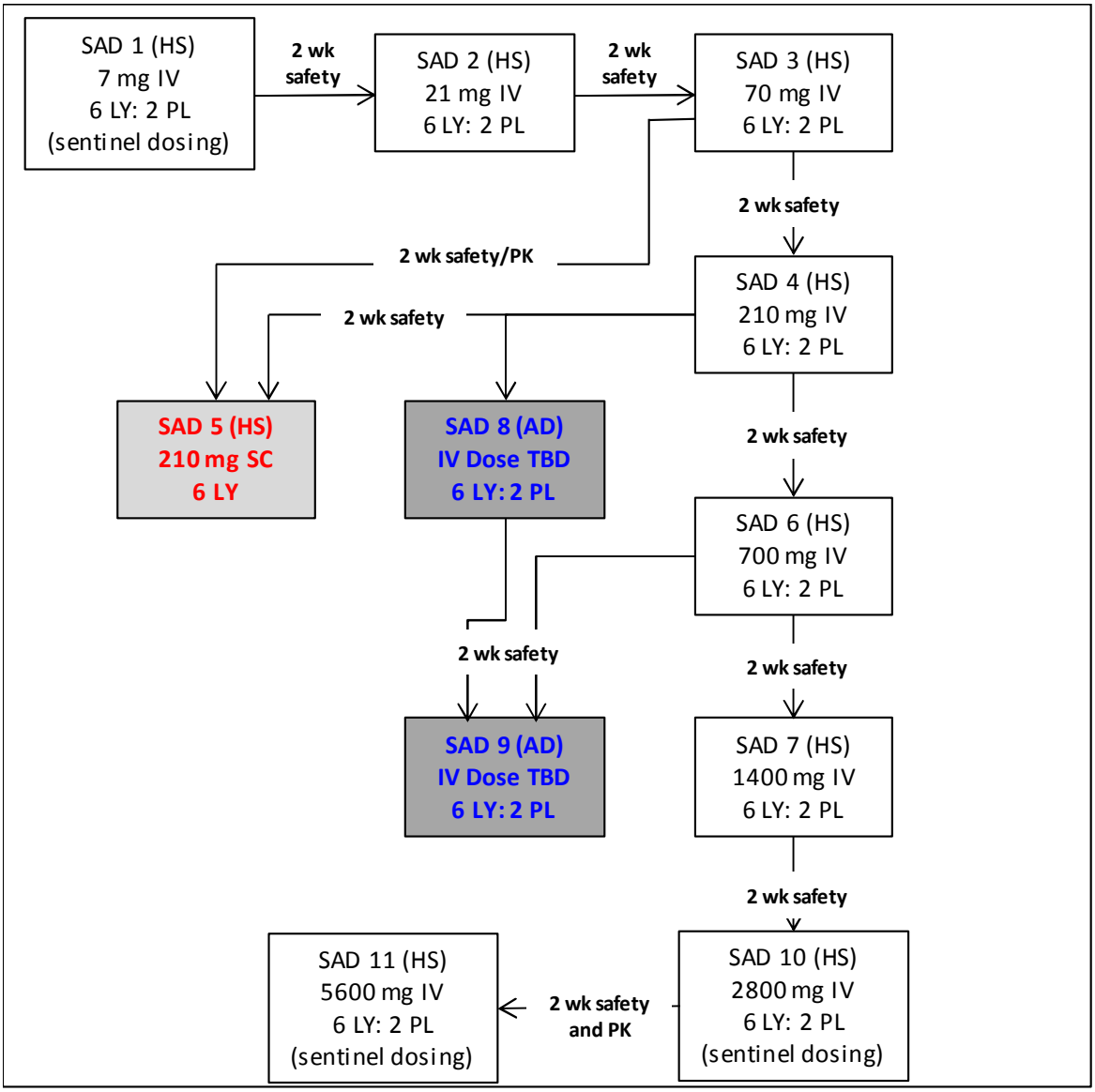
The PK data for LY3303560 obtained during the study may be used to assist in dose escalation decisions, but such data are not required for dose escalation, except for dose escalation from Cohorts 10 and 11. If the PK data reveal that the current sampling schedule does not allow for an adequate characterization of the PK profile, the blood sampling schedule for subsequent dose administrations may be adjusted. A maximum of 5 additional PK samples per subject may be

allowed if indicated by emerging data. See Section 10.3.7 for further information about PK reviews.

