Protocol: I8G-MC-LMDC(c)

Assessment of Safety, Tolerability, and Efficacy of LY3303560 in Early Symptomatic Alzheimer's Disease

NCT03518073

Approval Date: 29-Mar-2021

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Confidential Information

LY3303560

Multicenter, randomized, double-blind, placebo-controlled, Phase 2 study comparing up to 5600 mg of LY3303560 with placebo over 80 weeks in approximately 225 patients with early symptomatic AD.

Eli Lilly and Company
Indianapolis, Indiana, USA 46285

Protocol Electronically Signed and Approved by Lilly: 19 February 2018
Amendment (a) Electronically Signed and Approved by Lilly: 18 May 2018
Amendment (b) Electronically Signed and Approved by Lilly: 26 August 2019
Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 29-Mar-2021 GMT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	26-Aug-2019
Amendment (a)	18-May-2018
Original Protocol	19-Feb-2018

Amendment [c]

Overall Rationale for the Amendment:
This amendment includes changes to the statistical model used in analyses of primary and secondary outcomes, and modification to the scope of the third interim analysis.

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis	Changed the statistical model used in analyses of primary and secondary outcomes	Based on recent data assessments of non-LMDC datasets, disease progression model (DPM) offers reduced variability and hence improved power for detection of longitudinal treatment effect sizes in clinical measures
Section 7.3. Blinding Section 10.3.6. Interim Analyses	Amended analyses performed by the external DMC Removed the requirement for efficacy and/or futility assessments in third interim analysis	1) Current understanding of safety profile does not suggest continued treatment to end of study adds significant risk to participants. 2) Amendment (b) lengthened study from 18 months to 24 months based on the premise that there may be delayed efficacy between 18 and 24 months. Therefore, a futility analysis at 18 months may not accurately represent potential efficacy at 24 months. 3) Based on the timing of last patient visit, stopping study for futility at Interim 3 would result in study closure within a few months of planned last study visit.
Section 9.1.2.2. Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL)	Added Item 6a to ADCS-ADL subset of items Corrected upper limit in the range for the iADL score Corrected upper limit in the range for the bADLs	Correction
Section 10.1. Sample Size Determination	Added language to describe power calculations and the false-positive rate for the updated statistical model	Based on recent data assessments of non-LMDC datasets, DPM offers reduced variability and hence improved power for detection of longitudinal

Section # and Name	Description of Change	Brief Rationale
		treatment effect sizes in clinical measures
Section 10.3.1. General Statistical Considerations	Removed explicit reference to Bretz's graphical approach	With changing the primary analyses to DPM, a more general approach may be required to control Type I error
Section 10.3.1. General Statistical Considerations Section 10.3.6. Interim Analyses	Modification to the scope of the third interim analysis	Based on recent data assessments of non-LMDC datasets, DPM offers reduced variability and hence improved power for detection of longitudinal treatment effect sizes in clinical measures
Section 10.3.1.1. Handling of Missing Items for Scales	Changed requirements related to scoring of the ADAS-Cog_{13} scale	Correction
Section 10.3.3.1. Primary Analyses	Modified scope of the primary analysis	Based on recent data assessments of non-LMDC datasets, DPM offers reduced variability and hence improved power for detection of longitudinal treatment effect sizes in clinical measures
Section 10.3.3.2. Secondary Efficacy Analyses	Modification to the scope of the secondary analysis	Based on recent data assessments of non-LMDC datasets, DPM offers reduced variability and hence improved power for detection of longitudinal treatment effect sizes in clinical measures
Section 10.3.4.4. Electrocardiograms	Updated analysis of ECG data from MMRM to Analysis of covariance (ANCOVA)	Updated analysis of ECG data over time to current standard (ANCOVA by visit)
Section 10.3.6. Interim Analyses	Added language to provide flexibility to efficacy analyses performed by external DMC	Clarification
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore not detailed

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1. Synopsis

Title of Study:

Protocol I8G-MC-LMDC(c). Assessment of Safety, Tolerability, and Efficacy of LY3303560 in Early Symptomatic Alzheimer's Disease

Rationale:

Eli Lilly and Company (Lilly) is developing LY3303560, a humanized monoclonal antibody, which targets extracellular aggregated tau for the treatment of Alzheimer's disease (AD).

A Phase 1 study (I8G-MC-LMDA [LMDA]) is currently ongoing to evaluate the safety, tolerability, and pharmacokinetics (PK) of LY3303560 in healthy subjects and patients with AD. Safety and tolerability evaluations are being conducted over a wide range of single doses, and dose escalation does not occur until safety data from previous doses have been reviewed. Study LMDA aims to assess whether a maximum-tolerated dose can be established or to demonstrate the tolerability of a dose greater than the expected therapeutic dose.

A Phase 1 multiple-dose, dose-escalation study (I8G-MC-LMDD [LMDD]) is currently also ongoing to assess the safety, tolerability, PK, and pharmacodynamics (PD) of LY3303560 in patients with mild cognitive impairment due to AD or mild-to-moderate Alzheimer's Dementia.

