Protocol I8G-MC-LMDD(d)
Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LY3303560 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

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Confidential Information

LY3303560

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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Table of Contents

Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LY3303560 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

1. Protocol Synopsis

Title of Study:
Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LY3303560 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

Rationale:
Lilly is developing LY3303560 for the treatment of Alzheimer's disease (AD). This study (I8G-MC-LMDD [LMDD]) will be the second clinical study of LY3303560 and will evaluate the effects of repeated every 4 week (Q4W) administrations in patients with mild cognitive impairment (MCI) due to AD or mild to moderate AD over 6 months (7 doses), with the option of extending the treatment period up to 12 months (up to 6 further doses).

The study aims to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple doses of LY3303560 to define an appropriate dose range for further clinical research.

Objectives/Endpoints:

Objectives	Endpoints
Primary To assess the safety and tolerability after 16 weeks of multiple doses of LY3303560 in patients with MCI due to AD or mild to moderate AD	Safety and tolerability will be assessed by monitoring treatment-emergent adverse events (TEAEs)
Secondary • To assess the PK of LY3303560 in serum following multiple intravenous (IV) doses of LY3303560 in patients with MCI due to AD or mild to moderate AD	Maximum serum concentration (C_{max}) and the area under the serum concentration time curve during the dosing interval ($AUC\tau$)

Summary of Study Design:

This is a Phase 1b, multi-site, patient- and investigator-blind, placebo controlled, parallel-group study in patients with MCI due to AD or mild to moderate AD to assess the safety, tolerability, PK and PD of multiple IV doses of LY3303560.

Treatment Arms and Duration:

Patients will receive either LY3303560 or placebo as an IV infusion every 4 weeks (7 doses), after which they will be given the option of continuing the treatment up to 49 weeks (up to 6 further doses); the planned doses for Cohorts 1 and 2 are 70 and 210 mg, respectively.

Number of Patients:

A maximum of 24 patients will be enrolled.

In each cohort, up to 12 patients may be enrolled so that approximately 8 patients per cohort (6 LY3303560: 2 placebo) provide safety and PK data to steady state.

Statistical Analysis:

Safety: All summary statistics will be provided by cohort and visit. Patients who received placebo from both cohorts may be pooled into 1 group.

Safety parameters will be assessed including adverse events (AEs), magnetic resonance imaging (MRI), safety laboratory parameters, vital signs, and electrocardiogram (ECG) parameters. The parameters will be listed and summarised using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

Shift tables will be constructed for each dose group to assess the incidence of and changes in vasogenic oedema and microhaemorrhage counts pre- and post-dose based on MRI.

Suicide-related thoughts and behaviours based on the Columbia Suicide Severity Rating Scale (C-SSRS) will be listed by patient. Only time points and patients that show suicidal ideation/behaviour will be displayed (i.e., not all of the "no" responses will be displayed).

Potential QTc prolongation will be assessed using plots of PK data versus QTc values and providing frequencies by treatment for the following: the number of patients experiencing a maximum increase from baseline in QTcF interval according to the following categories - >30 ms and >60 ms; the number of patients with QTcF postdose values according to the following categories - >450 ms, >480 ms and >500 ms.

Pharmacokinetics: Pharmacokinetic parameters, including maximum drug concentration (C_{max}) and area under the concentration curve during the dosing interval ($AUC\tau$), will be calculated using standard non-compartmental methods of analysis and/or model-based approaches.

Imaging: Summary statistics of the flortaucipir F 18 standardised uptake value ratio (SUVr) will be provided by treatment (70 and 210 mg, and placebo) and visit (baseline and Visit 13 or Visit 20). Summary statistics of change from baseline and percentage change from baseline in SUVr will also be provided. Summary statistics may also be provided for SUVrs in individual and other composite brain regions if needed.

Changes in regional brain volume and functional connectivity in brain networks captured by MRI over the course of the study will be explored and summarised. Magnetic resonance imaging will be obtained every 8-12 weeks; therefore, a mixed model repeated measures (MMRM) may be conducted fitting baseline, treatment and study visit as fixed effects.

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

2. Schedule of Activities

2.1. Screening (Visit 1)

Study Schedule Protocol I8G-MC-LMDD (Screening Period)

		Comments
Visit	V1	Screening tests may occur up to 90 days before study drug administration. Tests may be conducted over approximately 3-5 screening visit days.
Day Relative to First Dose	-90	
Study Entry and Administrative Procedures		
Informed consent (before procedures/tests)	X	
Patient number assigned	X	
Demographics, height, weight, and habits	X	
Inclusion/exclusion review	X	
Previous/concomitant medications	X	
Preexisting conditions/AEs	X	
Cognitive Assessments		
MMSE	X	Cognitive assessments need not be done on the same visit day, but should be completed in the following order if done on the same day: 1) MMSE, 2) FCSRT-IR, 3) CDR, and 4) dCDT
FCSRT-IR	X	
CDR	X	
dCDT	X	
Safety Assessments		
Physical/neurological exam	X	
Single 12-lead digital ECG	X	
Vital signs	X	Supine blood pressure and pulse rate
C-SSRS (child)/SHSF	X	If the investigator determines that suicide-related behaviours have occurred, the Lilly SHSF and SHFU forms will be used to collect additional information to allow for a more complete assessment of these behaviours
Laboratory Assessments (local laboratory)		
Coagulation tests	X	
Clinical laboratory tests	X	See Appendix 2, Clinical Laboratory Tests, for details.
Imaging		
Lumbar x-ray	X	A lumbar x-ray may be performed to rule out potential contraindications to an LP. If an x-ray was performed within 12 months of screening, it may be used.
MRI	X	
Amyloid scan (if not previously performed)	X	Any previously taken positive amyloid scan must be reviewed by central reader to confirm amyloid status. Amyloid PET tracers may include, but are not limited to, florbetapir, florbetaben, flutemetamol.

Abbreviations: AE = adverse event; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale; dCDT = digital clock drawing test; ECG = electrocardiogram; FCSRT-IR = Free and Cued Selective Reminding Test with Immediate Recall; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; SHSF = Self-Harm Supplement Form; SHFU = Self-Harm Follow-Up.

2.2. MAD Treatment Period (Visits 2 to 19)

Study Schedule Protocol I8G-MC-LMDD
MAD Treatment Period (Visits 2 through 19)

Visit	V2[a] Rand	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19
Day Relative to First Dose	-8	1[b]	2	4	8	15	29[b]	57[b]	85[b]	113[b]	141[b]	169[b]	197[b]	225[b]	253[b]	281[b]	309[b]	337[b]
Week		1	1	1	2	3	5	9	13	17	21	25	29	33	37	41	45	49
Tolerance Interval for Visit (days)	±7[a]	0	±4 h	±1	±1	±1	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Dosing																		
Study medication administered		D1					D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13
Administrative Procedures																		
Body weight	X											0						0
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion review	X																	
Preexisting conditions/AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cognitive Assessments and Functional Scales[c,d]																		
ADAS-Cog_{14}	X											X						
ADCS-MCI-ADL24	X											X						
MMSE	X											X						
NTB	X											X						
dCDT	X						X	X	X	X	X	X	X	X	X	X	X	
Safety Assessments																		
Vital signs	X	0, 0.5, 2	24	72	X	X	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2
C-SSRS/SHSF	X	0	X	X	X	X	0	0	0	0	0	0	0	0	0	0	0	0
Physical examination		0			X			0	0	0	0	0	0	0	0	0	0	0
Neurological examination		0	24		X	X	0	0	0	0	0	0	0	0	0	0	0	0
Triplicate 12-lead digital ECG	X	0, 0.5, 2	24	72	X	X	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2	0, 0.5, 2

continued

Study Schedule Protocol I8G-MC-LMDD
MAD Treatment Period (Visits 2 through 19) (concluded)

Visit	V2[a] Rand	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19
Day Relative to First Dose	-8	1[b]	2	4	8	15	29[b]	57[b]	85[b]	113[b]	141[b]	169[b]	197[b]	225[b]	253[b]	281[b]	309[b]	337[b]
Week		1	1	1	2	3	5	9	13	17	21	25	29	33	37	41	45	49
Tolerance Interval for Visit (days)	±7[a]	0	±4 h	±1	±1	±1	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Dosing																		
Study medication administered		D1					D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13
Imaging																		
MRI[f]							X		X			X			X			X
Flortaucipir F 18 PET[d,h]	X[g]											X[h]						X[h]
Laboratory Assessments (central laboratory unless otherwise noted)																		
Lumbar puncture[d,j]	X[i]											X[l]						X[l]
Blood RNA	X						X											X
Pharmacogenetic sample	X																	
Clinical laboratory tests	X (local lab)	0	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Coagulation tests (local laboratory)[j,k]	X											X						X
Serum LY3303560 PK (hours)[e]		0.5, 2, 4, 8	24		X	X	0, 0.5, 2, 4, 8	0, 0.5, 2, 4, 8	0		0	0, 0.5, 2, 4, 8			0			0, 0.5, 2, 4, 8
Serum for immunogenicity	X				X	X	0		X			0			0			0
Plasma Tau PD (hours)[e]		0, 0.5, 2, 4, 8	24		X	X	0, 0.5, 2, 4, 8	0, 0.5, 2, 4, 8	0		0	0, 0.5, 2, 4, 8			0			0, 0.5, 2, 4, 8
Stored EDTA plasma and serum		0	24		X		0	0	0	0	0	0			0			0
Stored serum for possible exploratory immune safety laboratory tests	X								X			X			X			

Abbreviations: ADAS-Cog14 = 14-item Alzheimer's Disease Assessment Scale – Cognition; ADCS-MCI-ADL24 = 24-question Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients; AE = adverse event; CDR = Clinical Dementia Rating; CRF = case report form; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; D = dose; dCDT = digital clock drawing test; ECG = electrocardiogram; ED = early discontinuation; EDTA = ethylene diamine tetraacetic acid; FU = follow-up; IV = intravenous; LP = lumbar puncture; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NTB = Neuropsychological Test Battery; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; rand = randomisation; RNA = ribonucleic acid; SC = subcutaneous; SHSF = Self-Harm Supplement Form.

Note:

(i) PK time points indicated as zero (0) denote trough samples immediately prior to study drug infusions/injections. Other assessments denoted as "0" will be collected prior to study drug infusions/injections. Samples listed as non-zero numbers refer to hours after the start of the IV infusion.

(ii) The timings of safety, PK, and PD sampling are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon the safety and PK information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF. Failure to obtain samples due to clinical issues, such as problems with venous access, will not be considered a protocol violation.

(iii) Order of assessments should be as follows: ECGs, vital signs (after appropriate rest), PK (when applicable).

[a] Tests may be conducted over approximately 3-5 visit days.

[b] Patients may be admitted on Day -1, to perform pre-dose tests, at the discretion of the site. For the first 6 infusions, patients must be observed closely for at least 4 hours following each infusion of LY3303560. After the first 6 infusions, a minimum post-infusion observation time of 2 hours will be required for all subsequent infusions. If any patient shows symptoms of an infusion reaction, the observation time will be increased to a minimum of 8 hours for that infusion and all future infusions. If deemed necessary, for safety or feasibility reasons, patients may remain in the investigative site for a longer duration at the discretion of the investigator.

[c] Assessments need not be done on the same visit day but should be completed in the following order if done on the same day (with approximately 4 hours separating NTB and ADAS-Cog_{14} to avoid testing fatigue): 1) ADAS-Cog_{14}, 2) ADCS-MCI-ADL24, 3) MMSE, 4) NTB, and 5) dCDT. All cognitive and functional assessments must be performed before LP if on the same day; therefore, some of this testing may need to be performed on a separate day.

[d] When the flortaucipir F 18 PET scan and LP have been scheduled on the same visit, the PET scan should be performed at least 24 hours after the LP. Cognitive assessments must be performed before LP if done on the same day.

[e] Pharmacokinetic sample time points are relative to the beginning of the IV infusion. The 0.5 h PK sample should be collected immediately after the 0.5 h IV infusion is completed as close as possible to the end of the infusion), followed by ECGs and vital signs 5 to 10 minutes later. On the day of dosing, postdose samples should be collected from the opposite arm to that used to administer study drug for IV infusion.

[f] If a patient discontinues before the MRI, the patient will be requested to return for this procedure even though all other study evaluations may be forgone. The MRI must be performed before a LP if conducted on same day.

[g] The V2 flortaucipir F 18 PET scan must be performed, and notification of adequate technical scan quality received from the PET imaging core laboratory, before dosing. The scan is performed after the patient qualifies based on the results of the amyloid PET scan and other screening tests. It may be performed up to 28 days prior to dosing once all screening assessments have been completed.

[h] The flortaucipir F 18 PET scan should be conducted at Visit 13 should the patient follow the 25-week treatment regimen or at Visit 19 for the 49-week treatment regimen. The flortaucipir F 18 PET scan should be completed at Visit 20 if the patient discontinues treatment after Visit 13 and before Visit 19. Patients permanently discontinued from study treatment due to initiation of a prohibited medication known to prolong the QT-interval should not have an ED flortaucipir F 18 scan unless the scan can be performed prior to initiation of the prohibited medication. Patients who have continued on study after introduction of a drug known to prolong QT interval (with sponsor approval) need a minimum of 14 days or 5 half-lives, whichever is longer, without that drug prior to the flortaucipir scan.

[i] The baseline V2 LP will be performed no closer than 24 hours before first dose. Dosing may not proceed until patient has been at least 12 hours free of symptoms of post-LP headache, if present. Refer to Section 9.5.1 for details of sampling.