Previous diagram:



New diagram:



5.2. Number of Participants

For Cohorts 1 to 7, 10, and 11, up to ~~70~~90 healthy subjects may be enrolled so that approximately ~~54~~ 70 subjects (8 subjects per cohort, except for Cohort 5 [n=6]) reach at least Day 29 of the study.

5.4. Scientific Rationale for Study Design

[…]

Given planned doses for Cohorts 10 and 11 will approximate the NOAEL exposure in monkeys, sentinel dosing will also be conducted in these cohorts. In addition, the Bond and Lader, and Digit Span Forward and Backward test will be measured in these cohorts to assess potential CNS effects.

5.5. Justification for Dose

The proposed dose range is 7 to ~~1400~~ 5600 mg LY3303560. The doses were selected based upon the analysis of nonclinical PK, efficacy and toxicology data from studies conducted in Tg4510 tau transgenic mice expressing human four-repeat tau with the P301L mutation that is linked to hereditary tauopathy and cynomolgus monkeys.

A mechanistic PK/PD model was used to predict a clinically relevant LY3303560 dose range by estimating the steady-state reduction in aggregated tau in CSF at various doses. The CSF was used as a surrogate matrix to understand the disposition of aggregated tau in the ~~central nervous system~~ CNS. Model predictions suggested a clinical dose of 10.5 mg LY3303560 administered every 4 weeks (Q4W) and 385 mg LY3303560 Q4W will decrease CSF aggregated tau by approximately 20% and 90%, respectively. However, an update to the PK/PD model based on recent nonclinical findings in monkey suggest that the predicted clinical dose of LY3303560 may be higher than what was previously predicted. As such, the maximum dose to be evaluated in this study has been increased from 1400 to 5600 mg. A dose of 10.5 mg (20% decrease in CSF aggregated tau) is defined as the minimally anticipated biological effect level (MABEL). Therefore, a starting dose of 7 mg LY3303560 (approximately 0.1 mg/kg for a 70-kg person) is below the MABEL and thus considered an appropriate starting dose.

The safety of LY3303560 was assessed in ~~a~~ 5-week and 6-month toxicology studies~~y~~ in cynomolgus monkeys which included evaluation of safety pharmacology and toxicokinetics. The cynomolgus monkey is an appropriate large animal species to evaluate the safety of LY3303560 with respect to monomeric tau. The administration of LY3303560 in monkeys up to a maximum dose of 200 mg/kg/week (bolus IV) for 5 weeks or 6 months resulted in no compound-related adverse findings. It is anticipated that the mean exposure resulting from doses of LY3303560 to be administered in Cohorts 10 and 11 will approximate the mean exposure in monkeys dosed 200 mg/kg LY3303560 (the NOAEL), see Table LMDA.2. The safety and PK data from doses up to 1400 mg LY3303560 also support dosing in Cohorts 10 and 11. The safety of LY3303560 was also assessed in ~~a~~ 5-week and 6-month toxicology studies~~y~~ in a Tg4510 mouse model. The Tg4510 transgenic mouse is an appropriate species to evaluate the safety of LY3303560 with respect to binding aggregated tau and small tau fibrils. The administration of LY3303560 to Tg4510 mice up to a maximum SC dose of 200 mg/kg resulted in no compound-related adverse findings.

~~The nonclinical safety profile of LY3303560 in monkeys and Tg4510 mice supports clinical development dosing up to the planned dose of 20 mg/kg (1400 mg for a 70 kg person) based on ICH S6 guidelines (Table LMDA.2).~~

Table LMDA.6. Margin of Safety for Subcutaneous/Intravenous Administration of LY3303560 Based on Administered Dose and Predicted Exposure

	Dose	Dose Multiple[a] (Starting dose/ Maximum dose)	AUC0-168hr (µg•day~~hr~~/mL)	Exposure Multiple[a] (Starting dose/ Maximum dose)
Human[b]				
Starting Dose	7 mg (0.1 mg/kg)	–	~~799~~36.1[c]	–
Maximum Dose	~~1400~~ 5600 mg (8~~2~~0 mg/kg)	–	~~159,817~~35,400	–
Tg4510 mouse NOAEL[~~e~~d]	200 mg/kg	2000/2.5~~10~~	~~509,000~~15,458[e]	428~~637~~/0.4~~3.2~~
Monkey NOAEL[~~d~~f]	200 mg/kg	2000/2.5~~10~~	~~995,500~~47,083[e]	1304~~1,246~~/1.3

Abbreviations: $AUC_{0\text{-}168hr}$ = area under the serum concentration time curve from time zero through 168 hours postdose; NOAEL = no-observed-adverse-effect level~~; NOEL = no-observed-effect level~~.

a Dose multiple is the dose in animals divided by the dose in humans based on mg/kg basis. Exposure multiple is the calculated AUC in animals divided by the predicted AUC in humans.

b Clinical dose assumes a 70 kg subject; 7 mg = 0.1 mg/kg, ~~1400~~ 5600 mg = ~~20~~ 80 mg/kg.

c Observed data from Study LMDA (preliminary).