Study I8G-MC-LMDC (LMDC) is a Phase 2, double-blind, placebo-controlled study to evaluate the safety and efficacy of tau antibody (LY3303560) in patients with low-to-medium tau burden as measured by flortaucipir within a population who have early symptomatic AD (prodromal AD and mild dementia due to AD). Study LMDC will assess whether binding and clearance of aggregated (misfolded) tau can slow the progression of disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration over 100 weeks of treatment (26 doses, administered as an intravenous [IV] infusion once every 4 weeks [Q4W], starting at Visit 2 [Week 0] and ending at Visit 27 [Week 100], with endpoint cognitive assessments carried out at Visit 28 [Week 104]).

Progression of cerebral tauopathy associated with AD will be assessed by positron emission tomography (PET) scan using flortaucipir F 18, a marker of aggregated (misfolded) tau. Flortaucipir is an F-18-labeled small molecule that binds with high affinity and selectivity to aggregated tau pathology (but not normal monomeric tau) in ex vivo human brain sections. This biomarker is believed to provide a qualitative and quantitative measurement of deposited aggregated tau and its anatomical distribution in the brain. Absence of significant neocortical flortaucipir F 18 PET signal is believed to indicate that, although patients may be clinically manifesting cognitive impairment, levels of aggregated tau deposits are low and may not have spread beyond the medial/anterior temporal cortex, and at the group level may be associated with a relatively slow rate of cognitive deterioration. High and widespread flortaucipir F 18 signal indicates that aggregated tau deposits have already spread through much of the brain, and at the group level may be associated with a more rapid rate of cognitive deterioration. Thus,

implementation of flortaucipir F 18 scans aims to facilitate selection of participants with a low-to-medium tau accumulation for entry into the clinical trial.

Alzheimer's disease is also associated with pronounced brain atrophy, reflecting bulk neurodegenerative loss of gray and white matter. Progression of brain atrophy will be assessed by volumetric magnetic resonance imaging (vMRI), providing regional quantification of volume loss.

The patient population selected for the clinical trial is patients with AD having early symptomatic disease (that is, prodromal-to-mild AD dementia) and low-to-medium tau burden as measured by flortaucipir F 18 PET scans. Clinical–pathological correlations suggest that baseline imaging that allows staging based on neurofibrillary tangles could substantially improve the power of clinical trials aimed at changing the rate of progression of the disease (Qian et al. 2017). An early AD population defined clinically and pathologically (using tau PET imaging) is anticipated to be more homogeneous than populations defined by clinical symptoms alone. It is postulated that the early AD, low-to-medium tau burden population will be sufficiently early in their disease course to respond to treatments prior to more advanced disease when extensive irreversible neuronal loss occurs. Confirmation of amyloid status is not required because the flortaucipir F 18 PET study entry criteria confirm the presence of tauopathy of AD and the antibody target, and is highly associated with amyloid positivity (Lilly, data on file, A05 study).

Objective(s)/Endpoints:

Primary Objective	Primary Endpoint
To test the hypothesis that LY3303560 administered for 100 weeks will decrease the decline in cognitive and/or functional outcomes in patients with early symptomatic AD relative to placebo.	Change in cognition and function as measured by the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 104 weeks.
Secondary Objectives	**Secondary Endpoints**
To assess the effect of LY3303560 versus placebo on clinical progression in patients with early symptomatic AD.	Change in cognition and/or function from baseline to 104 weeks as measured by the change in: • Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog_{13}) score • Alzheimer's Disease Cooperative Study—instrumental Activities of Daily Living scale (ADCS-iADL) score • Clinical Dementia Rating Scale—Sum of Boxes (CDR-SB) score • Mini-Mental State Examination (MMSE) score
To assess the effect of LY3303560 versus placebo on brain aggregated tau deposition.	Change in brain aggregated tau deposition from baseline through 104 weeks as measured by flortaucipir F 18 PET scan.
To assess the effect of LY3303560 versus placebo on attenuating downstream markers of the neurodegenerative process in AD.	Change in brain volumetric measures from baseline through 104 weeks as measured by volumetric magnetic resonance imaging (vMRI).
Safety Objective	**Safety Endpoints**

To evaluate safety and tolerability of LY3303560.	• Safety assessments:
	  ○ Spontaneously reported AEs
	  ○ Clinical laboratory tests
	  ○ Vital sign and body weight measurements
	  ○ 12-lead ECGs
	  ○ Physical and neurological examinations
	  ○ Anti-drug antibodies
	• Magnetic resonance imaging (MRI) (treatment-emergent radiological findings)
	• Columbia Suicide Severity Rating Scale (C-SSRS)

Summary of Study Design:

Study LMDC is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of LY3303560 in subjects with early symptomatic AD with low-to-medium cerebral tau burden. The maximum possible duration of the study is 121 weeks that includes a screening period of up to 8 weeks, a treatment period of 100 weeks, a 4-week post last dose assessment, and an immunogenicity and safety follow-up period of up to 13 weeks following the last dose of study drug at Week 100.