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

[k] LPs are scheduled at either Visits 13, 19, 20, or early discontinuation. The corresponding coagulation test is required up to 2 weeks prior to the next scheduled LP.

[l] The LP should be conducted at Visit 13 should the patient follow the 25-week treatment regimen or at Visit 19 for the 49-week treatment regimen. The LP should be completed at Visit 20 if the patient discontinues treatment after Visit 13 and before Visit 19.

2.3. Follow-up Assessments (Visits 20 to 24)

Study Schedule Protocol I8G-MC-LMDD - MAD Treatment Period; Follow-up Assessments (Visits 20 to 24)

Visit	V20	V21	V22	V23	V24	ED
Day Relative to First Dose (for 25-week treatment phase)[a]	189	203	231	259	287	
Week (for 25-week treatment)[a]	27	29	33	37	41	
Day Relative to First Dose (for 49-week treatment phase)[a]	351	365	393	421	449	
Week (for 49-week treatment)[a]	51	53	57	61	65	
Tolerance Interval for Visit (days)	±7	±7	±7	±7	±7	
Administrative Procedures						
Body weight					X	X
Previous/concomitant medications	X	X	X	X	X	X
Inclusion/exclusion review						
Preexisting conditions/AEs	X	X	X	X	X	X
Cognitive Assessments and Functional Scales[b,c]						
ADAS-Cog_{14}	X					
ADCS-MCI-ADL24	X					
MMSE	X					
NTB	X					
dCDT	X				X	X
Safety Assessments						
Vital signs		X	X	X	X	X
C-SSRS/SHSF	X	X	X	X	X	X
Physical examination		X	X	X	X	X
Neurological examination		X	X	X	X	X
Triplicate 12-lead digital ECG		X	X	X	X	X
Imaging						
MRI				X		X
Flortaucipir F 18 PET[c,d]	X (if not done at V13 or 19)					X
Laboratory Assessments (central laboratory unless otherwise noted)						
Lumbar puncture[c,e,g]	X (if not done at V13 or 19)					X
Blood RNA						X
Pharmacogenetic sample						
Clinical laboratory tests		X	X	X	X	X
Coagulation tests (local laboratory)[e]	X (if not done at V13 or 19)					X
Serum LY3303560 PK (hours)[f]	X	X	X	X	X	X
Serum for immunogenicity					X	X
Plasma Tau PD (hours)[f]	X	X	X	X		X
Stored EDTA plasma and serum						X
Stored serum for possible exploratory immune safety laboratory tests						X

Abbreviations: ADAS-Cog_{14} = 14-item Alzheimer's Disease Assessment Scale – Cognition; ADCS-MCI-ADL24 = 24-question Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients; AE = adverse event; CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; D = dose; dCDT = digital clock drawing test; ECG = electrocardiogram; ED = early discontinuation; EDTA = ethylene diamine tetraacetic acid; IV = intravenous; LP = lumbar puncture; MAD = multiple ascending dose; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NTB = Neuropsychological Test Battery; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; rand = randomisation; RNA = ribonucleic acid; SC = subcutaneous; SHSF = Self-Harm Supplement Form.

Notes:

(i) Patients who have completed at least the 25-week treatment period will be followed up for 16 weeks after completion of dosing (Visits 20 to 24) as per the Schedule of Activities.

(ii) Pharmacokinetic time points indicated as zero (0) denote trough samples immediately prior to study drug infusions/injections. Other assessments denoted as "0" will be collected prior to study drug infusions/injections. Samples listed as non-zero numbers refer to hours after the start of the IV infusion.

(iii) The timings of safety, PK, and PD sampling are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon the safety and PK information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF. Failure to obtain samples due to clinical issues, such as problems with venous access, will not be considered a protocol violation.

(iv) Order of assessments should be as follows: ECGs, vital signs (after appropriate rest), PK (when applicable).

[a] All patients will be dosed for 25 weeks (Visits 3 to 13), after which they will be given the option to continue the treatment up to 49 weeks (Visits 14 to 19); the follow-up visits (Visits 20 to 24) for all patients will be conducted accordingly relative to their first dose.

[b] Assessments need not be done on the same visit day but should be completed in the following order if done on the same day (with approximately 4 hours separating NTB and ADAS-Cog_{14} to avoid testing fatigue): 1) ADAS-Cog_{14}, 2) ADCS-MCI-ADL24, 3) MMSE, 4) NTB, and 5) dCDT. All cognitive and functional assessments must be performed before LP if on the same day; therefore, some of this testing may need to be performed on a separate day.

[c] When the flortaucipir F 18 PET scan and LP have been scheduled on the same visit, the PET scan should be performed at least 24 hours after the LP. Cognitive assessments must be performed before LP if done on the same day.

[d] The flortaucipir F 18 PET scan should be conducted at Visit 13 should the patients follow the 25-week treatment or at Visit 19 for the 49 week treatment period. The flortaucipir F 18 PET scan should be completed at Visit 20 if the patient discontinues treatment after Visit 13 and before Visit 19. Patients permanently discontinued from study treatment due to initiation of a prohibited medication known to prolong the QT interval should not have an ED flortaucipir F 18 scan unless the scan can be performed prior to initiation of the prohibited medication. Patients who have continued on study after introduction of a drug known to prolong QT interval (with sponsor approval) need a minimum of 14 days or 5 half-lives, whichever is longer, without that drug prior to the flortaucipir scan.

[e] Coagulation test results should be reviewed before each LP. Concomitant medications should be reviewed to ensure that no changes to anticoagulation or antiplatelet therapy have occurred since the last coagulation test. The coagulation test is required up to 2 weeks prior to the LP, if LP is performed at Visit 20.

[f] Pharmacokinetic sample time points are relative to the beginning of the IV infusion. The 0.5 h PK sample should be collected immediately after the 0.5 h IV infusion is completed as close as possible to the end of the infusion. On the day of dosing, postdose samples should be collected from the opposite arm to that used to administer study drug for IV infusion.

[g] The LP should be conducted at Visit 13 should the patients follow the 25-week treatment or at Visit 19 for the 49-week week treatment period. The LP should be completed at Visit 20 if the patient discontinues treatment after Visit 13 and before Visit 19.

3. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterised 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 is hypothesised to induce tau aggregation, NFT formation, microtubule destabilisation, and neuronal toxicity. In AD, aggregated misfolded tau forms intraneuronal NFTs, which tend to spread sequentially from transentorhinal, to limbic, then neocortical regions, and correlate with severity of dementia and extent of neuronal loss. The stereotypical, temporal and neuroanatomical progression of neurofibrillary pathology in AD suggests that misfolded tau propagates along neuronal networks. The capability of misfolded tau "seeds" to spread across synapses and generate new aggregates is supported by cell culture and mouse models.

LY3303560 is a humanised monoclonal antibody that binds to aggregated tau from patients with AD and other tauopathies, such as progressive supranuclear palsy. In preclinical in vitro and in vivo studies, LY3303560 reduced trans-cellular spread of tau seeds and tau pathology propagation. By binding to aggregated tau, LY3303560 is hypothesised 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 for the treatment of AD. This study (I8G-MC-LMDD [LMDD]) will be the second clinical study of LY3303560 and will evaluate the effects of repeated every 4 week (Q4W) administrations in patients over 6 months (7 doses), with the option of extending the treatment period up to 12 months (up to 6 further doses).

The study aims to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple doses of LY3303560 in patients with mild cognitive impairment (MCI) due to AD or mild to moderate AD.In this amendment (b), the higher dose cohorts of LY3303560 (700 and 1400 mg) have been removed based on an update to the PK/PD model originally used to predict the LY3303560 efficacious dose range. The ongoing single-dose I8G-MC-LMDA (LMDA) study is exploring single doses of LY3303560 up to 5600 mg. Future multiple-dose studies with LY3303560 will evaluate higher dose levels using a Q4W dosing regimen. In addition, the duration of dosing in the LMDD study has been reduced from 12 to 6 months, based on emerging longitudinal and baseline data using tau positron emission tomography (PET) imaging, which suggests that the study is now insufficiently powered to assess the effects of LY3303560 on progression of tau pathology using flortaucipir F 18 PET over 12 months (see Appendix 6).

3.2. Background

LY3303560 binds preferentially to aggregated misfolded 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 and other tauopathies, and does not interfere with the binding of flortaucipir 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. Clinical Data

3.2.1.1. Study I8G-MC-LMDA

Study LMDA is an ongoing study assessing the safety, tolerability, PK, and PD of LY3303560 following single intravenous (IV) doses ranging from 7 to 5600 mg, and a single subcutaneous (SC) dose of 210 mg.

As of 06 November 2017, 54 subjects have completed the study and preliminary safety data indicate that IV doses up to 1400 mg and the SC 210-mg dose of LY3303560 have been well tolerated. A total of 28 treatment-emergent adverse events (TEAEs), regardless of causality, were observed in 12 subjects (28.6%) in the treated cohorts and a total of 5 TEAEs in 4 subjects (33%) in the pooled placebo group. All TEAEs were mild in severity and none were serious and no subject has withdrawn from the study because of an adverse event (AE). Across the treated cohorts, regardless of causality, upper respiratory tract infection was reported by 3 subjects (7.1%). Back pain, contusion, headache, and influenza-like illness were all reported by 2 subjects. All other TEAEs were reported by 1 subject each. Five subjects reported 1 TEAE each that was considered related to study treatment: hot flush, swelling, headache, bradyphrenia, and palpitations.

The decision to dose escalate to IV 5600 mg was made after the safety review of all 8 subjects in the IV 2800 mg was completed and determined that there were no safety concerns. As of 30 November 2017, 2 subjects have been dosed in the 5600-mg IV cohort. There have been no clinically significant changes in magnetic resonance imaging (MRI) scans and no infusion reactions have been observed to date. There have been no clinically significant findings with vital signs, electrocardiograms (ECGs), safety laboratory assessments or neurological examinations.

Preliminary interim PK data from Study LMDA following single doses of 7 to 2800 mg were evaluated in Caucasian and Japanese subjects. Overall, the PK parameters from Caucasian and Japanese subjects were similar. The initial estimate for clearance was approximately 0.2 L/day, volume of distribution at steady state was 3 to 5 L and mean half-life was 2 to 3 weeks. The PK of LY3303560 appears to be linear across the dose range studied. These draft data are consistent with the PK properties of immunoglobulin G (IgG) antibodies, and thus, the expected PK properties of LY3303560.

3.2.1.2. Study I8G-MC-LMDD

In this current study, as of 06 November 2017, data up to at least Day 57 from 9 patients, of whom 6 patients have received IV 70 mg LY3303560 Q4W, have been reviewed. The following blinded summary includes all TEAEs reported from the first dose to when the sixth patient received their third dose of LY3303560. A total of 16 TEAEs were observed in 5 out of 9 patients, all of which were mild to moderate in severity and none of which were serious. The most common TEAEs reported were bradycardia (n=4) and contact dermatitis (n=2); all reported by the same patient. The patient experienced 4 episodes of bradycardia, which were observed on infusion Days 29, 57, and 85. All episodes of bradycardia were asymptomatic and there were no clinically significant changes in ECGs. There were no other clinically significant changes in other safety measures for this patient, including MRI, vital signs, safety laboratory assessments, and neurological monitoring. The patient also had a history of bradycardia. There have been no infusion reactions observed to date.

Based on a review of the 70-mg LY33030560 safety data, it was deemed appropriate to dose escalate to the 210-mg LY3303560 cohort, which is ongoing.

Preliminary PK data from the first cohort (70 mg Q4W) of Study LMDD have been assessed. The PK observed following the first dose of 70 mg was consistent with the preliminary results of Study LMDA. In this preliminary assessment, minimal accumulation (as assessed using maximum drug concentration [C_{max}]) was observed between the first and second doses, with no additional accumulation apparent between the second and third doses. The accumulation ratio, as assessed between the first and third doses is 1.22, consistent with the value predicted using single dose data (1.26).

3.3. Benefit/Risk Assessment

The safety of LY3303560 was assessed in 5-week and 6-month toxicology studies in cynomologus monkeys, which included evaluation of safety pharmacology parameters and toxicokinetics. The administration of LY3303560 in monkeys up to a maximum dose of 200 mg/kg/week (bolus IV injection) for 5 weeks or 6-months resulted in no drug-related adverse findings. The safety of LY3303560 was also assessed in 5-week and 6-month toxicology studies in a transgenic mouse model (Tg4510) expressing human 4-repeat tau with P301L mutation that is linked to hereditary tauopathy. The administration of LY3303560 in transgenic Tg4510 mice up to a maximum SC dose of 200 mg/kg resulted in no drug-related adverse findings.

Procedure-related microscopic findings were observed for the IV and SC injection sites of monkeys, and SC injection sites of mice, and were consistent with the skin and vessels' response to venipuncture and administration of foreign material.

Administration of SC or IV LY3303560 may lead to injection-site or infusion reactions, respectively. Injection-site reactions may include pain, swelling, redness, or irritation at the site of injection. Infusion reactions may include fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. Patients should be monitored for injection-site and infusion reactions and provided with appropriate intervention or supportive care if reactions do not promptly resolve.

The potential for immunogenicity exists as administration of LY3303560 may cause the development of antibodies to LY3303560. Formation of antibodies against LY3303560 could be associated with infusion reactions, lower exposure to LY3303560, or the blocking or prolonging of any PD effect seen with LY3303560.