~~e~~d NOAEL determined in a ~~5-week~~6-month repeat dose toxicity study (Study 832~~1506~~6195).

e AUC is mean of male and female.

~~d~~f NOAEL determined in a ~~5-week~~6-month repeat dose toxicity study (Study 832~~1505~~6196).

Overall, the proposed starting dose of 7 mg LY3303560 is considered appropriate as it is below the calculated MABEL. ~~, and t~~The ~~proposed~~ projected mean exposure at the highest planned dose of 5600~~1400~~ mg is expected to approximate the NOAEL exposure observed in the ~~supported by the top dose of 200 mg/kg in the 1-month monkey~~ 6-month toxicology study in cynomolgus monkeys. Prior to dosing Cohort 11 (5600 mg), LY3303560 PK data from Cohort 10 (2800 mg) will be reviewed and the exposure for Cohort 11 (5600 mg) will be predicted. The dose to be administered in Cohort 11 may be adjusted if necessary to ensure the projected mean exposure does not exceed the mean monkey NOAEL exposure of 47,083 µg•day/mL.

6. Study Population

[…]

Screening may occur up to 28 days before enrollment for Cohorts 1 to 7, 10, and 11 (healthy subjects). Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Screening may occur up to ~~42~~70 days before enrollment for Cohorts 8 and 9 (patients with AD). Patients who are not enrolled within ~~42~~70 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility and exceptions to the ~~42~~70-day screening window may be granted as follows:

- ~~MRI: 56 days~~

- free and cued selective reminding test with immediate recall (FCSRT-IR), Mini Mental State Examination (MMSE), and Clinical Dementia Rating (CDR): 90 days
- florbetapir imaging: 120 days

6.1. Inclusion Criteria

[1a] For Cohorts 1 to 7, 10, and 11, are overtly healthy, as determined by medical history and physical examination

[3] are at least 30 years old at the time of screening for Cohorts 1 to 7, 10, and 11. For Cohorts 8 and 9, are at least 50 years old at the time of screening

[8] for healthy subjects (Cohorts 1 to 7, 10, and 11): are able and willing to give signed informed consent. For Cohorts 8 and 9, patients not capable of providing consent must provide assent; informed consent must be provided by a legally authorized representative

6.2. Exclusion Criteria

[28] for healthy subjects (Cohorts 1 to 7, 10, and 11): have used or intend to use over-the-counter or prescription medication (including herbal medications) within 7 days prior to dosing or during the study with the exception of vitamins and mineral supplements (not providing >100% of the recommended dietary allowance); thyroid replacement and/or estrogen hormone replacement; and occasional paracetamol/acetaminophen. If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the sponsor.

7.1. Treatment Administered

This study involves a comparison of LY3303560 and placebo, over a planned dose range of 7 to ~~1400~~ 5600 mg. Table LMDA.3 shows the treatment regimens.

For all cohorts except Cohorts 5, ~~and~~ 7, 10, and 11, the IP will be administered as a slow IV infusion over at least 30 minutes. Every attempt should be made to complete the infusion within 60 minutes. The infusion time for Cohorts 7 and 10 should be at least 60~~90~~ minutes, and for Cohort 11, at least 90 minutes.

7.4.1. Dose Decision/Escalation

[…]

Safety data will be the primary criteria for the dose escalation. In addition, if available at the time of dose escalation decision, PK (C_{max}, AUC, and total clearance [CL]) results will be used as supporting data for dose escalation, but such data are not required, aside from dose escalation from Cohort 10 to 11 (see below). No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly clinical pharmacologist/CRP.

[…]

For dose escalation from Cohort 10 to 11, LY3303560 PK data from Cohort 10 will be analyzed and the exposure at 5600 mg LY3303560 re-projected based on the observed PK at 2800 mg LY3303560. The PK projection will be reviewed before escalation to Cohort 11 and the dose to be administered in Cohort 11 may be adjusted if necessary to ensure the projected mean exposure does not exceed the mean monkey NOAEL exposure of 47,083 µg•day/mL.