Treatment Arms and Duration:

Patients will receive one of the following treatments for 100 weeks:

- **1400 mg LY3303560:** LY3303560 1400 mg IV infusion Q4W for 100 weeks (Visit 2 [Week 0] to Visit 27 [Week 100]).
- **5600 mg LY3303560:** LY3303560 5600 mg IV infusion Q4W for 100 weeks (Visit 2 [Week 0] to Visit 27 [Week 100]).
- **Placebo**: IV placebo infusion Q4W for 100 weeks (Visit 2 [Week 0] to Visit 27 [Week 100]).

Number of Patients (Approximate):

- Screened – approximately 1400
- Randomized – 285 (30 randomized for Group 1 [patients included in the first interim safety analysis] and 255 randomized for Group 2)
- Evaluable (Completers) – 225 (approximately 75 per treatment group)

Statistical Analysis:

All efficacy analyses will follow the intent-to-treat (ITT) principle unless otherwise specified. An ITT analysis is an analysis of data by the groups to which subjects are assigned by random allocation, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Unless otherwise noted, all pairwise tests of treatment effects will be conducted at a 2-sided alpha level of 0.05; 2-sided confidence intervals (CIs) will be displayed with a 95% CI.

Efficacy:

The primary objective of this study is to test the hypothesis that IV infusion of LY3303560 will slow the decline of AD as measured by the integrated Alzheimer's Disease Rating Scale (iADRS), which is a composite cognitive and functional measure, compared with placebo in patients with early symptomatic AD. The slowing in disease progression on iADRS will be evaluated using a disease progression model (DPM) as a primary assessment model. To test the hypothesis of a disease progression benefit, we calculate the posterior probability of superiority in cognitive/functional slowing, and if it is above a pre-specified threshold (which controls the experiment-wise type I error at 2.5%), then a claim of cognitive slowing will be made.

Each of the secondary efficacy outcomes will be assessed using DPM, mixed model repeated measures (MMRM), and natural cubic spline (NCS) analyses. These secondary efficacy outcomes include Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog_{13}), Alzheimer's Disease Cooperative Study—instrumental Activities of Daily Living Inventory (ADCS-iADL), Clinical Dementia Rating Scale—Sum of Boxes (CDR-SB), and Mini-Mental State Examination (MMSE). iADRS will also be assessed using MMRM and NCS analyses. Additional details are described in the statistical analysis plan (SAP).

Safety:

Safety will be assessed by summarizing and comparing between treatment arm adverse events (AEs), laboratory analytes, vital signs, magnetic resonance imaging (MRI) scans, electrocardiograms (ECGs), and immunogenicity for each defined study period: a treatment period of 100 weeks, a 4-week post last dose assessment, and an immunogenicity and safety follow-up period of up to 13 weeks following the last dose of study drug at Week 100.

Pharmacokinetics/Pharmacodynamics:

Compartmental modeling of LY3303560 PK data using nonlinear mixed effects modeling or other approaches may be explored, and population estimates for clearance and central volume of distribution may be reported. Depending on the model selected, other PK parameters may also be reported. Exploratory graphical analyses of the effect of dose level or demographic factors on PK parameters may be conducted. If appropriate, data from other studies of LY3303560 may be used in this analysis.

Pharmacokinetic/pharmacodynamic relationships between plasma LY3303560 concentration and flortaucipir F 18 standardized uptake value ratio (SUVr), vMRI measures, cognitive endpoints, or other markers of PD activity may be explored graphically. The relationship between the presence of antibodies against LY3303560 and PK, PD, safety, and/or efficacy may be assessed graphically. If warranted, additional analysis may be explored to evaluate potential interactions for anti-drug antibodies (ADA), PD, and other endpoints (PET or MRI measures, safety, etc.). Additional modeling may be performed based on the results of the graphical analyses.

2. Schedule of Activities

Table LMDC.2.1. Schedule of Activities

Schedule of Activities, Protocol I8G-MC-LMDC Visit 1 (Screening Period)

Period: Procedure	
Visit No.:	**V1**
End of Week Relative to Study Medication Start[a]	**Wk -8 through Wk -1**
Tolerance Interval for Visit (days)[a,b]	**-56 to 0**
PRELIMINARY SCREENING	
Entry and Administrative	
Abbreviated (or full) Informed Consent – participant and study partner[c]	X
Patient number assigned via IWRS	X
Demographics and habits	X
Medical history	X
Entry Diagnostics	
MMSE[d,o]	X
CBB	X
DCTClock	X
SCREENING	
Full Informed Consent – participant and study partner[d]	X
Inclusion/exclusion review	X
Physical/neurological examination[e]	X
Previous/concomitant medications	X
Preexisting conditions	X
Entry Diagnostics	
Safety Assessments	
Vital signs[f]	X
Height and weight[g]	X
ECG in triplicate[h]	X
C-SSRS[i]	X
Self-Harm Supplement Form	X[j]
Self-Harm Follow-up Form	X[j]
Laboratory Specimens	
Clinical chemistry, hematology	X[b]
High sensitivity C-reactive protein	X
HBsAg[k]	X
HCV RNA PCR[l]	X
Urinalysis	X
Plasma tau	X
Plasma phospho181tau and NfL	X
Biomarker storage	X
Screening PET Scans and MRI	
Flortaucipir F 18 PET Scan[m]	X
MRI[n]	X