This multiple-dose study (LMDD) will evaluate the safety, tolerability, and PK of repeated doses of LY3303560 over 6 months (with the option to extend the treatment up to 12 months). The study will also investigate the potential PD effect of LY3303560, primarily on the basis of progression of tau pathology using the tau tracer, flortaucipir F 18. Flortaucipir F 18 is an investigational tracer and was positive in the in vitro human ether-a-go-go-related gene (hERG) assay. However, the cardiovascular assessments performed during the dog toxicology studies showed no evidence that flortaucipir F 18 prolongs the QT interval at high multiples of relevant clinical doses. Nonetheless, until sufficient human cardiovascular data are available, subjects with a history of risk factors for Torsades de Pointes and subjects taking drugs known to prolong the QT interval are excluded from studies with this tracer. Long-term animal studies to assess the risk of cancer from Flortaucipir F 18 have not been conducted. The non-radioactive version of Flortaucipir F 18 has been tested in bacteria and short-term animal studies to assess the risk of cancer. In laboratory tests with bacteria cells, Flortaucipir F 18 showed positive results for genotoxicity (damage to genes). Damage to genes can lead to the development of cancer. However, further studies conducted in living animals with Flortaucipir F 18 at doses over 750 times the maximum human dose did not produce any evidence for damage to genes.

The estimated exposure to ionising radiation from flortaucipir and amyloid PET scans is 25.63 mSv based on a total of 3 PET scans.

As this is a Phase 1 study, it is anticipated that patients will not receive any clinical benefit. Cognitive and functional outcomes are incorporated into the study as exploratory measures and patients will be assessed regularly during their participation in the study. While changes in biomarkers of tau pathology may be observed after treatment with LY3303560, the exact clinical significance of any change in tau is unknown at present.

The dose range chosen for Study LMDD is based upon preclinical data and preliminary safety, tolerability and PK data from the ongoing single-dose study (LMDA). The highest planned dose is 210 mg, which is lower than the administered doses in Study LMDA that have been shown to be well tolerated. Preliminary data from Study LMDA indicate that LY3303560 is well tolerated up to 2800 mg when administered as a single IV dose, with no dose-limiting safety or tolerability findings to date. In Study LMDD, multiple IV doses of 70 mg have been administered to 9 patients with AD (7 LY, 2 placebo), and to date, no SAEs or infusion-related reactions have been reported.

In this current study, safety data for a particular dose cohort will be reviewed prior to dose escalation to the subsequent cohort (see Section 5.1.3). Safety data will be reviewed periodically during the treatment and follow-up periods.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of LY3303560 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

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

Table LMDD.1. Objectives and Endpoints

Objectives	Endpoints
Primary The primary objective of this study is to assess the safety and tolerability after 16 weeks of multiple doses of LY3303560 in patients with MCI due to AD or mild to moderate AD	Safety and tolerability will be assessed by monitoring treatment-emergent adverse events (TEAEs)
Secondary	
• To assess the PK of LY3303560 in serum following multiple IV doses of LY3303560 in patients with MCI due to AD or mild to moderate AD	Maximum serum concentration (C_{max}) and the area under the serum concentration time curve during the dosing interval ($AUC\tau$)
Exploratory Objectives	
• To evaluate the effects of multiple doses of LY3303560 on cognitive function in patients with MCI due to AD or mild to moderate AD	ADAS-Cog_{14}, ADCS-MCI-ADL24, NTB, MMSE, dCDT
• To evaluate the effects of multiple doses of LY3303560 on brain atrophy in patients with MCI due to AD or mild to moderate AD	Quantitative measures of brain atrophy derived from volumetric MRI scans
• To evaluate the effects of multiple doses of LY3303560 on brain functional connectivity in patients with MCI due to AD or mild to moderate AD	Quantitative measures of brain functional connectivity derived from functional MRI scans
• To evaluate the immunogenicity of multiple doses of LY3303560 in patients with MCI due to AD or mild to moderate AD	Detection of anti-drug antibodies (ADA)
• To evaluate the effects of multiple doses of LY3303560 on plasma and CSF biomarkers in patients with MCI due to AD or mild to moderate AD	Plasma tau concentration; CSF concentration of tau, p-tau, Aβ1-42, and neurogranin
• To evaluate the effects of multiple doses of LY3303560 on tau pathology using the tau tracer flortaucipir F 18 in patients with MCI due to AD or mild to moderate AD	Quantitative endpoints from flortaucipir F 18 PET scans
• To determine the CSF concentration of LY3303560 following multiple IV doses in patients with MCI due to AD or mild to moderate AD	Mean LY3303560 concentrations in CSF

Exploratory Objectives (continued)	
• To explore the safety and tolerability of LY3303560 in Japanese subjects in relation to non-Japanese subjects	Safety and tolerability will be assessed by monitoring TEAEs
• To explore the PK of LY3303560 in Japanese subjects in relation to non-Japanese subjects	C_{max} and AUCτ

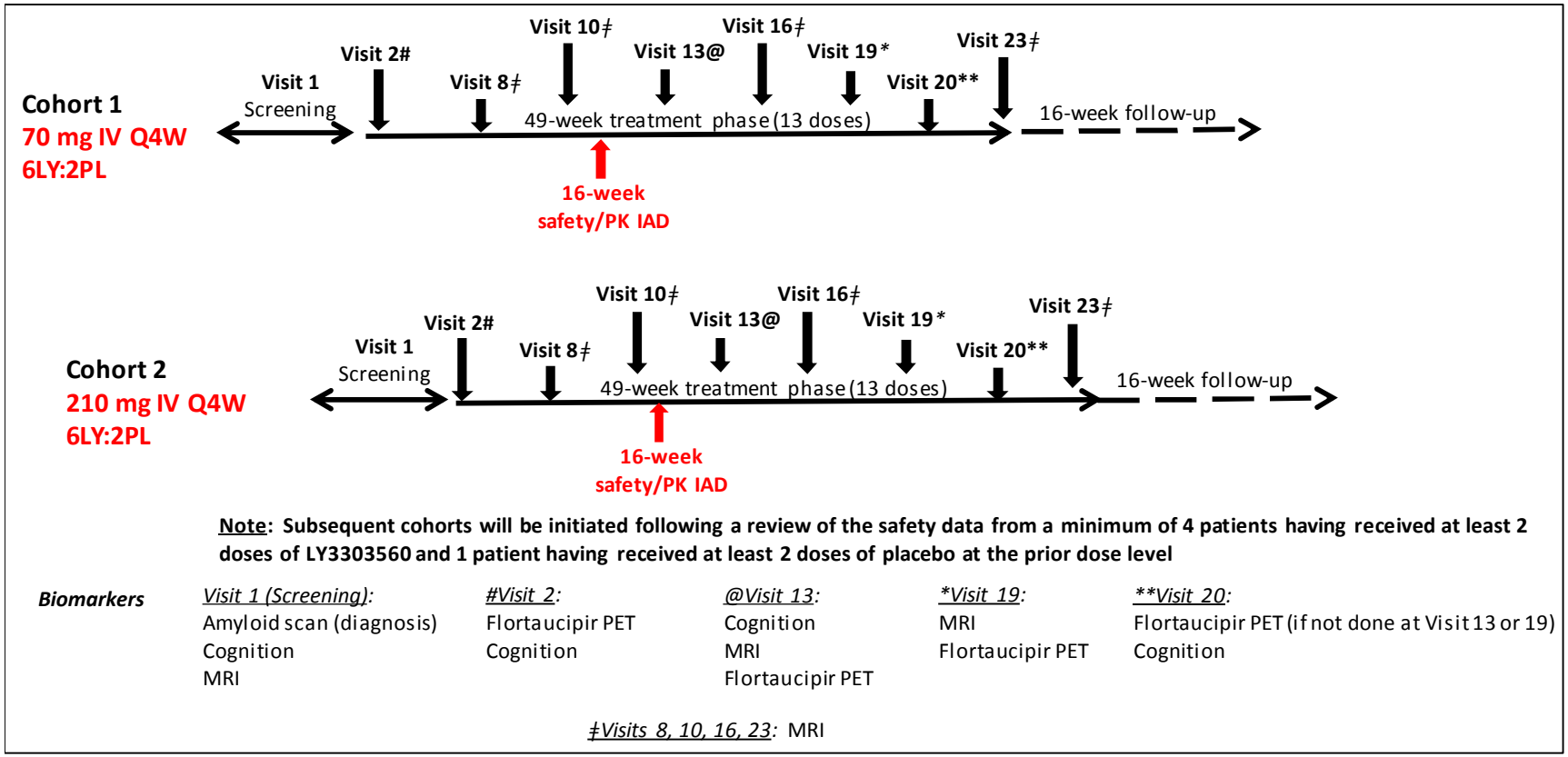
5. Study Design

5.1. Overall Design

This is a Phase 1b, multi-site, patient- and investigator-blind, placebo-controlled, parallel-group study in patients with MCI due to AD or mild to moderate AD to assess the safety, tolerability, PK and PD following multiple IV doses of LY3303560.

The planned IV doses of LY3303560 are 70 and 210 mg; however, dose levels may be adjusted based on emerging data from Study LMDA and from this current study, if indicated (Section 7.4).

Patients will be dosed Q4W for 25 weeks (7 doses) with LY3303560 or placebo, after which they will be given the option of continuing the treatment up to 49 weeks (up to 6 further doses), followed by a 16-week follow-up period after completion of dosing. Detail on the number of participants is given in Section 5.2 and Figure LMDD.1.



Abbreviations: IAD = interim access to data; IV = intravenous; LY = LY3303560; MRI = magnetic resonance imaging; Q4W = every 4 weeks; PET = positive emission tomography; PL = placebo.

Figure LMDD.1. Illustration of study design.

5.1.1. Screening and Randomisation for all Cohorts

At Visit 1, patients will undergo the screening tests outlined in the Schedule of Activities (Section 2). The screening tests may be conducted over approximately 3-5 screening visit days. For the screening amyloid scan, a prior positive amyloid PET scan using a validated tracer can also satisfy the inclusion criterion for amyloid-positivity as long as the scan is available for review by the central reader. Similar to the screening Visit 1, the Visit 2 randomisation tests may be conducted over 3-5 visit days. Patients will undergo a flortaucipir F 18 PET scan as part of Visit 2.

5.1.2. Dosing for all Cohorts

Patients will receive their study drug at the investigational site after all predose procedures have been completed and must be observed closely for at least 4 hours following each infusion of LY3303560 for the first 6 infusions. After the first 6 infusions, a minimum post-infusion observation time of 2 hours will be required for all subsequent infusions. If any patient shows symptoms of an infusion reaction, the observation time will be increased to a minimum of 8 hours for that infusion and all subsequent infusions.

If deemed necessary, for safety or feasibility reasons, patients may remain in the investigative site for a longer duration at the discretion of the investigator.

5.1.3. Treatment Phase

Each cohort will consist of 8 patients randomised (6 LY3303560: 2 placebo) to a 25-week MAD treatment period (7 doses), after which they will be given the option of continuing the treatment up to 49 weeks (up to 6 further doses, Visits 14 to 19). Patients who have completed at least the 25-week treatment period will be followed up for 16 weeks after completion of dosing (Visits 20 to 24) as per the Schedule of Activities in Section 2.

Safety and PK will be assessed throughout the study for each cohort.

Safety will be monitored by AEs, ECGs, vital signs (blood pressure and pulse rate), MRIs, neurological examinations, Columbia Suicide Severity Rating Scale (C-SSRS), and safety laboratory tests. In addition, blood samples for the assessment of immunogenicity will be taken at regular intervals throughout the dosing and follow-up periods. Each patient will have 1 screening (baseline) MRI prior to dosing with LY3303560, another after approximately 4 weeks, and then at approximately 12-week intervals thereafter as specified in the Schedule of Activities (Section 2), for the assessment of any potential imaging abnormalities. Tau imaging using flortaucipir F 18, cognitive and functional assessments (Neuropsychological Test Battery [NTB], the 14-item Alzheimer's Disease Assessment Scale – Cognition [ADAS-Cog_{14}], Mini-Mental State Examination [MMSE], digital clock drawing test [dCDT], and 24-question Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients [ADCS-MCI-ADL24]), and cerebrospinal fluid (CSF) (via single lumbar puncture) will be assessed/obtained as detailed in the Schedule of Activities in Section 2. If scheduled on the same day, the cognitive/functional testing should be conducted before the lumbar puncture (LP), and the LP should occur no closer than 24 hours before dosing. The patient must be free from any

post-LP headache for at least 12 hours before dosing. If the LP is performed on a separate day before the cognitive testing, the cognitive/functional testing should be performed at least 24 hours after the LP, and the patient must be free from any post-LP headache for at least 12 hours before dosing (see Section 9.5.1 for detail on CSF sampling).

As detailed in Section 7.4.1, dose escalation decisions will be made following a review of the safety data from a minimum of 4 patients having received at least 2 doses of LY3303560 and 1 patient having received at least 2 doses of placebo at the prior dose level. The subsequent cohort will not begin dosing until all 8 patients from the previous cohort have started dosing.

5.1.4. Japanese Patients

This study was designed to support further development of LY3303560 in Japanese patients. It was intended that approximately 3 Japanese patients would be enrolled in each cohort; however, recruitment to a cohort will not be contingent upon fulfilling these requirements. Japanese patient enrolment into these cohorts should ensure sufficient exposures at applicable doses to support future dosing (at least 1 Japanese patient exposed to LY3303560 in each cohort).