9.4.2. Vital Signs

[…]

Screening vital signs will be obtained in the sitting position (after at least 5 minutes sitting). In Cohorts 8 and 9 (patients with AD), for Visits 1 to 3, vital signs will be measured in the supine position only. For all other vital signs after study entry, subjects will rest in the supine position for at least 5 minutes and undergo supine blood pressure and pulse rate measurements. Subjects will sit for approximately 2 minutes then stand for approximately 2 minutes and undergo standing blood pressure and pulse rate measurements. If subjects are unable to stand, supine vital signs only will be recorded. If the subject is unable to stand or sit, omission of the standing or sitting vital signs will not be considered a protocol violation.

9.4.4.2. Alertness and Attention Assessments (Cohorts 10 and 11)

The Bond and Lader Visual Analog Scale (VAS), and Digit Span Forward and Backward Test will be performed according to the Schedule of Activities (Section 2).

9.4.4.2.1. Bond and Lader VAS

The Bond and Lader VAS (Bond et al. 1974) consists of 16 mood self-rating 100-mm lines between 2 opposite adjectives. The subject has to indicate on the line how he or she is feeling at the time of evaluation. The response is scored by measuring the distance in millimeters between the left end of the line and the subject's mark. This questionnaire derives 3 factors that assess self-rated alertness, self-rated calmness, and self-rated contentment. Approximately 5 minutes is needed to complete the questionnaire. Subjects will complete a training session for the VAS as

indicated in the Schedule of Activities (Section 2). This test will be completed approximately 5 minutes before all other assessments at the same time point.

9.4.4.2.2. Digit Span Forward and Backward Test

The Digit Span Forward and Backward subtest (Wechsler 2009) of the Wechsler Adult Intelligence Scale-IV (Wechsler 2008) is a brief test of attention. Digit Span is a series of orally presented number sequences that the examinee repeats verbatim for Digits Forward and in reverse for Digits Backward (Wechsler 2009).

Note: Subsequent heading numbering for the Magnetic Resonance Imaging, Injection-Site Assessments (Cohort 5), Columbia Suicide Severity Rating Scale (Cohorts 8 and 9), Imaging (Cohorts 8 and 9), Radiation Doses Associated with PET Imaging sections has been updated with the addition of the Alertness and Attention Assessments section.

10.1. Sample Size Determination

[…]

Up to ~~70~~90 healthy subjects may be enrolled to ensure that approximately ~~54~~70 subjects (8 subjects per cohort, except for Cohort 5 [n=6]) reach at least Day 29 of the study.

10.3.1.2. Statistical Evaluation of Safety

[…]

For Cohorts 10 and 11, results from the Bond and Lader VAS, and Digit Span Forward and Backward tests will be summarized by parameter and time point, including change from baseline.

10.3.2.2. Pharmacokinetic Statistical Inference

The serum PK parameters, C_{max} and $AUC_{0-\infty}$ or $AUC_{0-t_{last}}$, for LY3303560 obtained for healthy subjects (IV only) will be evaluated to estimate the dose-exposure proportionality of LY3303560 using a linear-effects power model (Smith et al. 2000). In this model, log-transformed dose will be the independent variable, and subject will be a random effect. Both C_{max} and AUC will be log-transformed prior to analysis. The least-square means for each treatment together with the treatment differences and associated 90% confidence intervals (CIs) will be estimated from the model. These estimates will be back-transformed to present geometric means, the ratios of geometric means, and the corresponding 90% CIs. Dose-exposure analysis will be conducted using the healthy subject IV cohorts (Cohorts 1, 2, 3, 4, 6, ~~and~~ 7, 10, and 11). Exploratory analyses of Japanese and non-Japanese subjects may be conducted. Additional dose-exposure analyses may be conducted using patient data.

11. References

Bond AJ, James DC, Lader MH. Physiological and psychological measures in anxious patients. *Psychol Med*. 1974;4(4):364-373.

Wechsler D. WAIS-IV administration and scoring manual. 4th ed. San Antonio, TX: Pearson; 2008.