Schedule of Activities, Protocol I8G-MC-LMDC, Visit 1 (Screening Period) Abbreviations and Footnotes

Abbreviations: CBB = CogState Brief Battery; C-SSRS = Columbia Suicide Severity Rating Scale; DCTClock = Digital Clock Drawing Test; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = informed consent form; IWRS = interactive web response system; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NfL = neurofilament light; No. = number; PCR = polymerase chain reaction; PET = positron emission tomography; RNA = ribonucleic acid; V = visit; Wk = week.

[a] The interval between the signing of the full ICF at V1 and V2 may be up to 56 days to allow for completion of V1 screening procedures, assessments, and evaluation of results from laboratory tests and ECGs. V1 is not considered complete until all screening procedures have been completed and results reviewed by the investigator to determine patient eligibility.

[b] Patients whose screening results are not available within the 56-day screening window from the time of signing the full ICF will remain eligible within V1 until these results become available if all other eligibility criteria have been met. Note: If all screening results confirming eligibility for the study have not been received by the site by Day 56 of the screening period, it will not be considered a protocol deviation, but clinical laboratory tests (blood hematology, chemistry, and urinalysis are to be repeated for that patient. Results of the repeated labs are to be reviewed by the investigator or qualified designee for assessment of the patient's continued eligibility. Repeat screening for MMSE, CBB, DCTClock, C-SSRS, ECG, flortaucipir F 18 PET, MRI, sample collection for plasma tau, plasma phospho181 tau, and biomarker storage, and laboratory testing for HBsAg, and HCV RNA PCR are not required.

[c] A preliminary screening informed consent may be obtained to collect demographics data and administer the MMSE, CBB, and the DCTClock. Patients who do not meet the MMSE screening criteria will proceed to complete the CBB and DCT Clock, but are not to have any other screening procedures performed. They may be rescreened once for the MMSE 8 weeks or more after the first screen. Study partners are not required to complete the preliminary screening informed consent. Patients who screen failed on the CBB in the previous version of this protocol may be reconsented and immediately rescreened using the MMSE. If the patient has a historical Lilly or Avid flortaucipir PET scan result showing low to medium tau, then the scan may be submitted to the PET imaging central reader to determine eligibility. If the historical PET scan is verified as eligible, then the patient does not need to meet screening MMSE eligibility criteria (see Section 5.1.1.1.1 and Section 5.1.1.1.6.1), although the MMSE data will be collected for statistical analysis.

[d] Patients who score 20 to 28 on the MMSE at Visit 1 or have a historical Lilly or Avid flortaucipir F 18 PET scan that meets eligibility may proceed to the remaining screening procedures beyond the CBB and DCTclock once they have given signed/dated informed consent for the full study and their study partner has given signed/dated informed consented to participate as a study partner.

[e] Complete physical and neurological examinations are to be performed at this visit. Additional details are provided in Section 9.4.1.

[f] Blood pressure and pulse will be measured in the sitting position only. Temperature will be collected with vital signs.

[g] Height and weight will be measured, with shoes removed at least for the height measurement at the screening visit.

[h] ECGs should be taken in triplicate at approximately 1-minute intervals. ECGs should be collected at approximately the same time of day, as much as possible, to minimize diurnal variation.

[i] The baseline version of the C-SSRS is to be administered at V1. Patients at imminent risk of suicide (positive response to Question 4 or 5 on the C-SSRS) will be excluded from participating in the study.

[j] The Self-Harm Supplement Form is completed after each C-SSRS administration to enter the number of discrete events of suicidal behavior identified. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then completion of the Self-Harm Follow-Up Form is required to collect additional information to allow for a more complete assessment of these behaviors.

[k] Patients with a history of hepatitis B are to have a serum HBsAg test at screening V1 and are excluded if the HBsAg test is positive.

[l] Patients who are HCV-antibody positive should have follow-up HCV RNA PCR testing at screening V1 and are excluded if HCV RNA PCR is positive.

[m] For patients who do not have an acceptable historical Lilly or Avid flortaucipir PET scan, a screening flortaucipir F 18 PET scan will be performed as part of the study eligibility criteria at all sites to determine patient eligibility for participation in Study LMDC (see Appendix 5). With the exception of an MRI, a patient must meet all other V1 eligibility criteria before having a screening flortaucipir F 18 PET scan. The flortaucipir F 18 PET scan will be submitted to a centralized PET imaging vendor designated by Lilly for an assessment of patient's eligibility. The flortaucipir F 18 PET screening criteria should be met (scan results consistent with sponsor-derived eligibility limits for flortaucipir F 18 PET) before the patient can undergo the MRI. A historical flortaucipir F 18 PET scan may be submitted to be considered for eligibility if performed within 6 months of V1. If the historical scan meets eligibility criteria but is performed more than 6 months prior to Visit 2, then another flortaucipir scan must be performed and used as the baseline scan (see Section 5.1.1.1.6.1) for analysis.