Evaluation of safety data from patients before dose escalation in Japan must include at least 1 Japanese patient on LY3303560. To avoid unblinding, there must be at least 2 Japanese patients in a cohort. Therefore, if fewer than 2 Japanese patients are enrolled in the cohort of patients evaluated for dose escalation, then dose escalation outside Japan will proceed, and additional Japanese patients will be recruited to allow dose escalation in Japan. Once the Japanese patients have the required safety evaluations, then patients in Japan may join in the ongoing dose-escalation cohort (see Section 5.1.3). For the purpose of safety evaluation in Japanese patients during the study, Japanese patients at sites in Japan and up to third-generation Japanese patients at sites outside of Japan will be included. The definition of up-to-third-generation Japanese is provided in Section 6. If necessary to make the judgment of dose escalation in the Japanese population, additional Japanese patients may be recruited and dosed to support the decision.

5.2. Number of Participants

In each cohort, up to 12 patients may be enrolled so that approximately 8 patients per cohort (6 LY3303560: 2 placebo) provide safety and PK data to steadystate.

A maximum of 24 patients will be enrolled.

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 patient.

5.4. Scientific Rationale for Study Design

This study will investigate the safety, tolerability, PK and PD of multiple IV doses of LY3303560 in patients with MCI due to AD and mild to moderate AD. Only patients with evidence of amyloid deposition will be recruited into the study as it has been shown that

advanced stages of tau pathology are associated with the presence of amyloid (Scholl et al. 2016; Schwarz et al. 2016), and both amyloid and tau are defining pathologies of AD (Montine et al. 2012). The presence of amyloid deposition will be confirmed by amyloid PET imaging using National Institute on Aging and Alzheimer's Association work group consensus guidelines (Albert et al. 2011; McKhann et al. 2011).

Placebo is included as the control, in a blinded manner for investigator/site staff and patients, to allow an unbiased assessment of the safety and PD data generated.

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 of imaging abnormalities with therapies targeting tau from the preclinical data for LY3303560 or from other tau therapeutics in the literature, MRI scans will be taken at predose, and thereafter at times specified in the Schedule of Activities (Section 2) after dosing with LY3303560 or placebo, in order to assess the potential for imaging changes, including, but not restricted to, vasogenic oedema and microhaemorrhage.

The inclusion of Japanese patients in this trial will facilitate the inclusion of Japanese patients in subsequent clinical trials.

The primary objective of investigating safety and tolerability of LY3303560 at steady state after administration of multiple IV doses will be evaluated, with evaluation of safety data from 8 patients (6 LY3303560: 2 placebo) in each cohort. It is anticipated that steady-state concentrations of LY3303560 will be achieved after approximately 4 months of dosing (4 doses), and so the minimum safety and PK data required to support future studies are up to Day 113.

5.5. Justification for Dose

Doses of 70 and 210 mg are planned for this study. The doses were selected based upon the preliminary safety and PK data at doses ranging from 7 to 2800 mg from Study LMDA, as well as nonclinical PK, efficacy and toxicology data from studies conducted in Tg4510 tau transgenic mice and cynomolgus monkeys.

In Study LMDA, single doses administered up to 70 mg LY3303560 have been well-tolerated (see Section 3.2.1), thus, the safety data up to 70 mg supports the starting dose of 70 mg in this study. Furthermore, safety data from higher single doses of LY3303560 in Study LMDA will be available prior to initiating the corresponding dose level in this study.

In humans, the predicted steady state concentration (C_{ss}) at the highest planned dose of 210 mg in Study LMDD is predicted to be 41.8 µg/mL (see Table LMDD.2). The calculated C_{ss} in monkey is 6,726 µg/mL at the NOAEL (200 mg/kg IV dosing) determined in the 6-month repeat dosing toxicity study (Study 8326196), which is approximately 160 times higher than the predicted human C_{ss} at 210 mg. The calculated C_{ss} in the Tg4510 mice is 2,208 µg/mL at the NOAEL (200 mg/kg SC dosing) determined in the 6-month repeat dosing toxicity study (Study 8326195) which is approximately 52 times higher than the predicted human C_{ss} at the highest dose of 210 mg IV (41.8 µg/mL) planned in Study LMDD.

Overall, the exposures and lack of findings in the 6-month toxicology studies in both the Tg4510 mice and monkeys, and the AE profile and preliminary PK in humans from Study LMDA, support the doses proposed in this study.

Table LMDD.2. Margin of Safety for Intravenous Administration of LY3303560 after 6 months of Dosing Based on Administered Dose and Predicted Human Exposure

	Dose	Dose Multiple[a] (Maximum Dose)	C_{avg} (µg/mL)	Exposure Multiple[a] (Maximum Dose)
Human Maximum Dose[b]	210 mg (3 mg/kg)	–	41.8	–
Tg4510 Mouse NOAEL[c]	200 mg/kg	266x[f]	2,208.3[e]	52
Monkey NOAEL[d]	200 mg/kg	266x[f]	6,726.2[e]	160

Abbreviations: C_{avg} = average steady-state serum concentration; NOAEL = no-observed-adverse-effect level.

a Dose multiple is the dose in animals divided by the dose in humans on a mg/kg basis. Exposure multiple is the calculated C_{avg} in animals divided by the predicted C_{avg} in humans after intravenous dosing. Multiples are rounded down to the nearest integer.

b Clinical (IV) dose multiple calculation assumes a 70-kg subject. Projected AUCτ at 210 mg Q4W is 1170 µg·day/mL.

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

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

e C_{avg} is the mean of male and female.

f Preclinical dosing was weekly/human dose was monthly (200 mg/kg x 4 weeks / 3 mg/kg).

6. Study Population

Eligibility of patients for study enrolment will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, ECG, and the research disease diagnostic criteria.

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 90 days prior to the first dose.

Patients recruited at the Japan sites must be Japanese. Japanese patients recruited outside of Japan should be up to third-generation Japanese to be included in the analysis as Japanese, defined as all of the patient's biological grandparents are of exclusive Japanese descent and were born in Japan.

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

6.1. Inclusion Criteria

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

[1] MCI 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 study partner over more than 6 months
- objective evidence of significantly impaired episodic memory characteristic of hippocampal dysfunction on testing:
    - Free and Cued Selective Reminding Test with Immediate Recall (FCSRT-IR): <27 for free recall (The episodic memory impairment can be isolated or associated with other cognitive changes at the onset or as the disease advances) (Auriacombe et al. 2010; Grober et al. 2010), and
    - Clinical Dementia Rating (CDR) of 0.5 to 2, global score; memory box score ≥0.5, and
    - MMSE of 16 to 30
- Has a florbetapir or other amyloid PET scan consistent with amyloid pathology at screening (the amyloid PET scan must be available to the central reader).

[2a] male patients:

- must abstain from intercourse for 24 hours after PET scans
- 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 medicinal product (IMP). At least one effective method of contraception will be used (for example, condoms with spermicide, oral contraceptives, intrauterine device, male sterilisation, 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 patients:

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

a) Infertile due to surgical sterilisation (hysterectomy, bilateral oophorectomy, or, for countries outside of Japan, 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 >40 mIU/mL.

[3] are at least 50 years old at the time of screening

[4] have a body weight of at least 50 kg (except for Japanese sites) and have a body mass index (BMI) of 18.0 to 35.0 kg/m^2 (for all sites), 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/or administration of the IMP for IV administration as per the protocol

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

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

[9] are able and willing to give signed informed consent

[10] have up to 2 reliable study partners who are in frequent contact with the patient (defined as at least 10 hours per week), one of whom at any one occasion: will accompany the patient to the study visits, will be available by telephone at designated times, and will provide a separate written informed consent to participate. A study partner should carry out his/her responsible part of the ADCS-MCI-ADL assessment. If a patient has more than 1 study partner, it is preferred that one of them will be primarily responsible for this assessment.

If the study partner(s) are not able to accompany the patient in person because of an unavoidable circumstance, they must be available by telephone for the following assessments:

- AEs and concomitant medications;
- relevant portions of the C-SSRS/self-harm supplement and follow-up forms, and
- CDR and ADCS-MCI-ADL (primary study partner if possible)

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

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

6.2. Exclusion Criteria

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

[11] are investigative site personnel directly affiliated with this study or immediate family members of investigative site personnel (immediate family is defined as a spouse, biological or legal guardian, child, or sibling)

[12] are Lilly employees or employees of third-party organisation(s) (TPOs) involved with the study who require exclusion of their employees; or have study partners who are Lilly employees or employees of TPOs involved in the study who require exclusion of their employees

[13] are currently enrolled in a clinical trial involving an IMP 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 (3 months and 4 months for sites in the EU and Japan, respectively) in a clinical trial involving an IMP. If the previous IMP has a long half-life, 3 months (4 months for sites in Japan) or 5 half-lives (whichever is longer) should have passed

[15] have previously completed or withdrawn from this study or any other study investigating LY3303560, and have previously received the IMP

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

[17] have significant allergies to humanised monoclonal antibodies, diphenhydramine, adrenaline, or methylprednisolone; or have a history of 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 immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)

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

[19] have an abnormal blood pressure or pulse rate as determined by the investigator

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

[21] regularly use known drugs of abuse and/or show positive findings on urinary drug screening that cannot be explained by regular concomitant medications

[22] have donated blood of more than 500 mL within the last month before start of dosing. For sites in Japan, have donated 400 mL or more blood in the last 12 weeks (males) or in the last 16 weeks (females), or any blood donation (including apheresis) within the last 4 weeks, or total volume of blood donation within 12 months is 1200 mL (males) / 800 mL (females) or more at screening

[23] have an average weekly alcohol intake that exceeds 14 units, or are unwilling to stop alcohol consumption 48 hours before dosing until at least 24 hours after dosing

[24] have an increased risk of seizures as evidenced by a history of head trauma with loss of consciousness within the last 5 years or any seizure (except childhood febrile seizure); prior electroencephalogram with epileptiform activity; 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)

[25] have any contraindications for MRI studies, including claustrophobia, or the presence of metal (ferromagnetic) implants or a cardiac pacemaker

[26] have a brain MRI (centrally read) demonstrating either: greater than 4 cerebral microhaemorrhages on a T2*-weighted gradient-echo sequence, regardless of their anatomical location; any macrohaemorrhage or prior evidence of macrohaemorrhage; or any other major intracranial pathology (except: atrophy, meningiomas without mass effect, benign pituitary microadenomas, and/or mild-to-moderate white-matter hyperintensities on fluid attenuation inversion recovery (FLAIR))

[27] have a history of intracranial haemorrhage, cerebrovascular aneurysm, or arteriovenous malformation, carotid artery occlusion, or epilepsy

[28] in the opinion of the investigator, the patient has a history of clinically significant stroke that is deemed to be a risk for study participation

[29] show evidence of clinically significant suicidal ideation as assessed by the C-SSRS

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

[31] have had any prior exposure to active or passive immune therapies directed against tau or Aβ protein

[32] have had a ventriculoperitoneal shunt within the last year

[33] have had gamma globulin (IgG) therapy within the last 6 months

[34] 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

[35] 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 randomisation (including less than 4 weeks since stopping AChEIs and/or memantine); or have received medications that affect the central nervous system, except treatments for AD, for less than 4 weeks at a stable dose

[36] have used stable medical therapy for less than 2 months by the time of randomisation for any concurrent medical condition that is not exclusionary

[37] are currently using or intend to use drugs known to significantly prolong the QT interval, or who have a known risk factor for Torsades de Pointes. A subject will not be excluded if they have been using stable medication that is known to potentially cause significant prolongation of the QT interval, but does not present with any clinically significant prolongation of the QT interval at screening, in the opinion of the investigator

[38] have previous (within last 12 months) and planned exposure to ionising radiation that, in combination with the planned administration of study PET ligands, would result in a cumulative exposure that exceeds local recommended exposure limits

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

[40] show clinically significant abnormalities in lumbar spine previously known or determined by screening lumbar x-ray (if performed)

[41] 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

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

[43] history of cancer within the past 5 years, with the exception of non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, non-progressive prostate cancer, or other cancers with low risk of recurrence or spread

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

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

6.3.2. Caffeine, Alcohol, and Tobacco

Consumption of caffeine-containing products is allowed.

Patients will not be permitted to consume alcohol from 48 hours before visits until at least 24 hours after dosing with study drug. When not at the investigative site, patients should be advised to limit alcohol consumption to no more than 14 units per week. Also, patients should be advised to limit alcohol consumption to no more than 3 units in any one day.

Patients will not be permitted to smoke at the investigative site and should not smoke for 48 hours prior to visiting the investigative site.

6.3.3. Activity

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

On LP days, movement will be restricted during the procedure and for an appropriate time after the LP, as determined by the investigator (see Section 9.5.1). Patients may also be required to stay overnight at the investigative site for monitoring following completion of the LP procedure.

6.4. Screen Failures

Patients who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times following a discussion between the investigator and sponsor. The interval between rescreening should be at least 8 weeks. Each time rescreening is performed, the individual must sign a new informed consent form (ICF). A repeat scan for technical reasons is not considered a rescreen. If a patient is unable to participate in a cohort due to the cohort being fully enrolled, he/she may be enrolled into a subsequent cohort after re-consenting to that cohort. Screening tests conducted in the previous cohort screening may be used for the subsequent cohort, as long as the screening tests are within the screening window of the subsequent cohort. All safety assessments that fall out of the screening window need to be repeated. Other assessments may not need to be repeated, including cognitive assessments, lumbar x-ray and florbetapir PET scan, based on consultation with the Lilly clinical pharmacologist/CRP.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of LY3303560 and placebo, with the planned doses of 70 and 210 mg. Table LMDD.3 shows the treatment regimens. Detailed instructions for the preparation, handling, and administration of LY3303560 will be provided by the sponsor in a pharmacy binder.