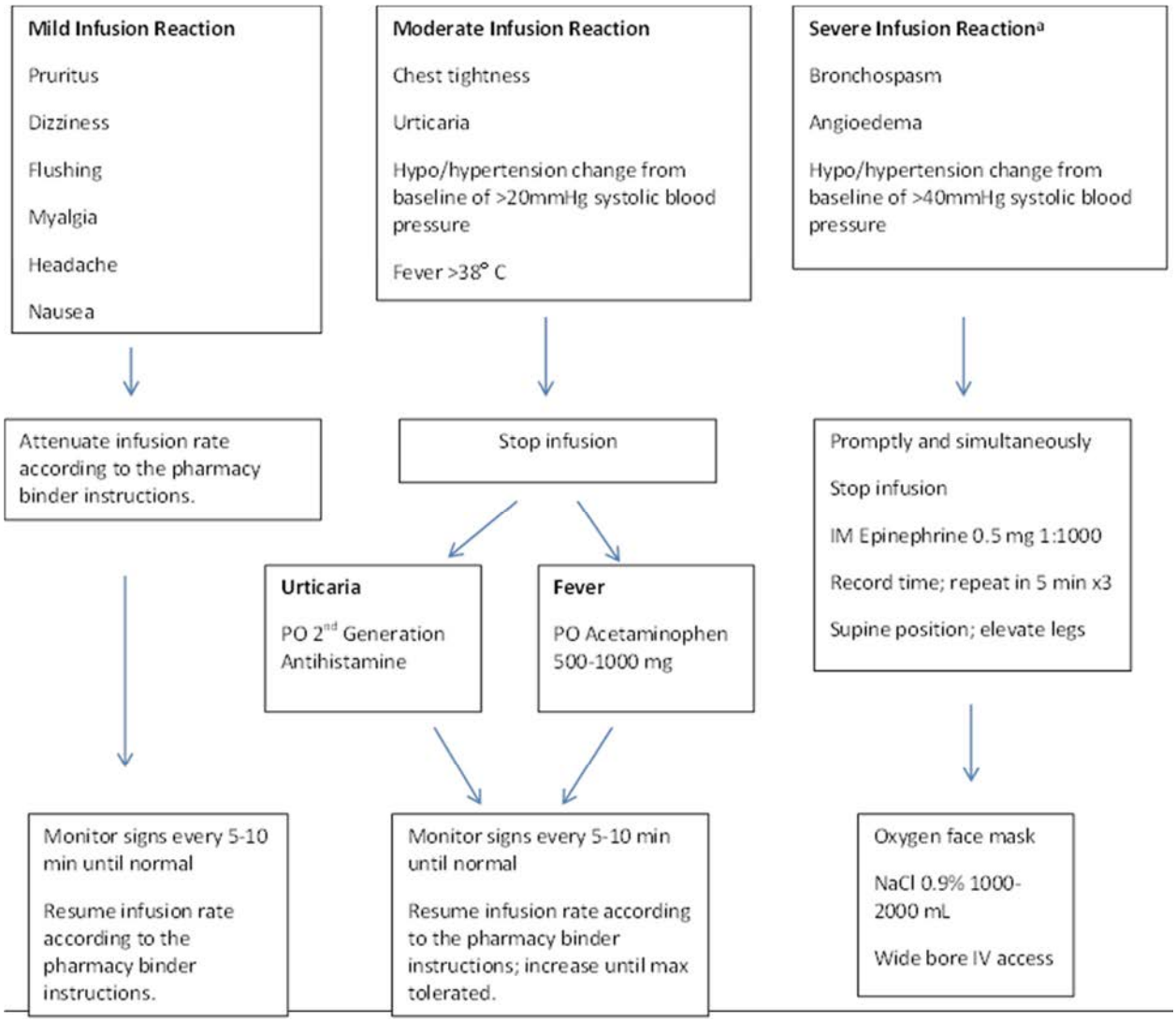
Wechsler D. Wechsler Memory Scale (WMS–IV) technical and interpretive manual. 4th ed. San Antonio, TX: Pearson; 2009.