[n] A screening MRI will be performed at V1 as part of the study eligibility criteria. The MRI scans will be reviewed by the investigator or qualified designee for immediate patient management. After the MRI scan is read locally, the scan is to be submitted to the centralized MRI vendor designated by Lilly for final determination of MRI eligibility. Results of centrally read MRIs will be used for data analysis and report-writing purposes and patient safety and eligibility will be reported back to sites.

[o] Assessment includes audio voice recording of the rater's questions and the patient and caregiver responses.

Schedule of Activities, Protocol I8G-MC-LMDC, Visit 2 through Visit 14 (Double-Blind Period)

Period: / Procedure	Rand												
Visit No.:	**V2**[a,b]	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
End of Week Relative to Study Medication Start	0	4	8	12	16	20	24	28	32	36	40	44	48
Tolerance Interval for Visit (days)	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Inclusion/exclusion review	X												
Contact IWRS – dispensation of study medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical/neurological examination[e]	X[f]			X[g]			X[g]			X[g]			
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Preexisting conditions/adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication administered[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient disposition													
Efficacy Measures													
ADAS-Cog_{13}[i, aa]	X			X			X			X			
ADCS-ADL[i, aa]	X			X			X			X			
CDR-SB[i, aa]	X			X			X			X			
MMSE[i, aa]				X			X			X			
CBB													
DCTClock[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessment													
C-SSRS[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]

Schedule of Activities, Protocol I8G-MC-LMDC, Visit 2 through Visit 14 (Double-Blind Period)

Period: / Procedure	Rand												
Visit No.:	**V2**[a,b]	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
End of Week Relative to Study Medication Start	0	4	8	12	16	20	24	28	32	36	40	44	48
Tolerance Interval for Visit (days)	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Laboratory Specimens[l]													
Clinical chemistry, hematology[m]	X	X	X	X			X			X			
High sensitivity C-reactive protein[m]	X	X	X	X			X			X			
Urinalysis[m]	X												
Serum for anti-LY3303560 antibody[m]	X	X	X	X	X		X			X			
Serum LY3303560[n,o]	X[n]	X[n]	X[n]	X[n]	X[o]		X[n]			X[o]			
Plasma total tau[m]	X	X	X	X	X		X			X			
Plasma phospho181tau and NfL[m]	X	X	X	X	X		X			X			
Blood for assessment of APOE genotype[m,p]	X												
Whole blood, plasma and serum for biomarker storage[m,q]	X				X		X			X			
Blood for pharmacogenomics[m,q,r]	X												
Other Safety Measures													
Weight	X			X			X			X			
Vital signs and body temperature[s,t]	X[t]	X	X	X[t]	X	X	X[t]	X	X	X[t]	X	X	X
ECG in triplicate[u]	X	X	X	X			X			X			
MRI[v]	[w]			X									
Additional Efficacy Measures													
Flortaucipir F 18 PET Scan[x]	[w]												

Schedule of Activities, Protocol I8G-MC-LMDC, Visit 15 through Visit 22 (Double-Blind Period)

Period: / Procedure								
Visit No.:	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**
End of Week Relative to Study Medication Start	52	56	60	64	68	72	76	80
Tolerance Interval for Visit (days)	±7	±7	±7	±7	±7	±7	±7	±7
Inclusion/exclusion review								
Contact IWRS – dispensation of study medication	X	X	X	X	X	X	X	X
Physical/Neurological examination[e]	X[g]			X[g]				X[f]
Previous/concomitant medications	X	X	X	X	X	X	X	X
Preexisting conditions/adverse events[e]	X	X	X	X	X	X	X	X
Study medication administered[h]	X	X	X	X	X	X	X	X
Patient disposition								X
Efficacy Measures								
ADAS-Cog_{13}[i, aa]	X			X				X
ADCS-ADL[i, aa]	X			X				X
CDR-SB[i, aa]	X			X				X
MMSE[i, aa]	X			X				X
CBB[i]	X							
DCTClock[i]	X	X	X	X	X	X	X	X
Safety Assessment								
C-SSRSi	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[k]	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]

Schedule of Activities, Protocol I8G-MC-LMDC, Visit 15 through Visit 22 (Double-Blind Period)

Period: Procedure								
Visit No.:	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**
End of Week Relative to Study Medication Start	52	56	60	64	68	72	76	80
Tolerance Interval for Visit (days)	±7	±7	±7	±7	±7	±7	±7	±7
Laboratory Specimens[l]								
Clinical chemistry, hematology[m]	X			X				X
High sensitivity C-reactive protein[m]	X			X				X
Urinalysis[m]	X			X				X
Serum for anti-LY3303560 antibody[m]	X			X				X
Serum LY3303560[n,o]	X[o]			X[o]				X[o]
Plasma total tau[m]	X			X				X
Plasma phospho181tau and NfL[m]	X			X				X
Blood for assessment of APOE genotype[m,p]								
Whole blood, plasma and serum for biomarker storage[m,q]	X			X				X
Blood for pharmacogenomics[m,q,r]								
Other Safety Measures								
Weight	X			X				X
Vital signs and body temperature[s,t]	X[t]	X	X	X[t]	X	X	X	X[t]
ECG in triplicate[u]	X			X				X
MRI[v]	X							
Additional Efficacy Measures								
Flortaucipir F 18 PET Scan[x]	X[x]							