The IMP will be administered as a slow IV infusion over at least 30 minutes.

The minimum time for close observation at the investigative site following dosing is 4 hours for the first 6 IV infusions and 2 hours for subsequent IV infusions. If any patient shows symptoms of an infusion reaction, the observation time will be increased to 8 hours for that infusion and all subsequent infusions. The site must have resuscitation equipment, emergency drugs, and appropriately trained staff available during dosing and while patients are under observation after dosing.

All IMP provided to the investigator will be stored in a secure location, and allocated and dispensed by appropriately trained, unblinded site personnel. The allocation and dispensing of the IMP will be fully documented and verified by a second person. Detailed records of the amounts of IMP received, dispensed and remaining at the end of the study will be maintained.

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

For purposes of scheduling, "dosing time" refers to the start of infusion.

Table LMDD.3. Treatments Administered

Treatment Name	LY3303560	Placebo
Dosage Formulation	lyophilised 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	intravenous infusion
Dosing instructions	Refer to pharmacy binder	

The investigator's designee is responsible for:

- explaining the correct use of the IMP to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of IMP 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

The IMP 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

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

7.2.1. Timing of Doses

Doses should be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the patient's CRF. For IV infusions, the actual duration time of the infusion will be recorded in the CRF. If the infusion is interrupted or terminated, this should be recorded in the CRF.

7.3. Blinding

This is a patient- and investigator-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomisation table and treatment assignments before the study is complete.

Investigative site pharmacists or pharmacy staff will be unblinded due to their involvement in dose preparation. In order to maintain the blind, these unblinded investigative site staff will not be involved in clinical assessments of patients or general conduct of the study.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All actions resulting in an unblinding event are to be recorded and reported by the IWRS.

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. Patient's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding of a study patient's treatment assignment is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

All events resulting in an unblinding event must be recorded and reported through the IWRS.

7.4. Dose Modification

7.4.1. Dose Decision/Escalation

Safety data (see below) will be the primary criteria for the dose escalation. The available PK data for LY3303560 obtained during the study may be used to assist in dose escalation decisions but these data are not required for every decision. No dose escalation can occur without prior discussion between investigator(s) and the Lilly clinical pharmacologist/CRP. In the case of disagreement, the decision of the investigator(s) will be followed, except in a situation where Lilly's proposal is the more conservative action (for example, where the investigator wishes to escalate and the Lilly clinical pharmacologist/CRP does not) in which case, the Lilly proposal will be followed.

Safety data (including MRI scans) up to Day 85 from the minimum number of subjects (see Section 5.1.3) will be reviewed by the sponsor and investigator(s) to determine if the current dose was well tolerated and the proposed dose level for the next cohort is appropriate (see Section 10.3.6). The safety data reviewed will include AEs, ECGs, vital signs (blood pressure and pulse rate), MRIs, neurological examinations, C-SSRS, and safety laboratory tests. See Section5.1.4 for details of the dose escalation for Japanese patients.

Safety data, in particular TEAEs, SAEs, and adverse laboratory abnormalities, will be independently assessed by the investigator, and will be considered related to the IMP unless there is clear evidence that the event is not related.

After review of these data, an agreement on the appropriate dose for the next cohort will be made by the investigator(s) and sponsor. For doses above 70 mg, the dose level of LY3303560 selected should also have been shown to be well tolerated with no safety concerns when administered as a single dose in the ongoing LMDA study, prior to initiating dosing at that dose level in this study.

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

1) One or more patient experiences an SAE that is considered related to LY3303560 administration
2) Two or more patients experience a 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)
3) Two or more patients at a dose level experience moderate or severe AEs that impair normal activities, and are considered related to LY3303560, but do not meet the CSE criteria

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

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 paracetamol/acetaminophen (500 to 1000 mg) and/or an antihistamine, and/or methylprednisolone (or other corticosteroid) may be administered orally 30 to 60 minutes prior to the start of infusion for subsequent patients.

Any decision to implement premedication for infusions in subsequent cohorts will be made by the investigator(s) 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, angio-oedema, throat irritation, rash, pruritus, myalgia, and dizziness. In the event that a significant infusion reaction occurs, the following guidance should be followed:

- the IMP infusion should be slowed or stopped, depending on the symptoms/signs present:
    - if slowed, the infusion should be completed at the slower rate (at least 50% of the original infusion rate [for example, an infusion rate of 100 mL/hr becomes 50 mL/hr or slower]), as tolerated and documented in the CRF. The slower rate of infusion will be used for subsequent infusions for that patient
    - if stopped, no further attempts to administer the IMP for that patient 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, adrenaline, and/or methylprednisolone.

Stored serum samples for possible exploratory immune safety laboratory testing (including but not limited to Beta tryptase, total immunoglobulin E, and immune complex testing) will be collected at time points indicated in the Schedule of Activities (Section 2).

Additionally, stored serum samples for possible exploratory immune safety laboratory testing should be collected approximately 60-120 minutes and 4-6 weeks after moderate or severe infusion reactions. Unscheduled samples may also be collected as needed.

Standardised 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 the IMP and only authorised 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 authorised site staff.

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

7.6. Treatment Compliance

The IMP will be administered at the investigative site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Patients on stable concomitant medication for treatment of AD and other chronic conditions at the time of study entry should continue their regular, unchanged dose throughout the study. Additional drugs for patients should be avoided during the study unless required for a study procedure, to treat an AE, or for the treatment of an ongoing medical problem (refer to Exclusion Criteria, Section 6.2). Occasional paracetamol/acetaminophen and antihistamine use, without prior consultation with a Lilly clinical pharmacologist, will be allowed.

If an infusion reaction occurs, rescue medications may be administered at the discretion of the investigator (see Section 7.4.2.2).

Use of drugs known to significantly prolong the QT interval are not permitted within 14 days or 5 half-lives, whichever is longer, prior to flortaucipir scans (refer to the PET Technical Operations Manual for a list of excluded drugs).

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

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Patients will be discontinued from the IMP in the following circumstances:

- an SAE occurs that is related to study drug
- an SAE occurs during the infusion of the study drug, irrespective of causality; in this event, the drug is to be discontinued immediately. No re-dosing or completion of dosing is to be considered for that patient if the SAE is deemed to be related to study drug
- a clinically significant systemic hypersensitivity reaction occurs following administration of the IMP (for example, drug-related symptomatic bronchospasm, allergy-related oedema/angio-oedema, 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 oedema
- symptomatic cerebral microhaemorrhage or an increase in the number of cerebral microhaemorrhage >2 over baseline or such that the total number of microhaemorrhages is >4
- a clinically significant neurological finding
- an occurrence of suicidal ideation, as defined by a "yes" answer to Questions 4 or 5 on the Suicidal Ideation portion of the C-SSRS

Patients who discontinue the study drug early should complete all remaining scheduled visits (omitting dosing) if feasible or, at a minimum, the early discontinuation procedures as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrolment criteria and was inadvertently enrolled, the patient must be discontinued from the study following the early discontinuation procedures, as detailed in the Schedule of Activities (Section 2).

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

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

  - the investigator decides that the patient should be discontinued from the study
  - the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication; in this event, discontinuation from the study occurs prior to introduction of the new agent

- Patient Decision
  - the patient (or designee, for example, study partner) requests that the patient be withdrawn from the study

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

Investigative sites will report emerging clinically significant events (including but not limited to SAEs, clinically significant infusion/injection site reactions and clinically significant MRI abnormalities) to Lilly as soon as possible after they occur, and no later than the timing for expedited AE reporting. Lilly will inform all sites across all geographies of any clinically significant events and/or related decisions as soon as possible after notification, but no later than the timing for expedited AE reporting.

In the case where the decision is taken to suspend dosing in the trial or terminate due to safety findings, this decision will be immediately (within 1 hour) communicated by Lilly to all investigators (for example, by phone and/or email). It will be a requirement that investigators respond upon receipt to confirm they understand and have taken the appropriate action prior to dosing any patients with study treatment. Any investigator not responding will be followed up by Lilly personnel within 24 hours and prior to any planned dosing.

8.3. Patients Lost to Follow-up

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

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

Appendix 4 provides a summary of the maximum 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 patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IMP or the study, or that caused the patient to discontinue the IMP before completing the study. The patient should be followed until the event resolves, stabilises 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 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 potential cause-and-effect relationship between the IMP, 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 patient's IMP 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 hospitalisation
- 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.

Although all AEs are recorded in the CRF after signing informed consent, SAE reporting begins after the patient has signed informed consent and has received IMP. However, if an SAE occurs after signing informed consent, but prior to receiving IMP, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a 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 IMP) 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 IMP or procedure. Suspected unexpected serious adverse reactions must be reported according to 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. 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.

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 randomisation. There is no known antidote for LY3303560; subjects should receive appropriate supportive care.

Refer to the IB for LY3303560.

9.4. Safety

9.4.1. Laboratory Tests

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

Supine blood pressure and pulse rate should be measured after at least 5 minutes resting in the supine position.

If orthostatic measurements are required, patients should be supine for at least 5 minutes and then stand for at least 3 minutes. If the patient feels unable to stand, supine vital signs only will be recorded.

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

9.4.3. Electrocardiograms

For each 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 patient receives the first dose of the IMP, 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. 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 should be stored at the investigational site.

At screening, 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 patient meets entry criteria.

At all other time points, ECGs will be obtained in triplicate at approximately 1-minute intervals and will be transmitted to 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 patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

Digital ECGs will be electronically transmitted to and stored at the central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, of 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. 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's sign.

Table LMDD.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 LMDD.4. Scoring of Neurological Examinations

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

9.4.5. 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 oedema and microhaemorrhage.

Specifics of the MRI acquisition protocol will be provided in an MRI Technical Operations Manual. A 3T scanner is preferred but a 1.5T scanner may be used if a 3T scanner is not available. However, the same scanner should be consistently used throughout the study for any particular patient. All MRI scans will be analysed by a central reader blinded to treatment.

9.4.6. Columbia Suicide Severity Rating Scale

By industry guidance regarding suicidality (US Food and Drug Administration [FDA]), any assessment of suicide-related thoughts and behaviours 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 behaviours in this study.

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviours during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine whether a suicide-related thought or behaviour has occurred. The C-SSRS will be administered as specified in the Schedule of Activities 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. The suggested wording for the scale questions has also been simplified. For these reasons, the child version has been chosen for this study.

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

considered when administering the scale. If a suicide-related thought or behaviour is identified at any time during the study, a thorough evaluation should be performed by a study physician, and appropriate medical care should be provided.

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

9.4.7. PET Imaging

An amyloid PET scan, utilising florbetapir F 18 (or florbetaben F 18 or flutemetamol F 18, if the sponsor approves) will be performed at screening if amyloid PET confirming amyloid pathology has not been conducted previously (and scans are not available to the central reader). Details of the acquisition protocols for each amyloid tracer will be provided in the PET Technical Operations Manual.

A total of 2 flortaucipir F 18 PET scans will be performed at time points specified in the Schedule of Activities (Section 2). At each flortaucipir F 18 PET imaging visit, patients will receive a single IV administration of approximately 370 MBq (10 mCi) flortaucipir F 18, with the scan being acquired approximately 75 minutes post injection. Details of the acquisition protocol will be provided in the PET Technical Operations Manual.

Patients with a history of risk factors for Torsades de Pointes or taking medications known to prolong the QT interval (as listed in the PET Technical Operations Manual) should not have a flortaucipir F 18 scan.

9.4.7.1. Radiation Doses Associated with PET Imaging

The estimated exposure to ionising radiation per patient enrolled in this study (effective dose) is summarised in Table LMDD.5. This includes contributions from amyloid PET imaging (either florbetapir F 18, florbetaben F 18 or flutemetamol F 18) and flortaucipir F 18 PET imaging with flortaucipir F 18, along with a low-dose CT scan at each imaging session required for attenuation correction.

For flortaucipir F 18 scans only, if the image is not interpretable based on predetermined criteria outlined at the central lab (for example, scanner failure, patient motion, etc.), the patient may be asked to schedule an additional visit requiring an additional injection of flortaucipir F 18. Each patient will undergo a maximum of 1 additional flortaucipir F 18 PET scan beyond those scheduled in this protocol. The additional PET scan will not be considered out of window or a protocol deviation.

Table LMDD.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[a] scan	10	370	7.43	1	7.43
Flortaucipir F 18 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 non-clinical CT scan is obtained (estimated at 0.4 mSv) as part of the PET scan attenuation correction process when the scan is done on a PET/CT scanner.

[a] Amyloid PET scanning using florbetapir F 18 represents the likely maximum effective dose in this study. Use of alternate radioligands is associated with lower effective doses (florbetaben F 18 injects 8.1 mCi/300 MBq radioactive dose per scan with an effective dose of 6.2 mSv; flutemetamol F 18 injects 5 mCi/185 MBq radioactive dose per scan with an effective dose of 6.32 mSv).

9.4.8. Safety Monitoring

The Lilly clinical pharmacologist or CRP 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 including monitoring of imaging abnormalities by MRI, infusion reactions, and injection site reactions.