Appendix 4. Blood Sampling Summary

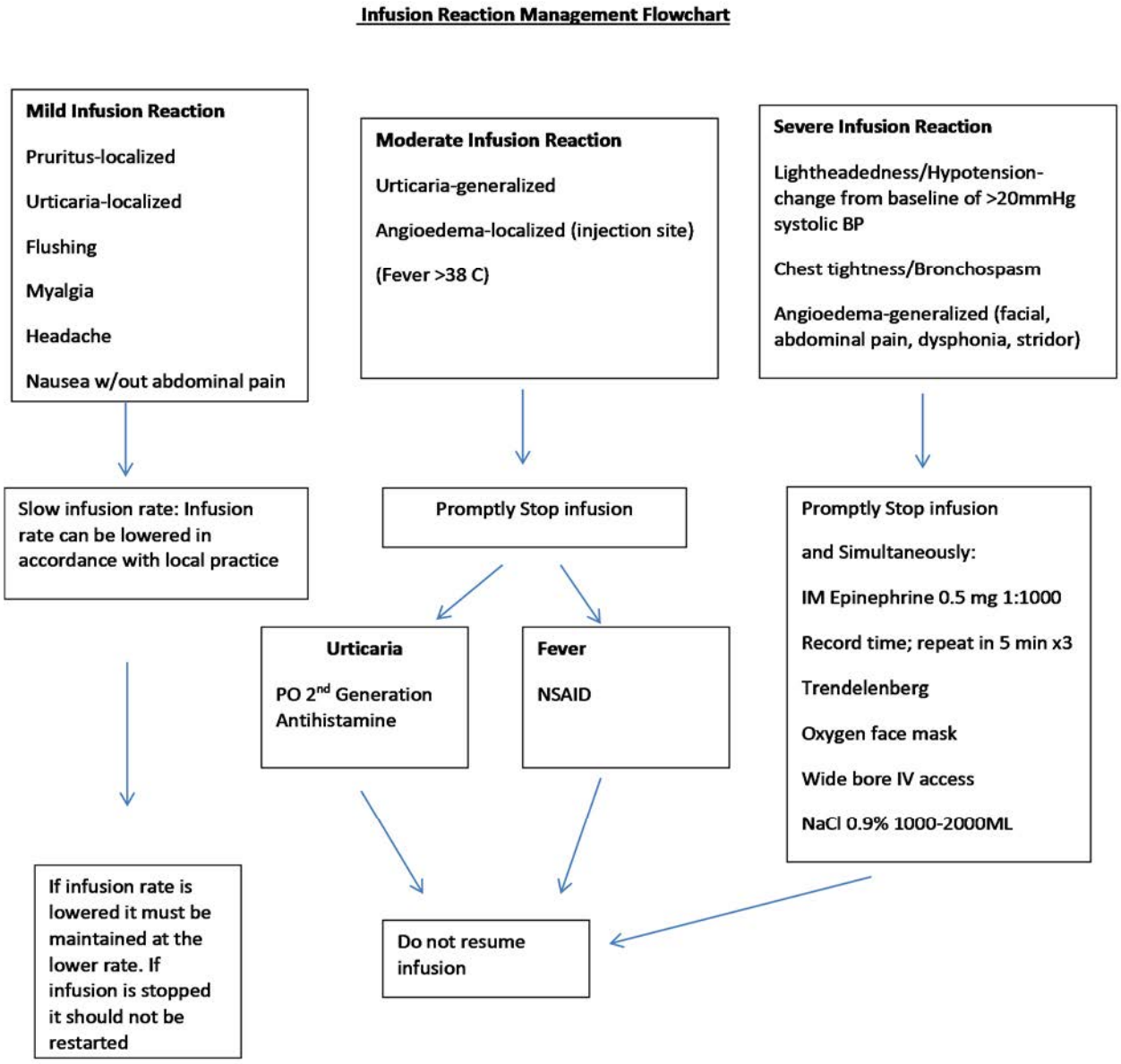
Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	25	1	25
Clinical laboratory tests[a]	12	10	120
LY3303560 serum PK[b]	3	~~19~~ 21 (+5)	~~57~~ 63 (+15)
Blood discard for cannula patency	1	7	7
Plasma tau PD samples[b]	0.5	~~17~~ 19 (+5)	~~8~~9.5 (+2.5)
Plasma PD samples for storage[b]	10	16 (+5)	160 (+50)
Serum PD samples for storage[b]	2	6 (+5)	12 (+10)
Immunogenicity	7.5	7	52.5
Stored serum sample for possible exploratory immune safety	14	3	42
Sample for genetic testing	10	1	10
RNA testing	10	2	20
Total			~~514~~ 521 (~~573~~598.5)
Total for clinical purposes [rounded up to nearest 10 mL]			~~520~~ 530 (~~580~~600)

Appendix 5. Management of Infusion Reactions

Previous diagram:



New diagram:



Abbreviations: BP = blood pressure; IM = intramuscular; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = by mouth.

[a] Continue supportive care in accordance with the symptoms/signs (Section 7.4.2.2).

Source: Adapted from Lichtenstein et al. 2015

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