Schedule of Activities, Protocol I8G-MC-LMDC, Visit 23 through Visit 28 (Double-Blind Period) and Visit 801 (Immunogenicity and Safety Follow-Up)

Period: / Procedure								
Visit No.:	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**ED[c]**	**V801[d]**
End of Week Relative to Study Medication Start	84	88	92	96	100	104		113
Tolerance Interval for Visit (days)	±7	±7	±7	±7	±7	±7		±14
Inclusion/exclusion review								
Contact IWRS – dispensation of study medication	X	X	X	X	X			
Physical/Neurological examination[e]			X[g]			X[f]	X[f]	
Previous/concomitant medications	X	X	X	X	X	X	X	X
Preexisting conditions/adverse events[e]	X	X	X	X	X	X	X	X
Study medication administered[h]	X	X	X	X	X			
Patient disposition						X	X	X
Efficacy Measures								
ADAS-Cog_{13}[i, aa]			X			X	X	
ADCS-ADL[i, aa]			X			X	X	
CDR-SB[i, aa]			X			X	X	
MMSE[i, aa]			X			X	X	
CBB[i]						X	X	
DCTClock[i]	X	X	X	X	X	X	X	
Safety Assessment								
C-SSRSi	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[k]	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]

Schedule of Activities, Protocol I8G-MC-LMDC, Visit 23 through Visit 28 (Double-Blind Period) and Visit 801 (Immunogenicity and Safety Follow-Up)

Period: Procedure								
Visit No.:	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**ED[c]**	**V801[d]**
End of Week Relative to Study Medication Start	84	88	92	96	100	104		113
Tolerance Interval for Visit (days)	±7	±7	±7	±7	±7	±7		±14
Laboratory Specimens[l]								
Clinical chemistry, hematology[m]			X			X	X	
High sensitivity C-reactive protein[m]			X			X	X	
Urinalysis[m]			X			X	X	
Serum for anti-LY3303560 antibody[m]			X			X	X	X
Serum LY3303560[n,o]			X[o]			X[o]	X[o]	X[o]
Plasma total tau[m]			X			X	X	
Plasma phospho181tau and NfL[m]			X			X	X	
Blood for assessment of APOE genotype[m,p]								
Whole blood, plasma and serum for biomarker storage[m,q]			X			X	X	
Blood for pharmacogenomics[m,q,r]								
Other Safety Measures								
Weight			X			X	X	
Vital signs and body temperature[s,t]	X	X	X[t]	X	X	X[t]	X[t]	X
ECG in triplicate[u]			X			X	X	
MRI[v]						X	X	
Additional Efficacy Measures								
Flortaucipir F 18 PET Scan[x]						X[x]	X[x,y]	

Schedule of Activities, Protocol I8G-MC-LMDC, Visit 2 through Visit 801, Abbreviations and Footnotes

Abbreviations: ADA = anti-drug antibodies; ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale—Cognitive subscore; ADCS-ADL = Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory; APOE = apolipoprotein subtype E; CBB = CogState Brief Battery; CDR-SB = Clinical Dementia Rating—Sum of Boxes; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; DCTClock = Digital Clock Drawing Test; ECG = electrocardiogram; ED = early discontinuation; IV = intravenous; IWRS = interactive web response system; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NfL = neurofilament light; No. = number; PET = positron emission tomography; TE = treatment-emergent; Rand = randomization; V = visit.

[a] Confirm that the patient has met all V1 eligibility criteria before proceeding with V2 procedures.

[b] At V2, appointments should be made for all remaining visits and should be scheduled as close as possible to the target date, relative to V2. Procedures for some visits may take more than 1 day.

[c] If a patient discontinues before the double-blind period endpoint (V28 at Week 104), the ED procedures and CRFs should be completed. The patient should be encouraged to return to the site 13 weeks after the ED visit for an immunogenicity follow-up visit (V801).

[d] Patients are to return to the site for collection of blood samples and safety assessments for assessment of immunogenicity status at V801 (Week 113). Follow-up for patients experiencing clinically significant events associated with TE-ADA status is described in Section 9.4.7.2.

[e] Any clinically significant changes from baseline on follow-up physical/neurological examinations should be noted on the AE page.

[f] Complete physical and neurological examinations are to be performed at this visit prior to study drug administration. Additional details are provided in Section 9.4.1.

[g] Brief physical and neurological examinations are to be performed at this visit prior to study drug administration. Additional details are provided in Section 9.4.1.