If a study 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 patient safety and compliance with regulatory guidance, the investigator is to consult with the Lilly-designated clinical pharmacologist or 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 Unblinding/Blinding Plan.

9.4.9. Immunogenicity Assessments

As detailed in the Schedule of Activities (Section 2), blood samples for immunogenicity testing will be collected to determine antibody production against LY3303560. Additional samples may be collected if there is a possibility that an AE is immunologically mediated. In case of a hypersensitivity reaction, serum drug concentrations will also be measured to aid interpretation of the immunogenicity data.

Additional samples for immunogenicity testing will be taken approximately every 3 months after the last follow-up visit when:

1) Patients have an anti-drug antibody (ADA) titre of 1:5120 or higher at the final follow-up visit. Samples for immunogenicity will be taken approximately every 3 months until the titres drop below 1:5120, for up to a maximum of 1 year after last dose
2) Patients have increasing ADA titres at the final follow-up visit compared to previous titres. Samples for immunogenicity will be taken up to a maximum of 1 year after the last dose or until the titres begin to decrease (and also drop below 1:5120, if the titre was 1:5120 or higher at the final follow-up visit)
3) Patients had an immunologically mediated AE judged to be potentially associated with ADAs at any time during treatment and have a positive ADA titre at the last follow-up visit. Samples for immunogenicity will be taken up to a maximum of 1 year after the last dose.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3303560. Antibodies may be further characterised and/or evaluated for their ability to neutralise the activity of LY3303560.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and Ethical Review Boards (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 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. 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

A lumbar x-ray may be performed at screening to rule out potential contraindications to an LP, such as significant osteoarthritic disease and bone overgrowth. If an x-ray was conducted within 12 months of screening, it may be used.

The LP procedure will be conducted under local anaesthesia by an appropriately qualified person. At each LP, a maximum of 20 mL (including up to 5 mL for local laboratory testing) of CSF will be collected. The first 5 mL of CSF will be collected in a separate container and sent to a local laboratory for testing of white blood cell count, red blood cell count (where possible), total protein, and glucose. In addition, each CSF sample will be visually inspected for evidence of blood contamination. The results of the visual inspection and local laboratory CSF analyses are to be documented on the electronic CRF (eCRF). Grossly evident blood by visual inspection will be reported as positive and documented in the CRF.

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

The remaining CSF will be collected to measure concentrations of CSF biomarkers in all patients and LY3303560 concentrations in patients who are assigned to receive LY3303560. All CSF aliquots remaining after analysis will be stored for exploratory work (Section 9.8).

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

9.5.2. Bioanalysis

Samples will be analysed 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 method. Analyses of samples collected from placebo-treated patients are not planned.

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

9.6. Pharmacodynamics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected for measurement of plasma tau concentrations if a suitable assay exists. A maximum of 5 additional time points per 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. The samples will be stored for a maximum of 15 years after the last 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 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, and the mechanism of action of LY3303560. 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, for all cohorts, PD samples should be collected from the arm that did not receive the IV infusion of study drug.

9.6.1. Exploratory Cognitive and Functional Assessments

The tests of cognitive function (ADAS-Cog_{14}, NTB, MMSE, CDR, ADCS-MCI-ADL24, dCDT, 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. Cognitive and functional tests may be conducted on separate days within the particular visit's allowed window. However, tests that are performed on the same day should be done in a specific order. Screening tests should be completed in this order: 1) MMSE, 2) FCSRT-IR, 3) CDR, and 4) dCDT. Tests during the study, if done on the same day, should be performed in this order with a minimum of 4 hours separating ADAS-Cog_{14} and NTB testing to avoid testing fatigue: 1) ADAS-Cog_{14}, 2) ADCS-MCI-ADL24, 3) MMSE, 4) NTB, and 5) dCDT. The study partner (or one of the study partners if there are 2) should be present or available by telephone for the assessment of CDR and ADCS-MCI-ADL (this should be the primary study partner for ADCS-MCI-ADL). When cognitive/functional assessments and LP are scheduled on the same day, all cognitive/functional assessments must be performed before the LP.

9.6.1.1. Alzheimer's Disease Assessment Scale-Cognitive Subscale

The ADAS is a rater-administered instrument that was designed to assess the severity of the dysfunction in the cognitive and non-cognitive behaviours characteristic of persons with AD (Rosen et al. 1984); ADAS-Cog refers to the cognitive subscale which was originally designed with 11 items (the ADAS-Cog_{11}). An expanded version that includes 3 additional items more sensitive to patients at earlier stages of AD, the ADAS-Cog_{14} (Mohs et al. 1997), will be used in this study. It consists of 14 items assessing areas of cognitive function most typically impaired in AD: orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures. The ADAS-Cog_{14} scale ranges from 0 to 90, with higher scores indicating greater disease severity.

9.6.1.2. Neuropsychological Test Battery

The NTB is a cognitive tool for clinical trials in the field of AD. The NTB is a collection of several written and oral tests that examines verbal and non-verbal brain functions. The NTB shows linear annual cognitive changes across a wide range of MMSE scores as compared to the

ADAS-Cog_{14} and is more sensitive than the ADAS-Cog_{14} among patients with mild impairment (Harrison et al. 2007).

9.6.1.3. Mini–Mental Scale Examination

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

9.6.1.4. Clinical Dementia Rating

The CDR is a clinical staging instrument for dementia (Morris 1993). It characterises 6 domains of cognitive and functional performance: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semistructured interview of the patient and a reliable informant or collateral source (e.g., a family member). The CDR table provides descriptive anchors that guide the clinician in making appropriate ratings based on interview data and clinical judgment.

In addition to ratings on a 5-point scale for each domain (except for personal care, which is rated on a 4-point scale), an overall CDR score is derived by standard algorithm. This score is useful for globally staging the level of impairment: 0 indicates no impairment; 0.5, 1, 2, and 3 indicate very mild, mild, moderate, and severe dementia, respectively.

The CDR and Clinical Dementia Rating-Sum of Boxes (CDR-SB) will be evaluated at screening. 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.

9.6.1.5. Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for MCI Patients

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

9.6.1.6. 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) and will be evaluated at screening only. The 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. Only Form A of the FCSRT-IR will be used in this study.

9.6.1.7. Digital Clock Drawing Test

The Clock Drawing Test (CDT) is used to measure constructional, spatial, and executive abilities, and deficits in the conception of time. On a blank sheet of paper, the patient will be asked to draw a clock showing 10 minutes past 11 (the “command” clock). Next, the patient will be asked to copy a pre-drawn clock showing the same time (the “copy” clock). This test requires different cognitive capabilities in the 2 drawing conditions: the command clock relies more heavily on memory and language; the copy clock relies more on executive function and visual-spatial perception (Rouleau et al. 1996).

The dCDT uses a novel digitising ballpoint pen that functions in the subject's hand as an ordinary ballpoint pen, but digitally records its position on the paper and encrypts the data. Changes in pen position (that cannot be seen by the naked eye) are measured and data are time-stamped to enable the system to capture the entire sequence of behaviours, for example, every stroke, pause or hesitation (Souillard-Mandar et al. 2016).

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 oedema 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 programme. 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 patient number. These samples and any data generated can be linked back to the patient only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last 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 utilised, 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, PDs, 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, RNA, proteins, lipids, and other cellular elements.

Serum, plasma, CSF, and whole blood ribonucleic acid (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 LY3303560, mechanism of action of LY3303560, and/or research method development, or for validating diagnostic tools or assay(s) related to neurodegenerative diseases.

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

Samples will be retained for a maximum of 15 years after the last 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

A total of 24 patients may be enrolled to ensure 16 complete the study. The sample sizeis customary for Phase 1 studies evaluating safety, PK and/or PD parameters.

It is expected that at least 4 Japanese patients will be enrolled into the study. Patients will be stratified by Japanese/non-Japanese but not by disease severity at randomisation.

Patients who are randomised but do not complete the study may be replaced to ensure that enough patients complete the study (see Section 5.2).

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

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

10.2.2. Study Participant Characteristics

The patient's age, sex, race, weight, height, APOE status, and/or other demographic characteristics will be recorded and may be used in the PK, PD, and safety analyses as quantitative or classification variables. These characteristics will be listed and summarised at baseline, with the exception of weight, which will also be summarised over time.

10.3. Statistical Analyses

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

Pharmacokinetic analyses will be conducted on the full analysis set. This set includes all data from all randomised patients receiving at least 1 dose of the IMP according to the treatment the patients actually received. Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements. Pharmacodynamic analyses will be conducted on all randomised participants who take at least 1 dose of study treatment and have at least 1 postdose PD measurement relevant to the endpoint.

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

Analyses will be reported by dose. Patients receiving placebo will be pooled into 1 group.

All total and subscale scores will be derived from individual items. If any individual item is missing, the corresponding total and subscale scores will be considered missing, except for the

$ADAS\text{-}Cog_{14}$, which will be imputed. The imputation algorithm will be specified in the statistical analysis plan (SAP).

No formal hypothesis tests are planned.Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All IMP and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarised using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with IMP as perceived by the investigator. Symptoms reported to occur prior to randomisation 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 IMP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

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

Shift tables will be constructed for each dose group to assess the incidence of and changes in vasogenic oedema and microhaemorrhage counts pre- and post-dose (by time) based on MRI.

Suicide-related thoughts and behaviours based on the C-SSRS will be listed by patient. Only time points and patients that show suicidal ideation/behaviour will be displayed (i.e., not all of the "no" responses will be displayed).

An assessment of potential QTc prolongation will be carried out in 2 ways:

1. A summary of the number of patients experiencing a maximum increase from baseline in QTcF interval will be summarised for each treatment according to the following categories: >30 ms and >60 ms. In addition, there will be a summary by treatment of the number of patients with QTcF postdose values in the following categories: >450 ms, >480 ms and >500 ms.
2. Scatter plots will be created of QTcF versus LY3303560 concentration and change from baseline QTcF versus LY3303560 concentration (for time points where there is matched LY3303560 concentration and QTcF available). 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; the reference line will be 10, 30 and 60 ms for the 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.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Standard non-compartmental methods of analysis and model-based approaches using non-linear mixed effects modeling (NONMEM) or other appropriate software may be implemented to estimate PK parameters including C_{max}, area under the concentration curve during the dosing interval (AUCτ), half-life, clearance, and volume of distribution after IV administration of LY3303560. The accumulation ratio, expressed as either AUCτ, C_{max}, or minimum observed drug concentration (C_{min}), may be reported.

An analysis of the effect of dose, concentration or demographic factors on the PK parameters may be conducted.

An analysis relating LY3303560 serum exposure to LY3303560 CSF concentrations may be conducted.

Exploratory PK analysis comparing Japanese and non-Japanese subjects may be conducted.

10.3.3. Imaging Analyses

Summary statistics of the flortaucipir F 18 standardised uptake value ratio (SUVr) will be provided by treatment (70 and 210 mg, and placebo) and visit (baseline and Visit 13 or Visit 20). Summary statistics of change from baseline and percentage change from baseline in SUVr will also be provided. Summary statistics may also be provided for SUVrs in individual and other composite brain regions if needed.

Changes in regional brain volume and functional connectivity in brain networks captured by MRI over the course of the study will be explored and summarised. Magnetic resonance imaging will be obtained every 8-12 weeks; therefore, a mixed model repeated measures (MMRM) may be conducted fitting baseline, treatment and study visit as fixed effects.

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

10.3.4. Exploratory Pharmacodynamic Analyses

10.3.4.1. Pharmacodynamic Parameter Estimation

The concentration of plasma tau, and the concentration of CSF biomarkers, including tau, p-tau, Aβ1-42 and neurogranin, will be determined. Plasma and CSF biomarker data will be summarised statistically and/or illustrated graphically by time and dose. The mean change in concentration of the plasma and CSF biomarkers from predose will be evaluated.

No formal statistical analyses of biomarkers are planned.

10.3.4.2. Cognition Analyses

ADAS-Cog$_{14}$, NTB, MMSE, dCDT, and ADCS-MCI-ADL24 will all be summarised and may be analysed using an MMRM with preinfusion cognitive measures as a baseline covariate and fixed effects of dose and study visit. All cognition analyses are exploratory and underpowered to detect a clinically meaningful effect.

Correlations between cognition endpoints and flortaucipir F 18 SUVr may be explored.

10.3.4.3. Evaluation of Immunogenicity

The frequency of antibody formation to LY3303560 will be determined. If a neutralisation assay is performed, the frequency of neutralising antibodies will be determined. The relationship between the presence (or absence) of antibodies and clinical parameters (AEs, efficacy measures, and so on) will be assessed. Likewise, the relationship between the presence of antibodies and the PK parameters and PD response to LY3303560 will be assessed.

10.3.5. Exploratory Pharmacokinetic/Pharmacodynamic Analyses

A model-based approach may be implemented using NONMEM or other appropriate software to estimate PK/PD parameters. Exploratory analyses may be conducted to characterise the relationship between changes in cognition endpoints, plasma and/or CSF biomarkers, and exposure of LY3303560.

10.3.6. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

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

Safety and/or PK interim access to data (IAD) reviews are scheduled to occur throughout the study.

The investigator(s) and the Lilly study team will make the determination regarding dose escalation based on their review of the safety and tolerability data, along with available PK data, as applicable. Anti-drug antibody titres will also be reviewed, if available. The investigator will remain blinded and the Lilly study team will be unblinded during these reviews for dose escalation. The specifics about the timing of the dose escalation reviews and the procedures for selecting doses are described in the study design and dose modification sections of the protocol (Sections 5 and 7.4, respectively).