[h] Study drug will be administered by IV administration at investigative study site. Patients should be observed for a minimum of 2 hours following each infusion for the first 3 infusions. After the first 3 doses, a minimal post-infusion observation time of 60 minutes will be required for all subsequent infusions.

[i] When administered, cognitive and functional assessments (ADAS-Cog_{13}, ADCS-ADL, CDR, MMSE, CBB, and DCTClock) should be performed first before medical procedures that could be stressful for the patient (for example, blood draws).

[j] The "since last visit" version of the C-SSRS will be administered at all visits after V1 (Weeks -8 through -1) to the patient with the study partner/study informant present, after the cognitive and functional assessments.

[k] The Self-Harm Supplement Form is completed after each C-SSRS administration to enter the number of discrete events of suicidal behavior identified. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then completion of the Self-Harm Follow-Up Form is required to collect additional information to allow for a more complete assessment of these behaviors.

[l] Unscheduled laboratory tests may be performed at the discretion of the investigator.

[m] Labs are to be collected prior to administration of the IV study medication. Record the date and times of sample collection on the Lab Requisition Form.

[n] Predose (before beginning the infusion) and postdose (within 30 minutes of completion of the infusion) samples for IV study medication should be collected from the arm that did not receive the infusion. (Note: Sites are permitted to collect the predose sample from the indwelling catheter prior to start of infusion). These samples will be collected at V2 (Week 0), V3 (Week 4), V4 (Week 8), V5 (Week 12), and V8 (Week 24). At V2, only the postdose sample will be collected.

[o] A single predose LY3303560 sample should be collected before beginning the infusion at V6 (Week 16), V11 (Week 36), V15 (Week 52), V18 (Week 64), V22 (Week 80), V25 (Week 92), and V28 (Week 104). In addition, a single sample for serum LY3303560 should be collected at ED (a visit at which the patient may not receive a study drug infusion). Record the actual date and times of sample collection on the Lab Requisition Form.

[p] A blood sample will be collected to determine APOE genotype. The APOE may be collected at an alternative visit if it cannot be collected at V2.

[q] Blood for biomarker storage, and blood for pharmacogenomic samples are to be collected unless not allowed or unfeasible due to local regulations prohibiting sample transport outside of the country.

[r] Pharmacogenomic samples may be collected at an alternative visit if they cannot be collected at V2. It will not be a protocol deviation if a biomarker storage sample cannot be collected for technical reasons (for example, if the site is unable to collect enough blood via venipuncture).

[s] Sitting blood pressure and pulse will be measured after 5 minutes in the sitting position at **all** visits prior to administration of study drug. Temperature will be collected with sitting vital signs.

[t] In addition, orthostatic blood pressure and pulse will be measured at V2 (Week 0), V5 (Week 12), V8 (Week 24), V11 (Week 36), V15 (Week 52), V18 (Week 64), V22 (Week 80), V25 (Week 92), and V28 (Week 104), or ED, and at unscheduled visits after 5 minutes in the supine position and after 3 minutes standing.

[u] Electrocardiograms should be taken in triplicate at approximately 1-minute intervals. Electrocardiograms should be collected at approximately the same time of day, as much as possible, to minimize diurnal variation. Electrocardiograms are to be performed prior to the administration of IV study medication (LY3303560 and IV placebo).

[v] If MRI is performed on the same day as cognitive and functional assessments, then it should be performed after cognitive and functional tests. Magnetic resonance imaging may be performed before other visit procedures, including cognitive and functional tests, but in that case it must be performed at least 1 day before other visit procedures.

[w] The screening flortaucipir F 18 PET scan and MRI performed at V1 (or accepted from a permitted historical scan) serve as the baseline flortaucipir F 18 PET scan and MRI.

[x] Before the flortaucipir F 18 PET scan is performed, the investigator should review the patient's medical history to verify there is no risk factor for Torsades de Pointes and review the most recent ECG. If clinically meaningful abnormalities are noted on the ECG, the advisability of the flortaucipir scan should be considered by the investigator in consultation with the Lilly-designated medical monitor.

[y] Patients who discontinue from the study early will have a flortaucipir scan performed at the ED visit only if they have completed V11 and it has been at least 6 months since their previous scan.

[z] Footnote z was deleted.

[aa] Assessment includes the audio voice recording of the rater's questions and the patient and caregiver responses to assessment questions.

3. Introduction

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

Tau is an axonal microtubule-binding protein that normally promotes microtubule assembly and stability. In AD and other neurodegenerative diseases, collectively termed tauopathies, hyperphosphorylated misfolded tau causes tau aggregation, tau seeding, NFT formation, microtubule destabilization, and neuronal toxicity (Wang and Mandelkow 2016). Over time, tau accumulates in the brains of patients with AD, and forms intraneuronal NFTs, with tau pathology spreading in sequence from transentorhinal, to limbic, to neocortical regions (Braak and Braak 1991; Delacourte et al. 1999). The spread of tau pathology is correlated with neuronal loss, clinical symptoms, and progression in AD and other neurodegenerative diseases, such as progressive supranuclear palsy (PSP) (Duyckaerts et al. 1987).