For each cohort, IADs for review of safety data, including ADA titres (if available), and PK data will be conducted at 16 weeks (4 weeks after the fourth dose [Day 113]) to evaluate the safety, PK and PD of LY3303560 at steady state. Across the study, a review of safety data, including ADA titres (along with PK data, if applicable) will be conducted at approximately quarterly intervals throughout the treatment and follow-up period. These IADs may align with (and be included in) other pre-planned IADs or may be separate.

Additional IADs may also be conducted to summarise data for internal decision-making and/or support of subsequent clinical studies/regulatory agency submissions/IB annual updates, as required.

There will be regular reviews of PD data by the Lilly study team.

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Appendix 1. Abbreviations and Definitions

Term	Definition
Aβ	Amyloid-beta (amyloid-β)
AD	Alzheimer's disease
ADA	Anti-drug antibody
ADAS-Cog$_{14}$	14-item Alzheimer's Disease Assessment Scale – Cognition
ADCS-MCI-ADL24	24-question Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for patients with MCI
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 unfavourable 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
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]).
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 patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BMI	body mass index
CDR/CDR-SB	Clinical Dementia Rating/CDR-Sum of Boxes
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum drug concentration
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.
CP	Clinical Pharmacologist
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.
CSE	clinically significant event
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
dCDT	Digital clock drawing test
ECG	Electrocardiogram
EDTA	Ethylene diamine tetraacetic acid
enrol	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.[
ERB	Ethical review board
FCSRT-IR	Free and Cued Selective Reminding Test with Immediate Recall
Florbetaben Florbetapir Flutemetomol	PET scanning radiopharmaceutical compounds containing the radionuclide fluorine-18 approved by the FDA as a diagnostic tool for AD.
Flortaucipir F 18 (18F-AV-1451, also known as [F-18]T807 or LY3191748)	Investigational PET scanning radiopharmaceutical compound containing the radionuclide fluorine-18 that binds with high affinity and selectivity to aggregated tau pathology.
GCP	Good clinical practice
IAD	Interim access to data
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation

IMP	investigational medicinal product
IND	Investigational New Drug: An application to the FDA to allow testing of a new drug in humans.
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Investigational medicinal product (IMP)	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 authorised form, or marketed products used for an unauthorised indication, or marketed products used to gain further information about the authorised form.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	Intravenous
IWRS	interactive web response system
LP	Lumbar puncture
MAD	Multiple-ascending dose
MCI	Mild cognitive impairment
MMRM	mixed model repeated measures
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUBADA	Multi-block barycentric discriminant analysis
NFT	Neurofibrillary tangle
Non-investigational medicinal product (non-IMP)	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.
NTB	Neuropsychological Test Battery
PET	Positron emission tomography
PK/PD	Pharmacokinetic(s)/pharmacodynamic(s)

Q4W	every 4 weeks
QTc/QTcF	corrected Q-T interval/Q-T interval corrected using the Fridericia formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
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.
SHFU	Self-harm follow-up assessment
SHSF	Self-harm supplement form
SUSARs	Suspected unexpected serious adverse reactions
SUVr	Standardised uptake value ratio
TEAE	Treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
TPO	third-party organisation

Appendix 2. Clinical Laboratory Tests

Laboratory Tests at Screening and During the Study (Performed at Local Laboratory)

Haematology:
- Haematocrit
- Haemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell haemoglobin
- Mean cell haemoglobin concentration
- Leucocytes (WBC)
- Cell morphology (absolute or relative % counts)
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Platelets

Clinical chemistry:
- Sodium
- Potassium
- Bicarbonate[d]
- Chloride
- Calcium
- Glucose (random)
- Blood urea nitrogen
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase
- Aspartate aminotransferase (SGOT)
- Alanine aminotransferase (SGPT)
- Creatinine

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

Ethanol testing[b,c]
Urine drug screen[c]
Hepatitis B surface antigen[e]
Hepatitis C antibody[e]
HIV[e]
FSH (females only; if required to confirm postmenopausal status)[e]

Coagulation:
- Prothrombin time/international normalised ratio
- Activated partial thromboplastin time

Abbreviations: CRU = clinical research unit; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; SGOT = serum glutamic oxaloacetic transaminase; SGPT = glutamic-pyruvic transaminase; RBC = red blood cell; WBC = white blood cell.

[a] Test only if dipstick result is abnormal.
[b] At site discretion this may be a serum, breath, or urine sample.
[c] Urine drug screen and ethanol level may be repeated before admission to the CRU.
[d] May not be collected in Japan.
[e] Performed at screening only.

Laboratory Tests During the Study (Performed at Central Laboratory)

Haematology[a]:
- Haematocrit
- Haemoglobin
- Erythrocyte count (RBC)[a]
- Mean cell volume
- Mean cell haemoglobin
- Mean cell haemoglobin concentration
- Leucocytes (WBC)
- Cell morphology (absolute or relative % counts)
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Platelets

Urinalysis[a]:
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Microscopic examination of sediment[b]

Clinical chemistry[a]:
- Sodium
- Potassium
- Bicarbonate[c]
- Uric acid
- Chloride
- Calcium
- Glucose
- Blood urea nitrogen
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase
- Aspartate aminotransferase (SGOT)
- Alanine aminotransferase (SGPT)
- Creatinine
- Total cholesterol
- Low-density lipoprotein cholesterol
- High-density lipoprotein cholesterol

Anti-LY antibodies/immunogenicity[d]

Exploratory immune safety laboratory tests[e]

Abbreviations: LY = LY3303560; SGOT = serum glutamic oxaloacetic transaminase; SGPT = glutamic-pyruvic transaminase; RBC = red blood cells; WBC = white blood cells.

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

[b] Test only if dipstick result is abnormal.

[c] May not be collected in Japan.

[d] Results will be validated by the central laboratory.

[e] If testing ordered, will be performed at central laboratory.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

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

Ethical Review

The investigator must give assurance that the ethical review board (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 International Conference on Harmonisation (ICH) guideline on Good Clinical Practice (GCP).

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

- the current Investigator's Brochure (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 third party organisation.

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

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

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

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 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 or its designee, 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 or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Blood and CSF Sampling Summary

The following tables summarise the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. In addition, CSF sampling during the study is also summarised. Fewer venipunctures and blood draws and CSF draws may actually occur, but this will not require a protocol amendment.

Protocol I8G-MC-LMDD Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	26	1	26
Clinical laboratory tests[a]	12	20	240
Blood RNA	10	4	40
Coagulation tests	6	2	12
Serum LY3303560 PK[b]	3	35 (+5)	105 (15)
Blood discard for cannula patency	3	24	72
Serum for immunogenicity	6	9	54
Pharmacogenetic sample	10	1	10
Plasma for Tau PD[b]	2	35 (+5)	70 (10)
Stored EDTA plasma sample	10	12	120
Stored serum sample	2	12	24
Serum sample for exploratory immune safety	14	5	70
Total			843 (868)
Total for clinical purposes (rounded to nearest 10 mL)			850 (870)

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

[b] 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.

Protocol I8G-MC-LMDD CSF Sampling Summary[a]

Purpose	Maximum CSF Volume per Sample (mL)	Maximum Number of CSF Samples	Maximum Total Volume (mL)
CSF PK and PD	20[b]	3	60
Total			60
Total for clinical purposes (rounded up to nearest 10 mL)			60

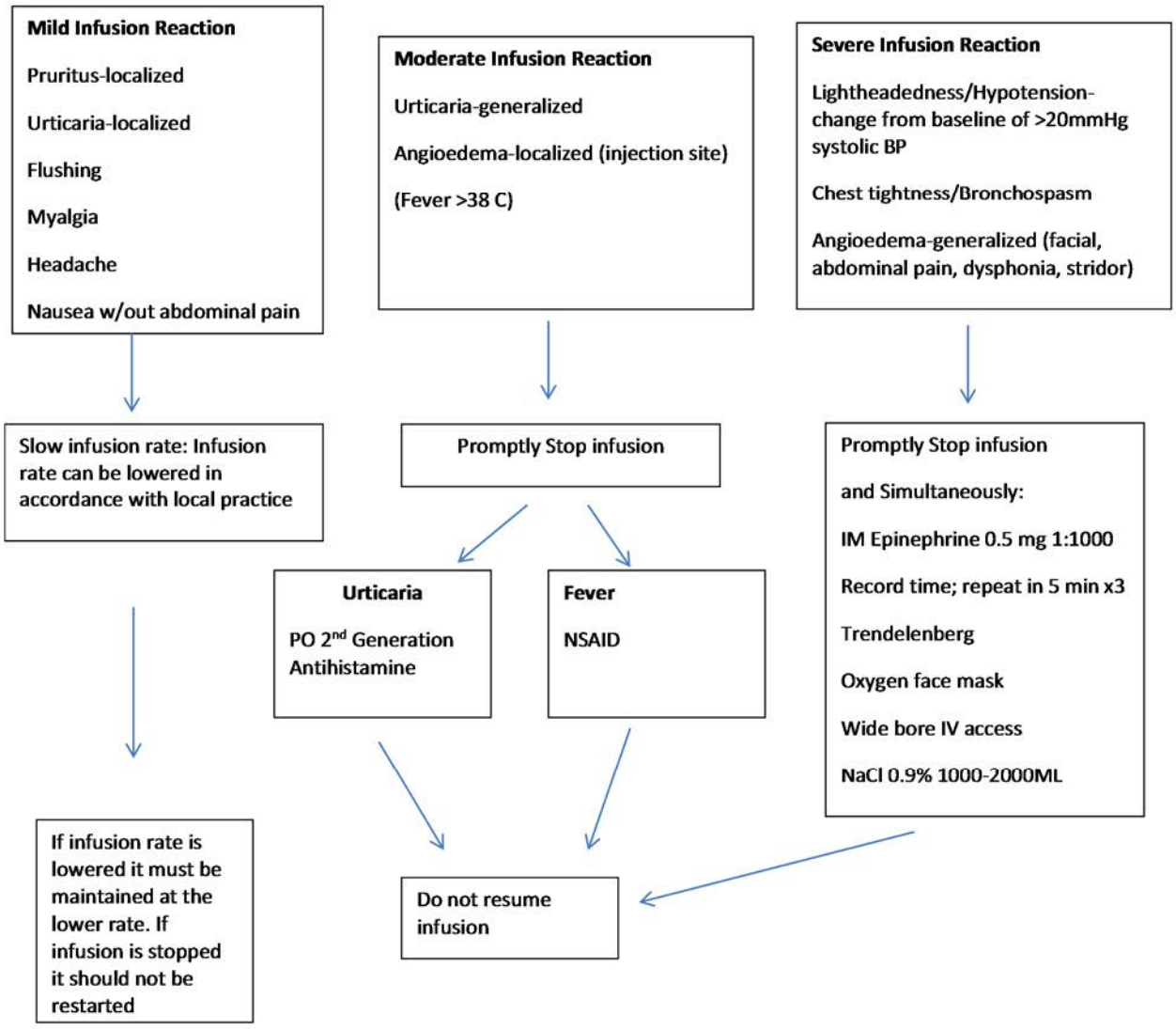
Abbreviations: CSF = cerebrospinal fluid; PD = pharmacodynamics(s); PK = pharmacokinetics.

[a] Additional samples may be drawn if needed for evidence of CSF contamination.

[b] For Japan sites, 10 mL.

Appendix 5. Management of Infusion Reactions

Infusion Reaction Management Flowchart



Abbreviations: BP = blood pressure; IM = intramuscular; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = by mouth.
Continue supportive care in accordance with the symptoms/signs (Section 7.4.2.2).
Source: Adapted from Lichtenstein et al. 2015.

Appendix 6. Protocol Amendment I8G-MC-LMDD(d) Summary
Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LY3303560 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease

Overview

Protocol I8G-MC-LMDD "Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LY3303560 in Patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease" has been amended. The new protocol is indicated by Amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes made to this protocol are as follows:

- In the Schedule of Activities in Section 2, the lumbar puncture at Visit 13, which was removed in protocol amendment (c), has been reinstated to accommodate patients who are following the 25-week dosing period. A flortaucipir F 18 PET scan has been added to Visit 13 for the same reason.
- The Schedule of Activities in Section 2 has been amended to show the LP and flortaucipir F 18 PET scan are not required at Visit 20 for patients who have had an LP or PET scan at Visits 13 or 19. A flortaucipir F 18 PET scan has been added to Visit 19 for patients following the 25-week treatment period.
- The Schedule of Activities (Section 2) has been amended to show that, after a patient has had 6 infusions with no infusion reaction, the observation period for subsequent infusions is reduced. However, should any infusion reaction occur for any patient, the monitoring period will be increased to at least 8 hours for all subsequent infusions. To date, there have been no infusion reactions observed in 9 subjects in Cohort 1 (70 mg LY3303560) who have reached at least 6 months of dosing and 9 subjects in Cohort 2 (210 mg LY3303560) who have reached at least 3 months of dosing.

Revised Protocol Sections

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

Section 2.2. MAD Treatment Period (Visits 2 to 19)

Study Schedule Protocol I8G-MC-LMDD
MAD Treatment Period (Visits 2 through 19) (concluded)

Visit	V2[a] Rand	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19
Day Relative to First Dose	-8	1[b]	2	4	8	15	29[b]	57[b]	85[b]	113[b]	141[b]	169[b]	197[b]	225[b]	253[b]	281[b]	309[b]	337[b]
Week		1	1	1	2	3	5	9	13	17	21	25	29	33	37	41	45	49
Tolerance Interval for Visit (days)	±7[a]	0	±4 h	±1	±1	±1	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Imaging																		
Flortaucipir F 18 PET[d,h]	X[g]											X[h]						X[h]
Laboratory Assessments (central laboratory unless otherwise noted)																		
Lumbar puncture[d,j]	X[i]											X[l]						X[l]

b Patients may be admitted on Day -1, to perform pre-dose tests, at the discretion of the site. For ~~all dosing days~~the first 6 infusions, patients must be observed closely for at least 4 hours following each infusion of LY3303560.~~after dosing and will remain in the investigative site for at least 8 hours after dosing.~~After the first 6 infusions, a minimum post-infusion observation time of 2 hours will be required for all subsequent infusions. If any patient shows symptoms of an infusion reaction, the observation time will be increased to a minimum of 8 hours for that infusion and all future infusions. If deemed necessary, for safety or feasibility reasons, patients may remain in the investigative site for a longer duration at the discretion of the investigator.

h The flortaucipir F 18 PET scan should be conducted at Visit 13 should the patient follow the 25-week treatment regimen or at Visit 19 for the 49-week treatment regimen. The flortaucipir F 18 PET scan should be completed at Visit 20 if the patient discontinues treatment after Visit 13 and before Visit 19. Patients permanently discontinued from study treatment due to initiation of a prohibited medication known to prolong the QT-interval should not have an ED flortaucipir F 18 scan unless the scan can be performed prior to initiation of the prohibited medication. Patients who have continued on study after introduction of a drug known to prolong QT interval (with sponsor approval) need a minimum of 14 days or 5 half-lives, whichever is longer, without that drug prior to the flortaucipir scan.

k LPs are scheduled at either Visits 13, 19, 20, or early discontinuation. The corresponding coagulation test is r~~R~~equired ~~at least~~up to 2 weeks prior to the next scheduled LP. ~~(Visit 20 or early discontinuation).~~

l The LP should be conducted at Visit 13 should the patient follow the 25-week treatment regimen or at Visit 19 for the 49-week treatment regimen. The LP should be completed at Visit 20 if the patient discontinues treatment after Visit 13 and before Visit 19.

2.3. Follow-up Assessments (Visits 20 to 24)

Study Schedule Protocol I8G-MC-LMDD - MAD Treatment Period; Follow-up Assessments (Visits 20 to 24)

Visit	V20	V21	V22	V23	V24	ED
Day Relative to First Dose (for 25-week treatment phase)[a]	189	203	231	259	287	
Week (for 25-week treatment)[a]	27	29	33	37	41	
Day Relative to First Dose (for 49-week treatment phase)[a]	351	365	393	421	449	
Week (for 49-week treatment)[a]	51	53	57	61	65	
Tolerance Interval for Visit (days)	±7	±7	±7	±7	±7	
Imaging						
MRI~~d~~				X		X
Flortaucipir F 18 PET[c,d]	X (if not done at V13 or 19)					X
Laboratory Assessments (central laboratory unless otherwise noted)						
Lumbar puncture[c,e,~~g~~]	X (if not done at V13 or 19)					X

Notes:

(i) Patients who have completed at least the 25-week treatment period will be followed up for 16 weeks after completion of dosing (Visits 20 to 24) ~~and will return to the investigational site for safety assessments, PK, and plasma tau (PD) sampling on Visits 20 to 24~~ as per the Schedule of Activities.

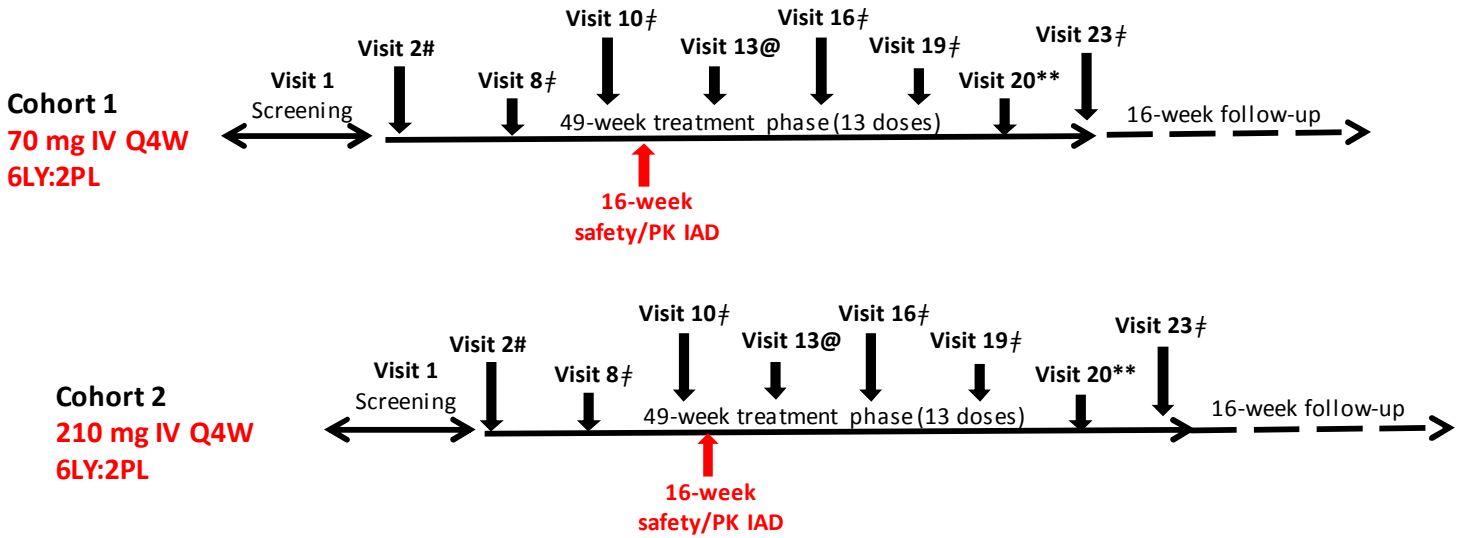
d The flortaucipir F 18 PET scan should be conducted at Visit 13 should the patients follow the 25-week treatment or at Visit 19 for the 49 week treatment period. The flortaucipir F 18 PET scan should be completed at Visit 20 if the patient discontinues treatment after Visit 13 and before Visit 19. Patients permanently discontinued from study treatment due to initiation of a prohibited medication known to prolong the QT interval should not have an ED flortaucipir F 18 scan unless the scan can be performed prior to initiation of the prohibited medication. Patients who have continued on study after introduction of a drug known to prolong QT interval (with sponsor approval) need a minimum of 14 days or 5 half-lives, whichever is longer, without that drug prior to the flortaucipir scan. ~~If patients have had a flortaucipir F 18 PET scan at Visit 13 (as per amendment (b)), they will not be required to have another scan at Visit 20~~.

e Coagulation test results should be reviewed before each LP. Concomitant medications should be reviewed to ensure that no changes to anticoagulation or antiplatelet therapy have occurred since the last coagulation test. The coagulation test is required up to 2 weeks prior to the LP, if LP is performed at Visit 20.

g The LP should be conducted at Visit 13 should the patients follow the 25-week treatment or at Visit 19 for the 49-week week treatment period. The LP should be completed at Visit 20 if the patient discontinues treatment after Visit 13 and before Visit 19.

5.1. Overall Design

Previous diagram:



Note: Subsequent cohorts will be initiated following a review of the safety data from a minimum of 4 patients having received at least 2 doses of LY3303560 and 1 patient having received at least 2 doses of placebo at the prior dose level

Biomarkers	*Visit 1 (Screening):*	*#Visit 2:*	*@Visit 13:*	***Visit 20:*
	Amyloid scan (diagnosis) Cognition MRI	Flortaucipir PET Cognition	Cognition MRI Flortaucipir PET	Flortaucipir PET (if not done at Visit 13) Cognition

≠Visits 8, 10, 16, 19, 23: MRI

Revised diagram:

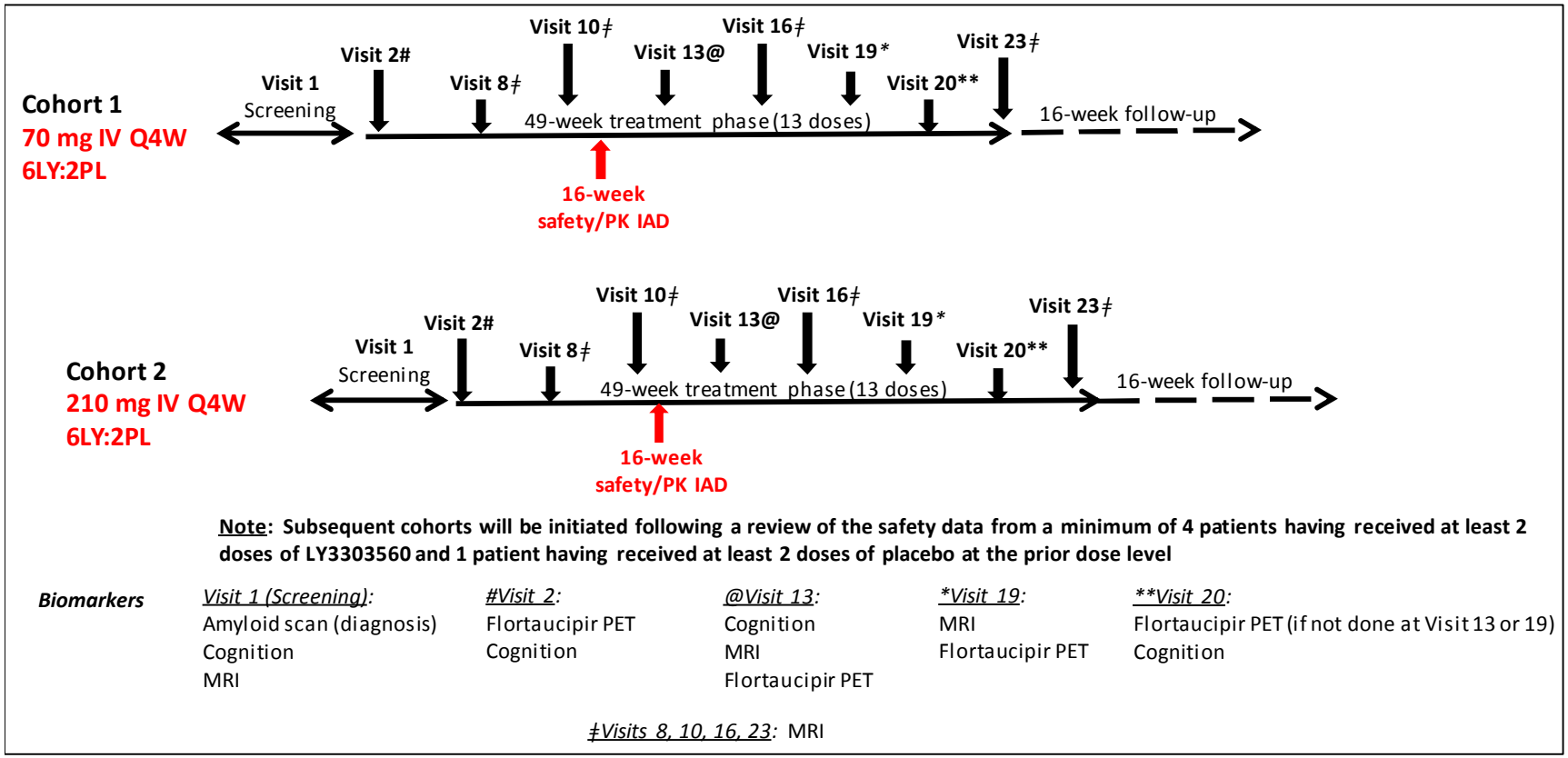


Figure LMDD.1. Illustration of study design.

5.1.2. Dosing for all Cohorts

Patients will receive their study drug at the investigational site after all predose procedures have been completed and must be observed closely for at least 4 hours following each infusion of LY3303560 for the first 6 infusions. After the first 6 infusions, a minimum post-infusion observation time of 2 hours will be required for all subsequent infusions~~, and remain in the investigative site for at least 8 hours, after each administration~~. If any patient shows symptoms of an infusion reaction, the observation time will be increased to a minimum of 8 hours for that infusion and all subsequent infusions.

5.1.3. Treatment Phase

Each cohort will consist of 8 patients randomised (6 LY3303560: 2 placebo) to a 25-week MAD treatment period (7 doses), after which they will be given the option of continuing the treatment up to 49 weeks (up to 6 further doses, Visits 14 to 19). Patients who have completed at least the 25-week treatment period will be followed up for 16 weeks after completion of dosing (Visits 20 to 24) ~~and will return to the investigational site for safety assessments and PK and biomarker sampling throughout Visits 20 to 24~~ as per the Schedule of Activities ~~(see~~in Section 2~~ for the Schedule of Activities)~~.

7.1. Treatment Administered

[…]

The minimum time for close observation at the investigative site following dosing is 4 hours for the first 6 IV infusions and 2 hours for subsequent IV infusions. If any patient shows symptoms of an infusion reaction, the observation time will be increased to 8 hours for that infusion and all subsequent infusions. The site must have resuscitation equipment, emergency drugs, and appropriately trained staff available during dosing and while patients are under observation after dosing.

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