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

3.1. Study Rationale

Eli Lilly and Company (Lilly) is developing LY3303560, a humanized monoclonal antibody, which targets extracellular aggregated tau for the treatment of AD.

A Phase 1 study (I8G-MC-LMDA [LMDA]) is currently ongoing to evaluate the safety, tolerability, and pharmacokinetics (PK) of LY3303560 in healthy subjects and patients with AD. Safety and tolerability evaluations are being conducted over a wide range of single doses, and dose escalation does not occur until safety data from previous doses have been reviewed. Study LMDA aims to assess whether a maximum-tolerated dose can be established or to demonstrate the tolerability of a dose greater than the expected therapeutic dose.

A Phase 1 multiple-dose, dose-escalation study (I8G-MC-LMDD [LMDD]) is currently also ongoing to assess the safety, tolerability, PK, and pharmacodynamics (PD) of LY3303560 in patients with mild cognitive impairment due to AD or mild-to-moderate Alzheimer's dementia.

Study I8G-MC-LMDC (LMDC) is a Phase 2, double-blind, placebo-controlled study to evaluate the safety and efficacy of tau antibody (LY3303560) in patients with low-to-medium tau burden as measured by flortaucipir within a population who have early symptomatic AD (prodromal AD and mild dementia due to AD). Study LMDC will assess whether binding and clearance of

aggregated (misfolded) tau can slow the progression of disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration over 100 weeks of treatment (26 doses, administered as an intravenous [IV] infusion once every 4 weeks [Q4W] starting at Visit 2 [Week 0] and ending at Visit 27 [Week 100], with end of treatment cognitive assessments carried out at Visit 28 [Week 104]).

Progression of cerebral tauopathy associated with AD will be assessed by positron emission tomography (PET) scan using flortaucipir F 18, a marker of aggregated (misfolded) tau. Flortaucipir is an F-18-labeled small molecule that binds with high affinity and selectivity to aggregated tau pathology (but not normal monomeric tau) in ex vivo human brain sections. This biomarker is believed to provide a qualitative and quantitative measurement of deposited aggregated tau and its anatomical distribution in the brain. Absence of significant neocortical flortaucipir F 18 PET signal is believed to indicate that, although patients may be clinically manifesting cognitive impairment, levels of aggregated tau deposits are low and may not have spread beyond the medial/anterior temporal cortex, and at the group level may be associated with a relatively slow rate of cognitive deterioration. High and widespread flortaucipir F 18 signal indicates that aggregated tau deposits have already spread through much of the brain, and at the group level may be associated with a more rapid rate of cognitive deterioration. Thus, implementation of flortaucipir F 18 scans may facilitate selection of participants with a low-to-medium tau accumulation for entry into the clinical trial.

Alzheimer's disease is also associated with pronounced brain atrophy, reflecting bulk neurodegenerative loss of gray and white matter. Progression of brain atrophy will be assessed by volumetric magnetic resonance imaging (vMRI), providing regional quantification of volume loss.

The patient population selected for the clinical trial is patients with AD having early symptomatic disease (that is, prodromal-to-mild AD dementia) and with low-to-medium tau burden as measured by flortaucipir F 18 PET scans. Clinical–pathological correlations also strongly suggest that baseline imaging that allows staging based on neurofibrillary tangles could substantially improve the power of clinical trials aimed at changing the rate of progression of the disease (Qian et al. 2017). An early AD population defined clinically and pathologically (using tau PET imaging) is anticipated to be more homogeneous than populations defined by clinical symptoms alone. It is postulated that the early AD, low-to-medium tau burden population will be sufficiently early in their disease course to respond to treatments prior to more advanced disease when extensive irreversible neuronal loss occurs. Confirmation of amyloid status is not required because the flortaucipir F 18 PET study entry criteria confirm the presence of tauopathy of AD and the antibody target, and is invariably associated with amyloid positivity (Lilly, data on file, A05 study).

3.2. Background

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

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

In vitro, LY3303560 inhibits cell-based tau propagation, binds to brain sections derived from patients with AD or tauopathy, and does not interfere with the binding of the tau PET tracer flortaucipir to NFTs. 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. Nonclinical Studies

The safety of LY3303560 was evaluated in transgenic Tg4510 mice by subcutaneous (SC) injection of 0, 2, 20, or 200 mg/kg once weekly for 5 doses or once weekly for 26 doses. In the 6-month study, minor test article-related clinical chemistry findings in animals administered 200 mg/kg included minimally higher globulin concentration resulting in higher total protein concentration and lower albumin:globulin ratio. These changes were suggestive of inflammatory response; however, inflammation was not evident in leukocyte counts, and no correlative findings of inflammation were noted microscopically. This increased globulin concentration may have been due to the presence of the test article (an immunoglobulin [Ig]). At the highest dose tested (200 mg/kg/week), there were no-observable-adverse-effects in the mouse and monkey in both the 5-week and 6-month studies. This was defined as NOAEL.

The safety of LY3303560 was also evaluated in cynomolgus monkeys by SC (0, 2, 20 mg/kg) or IV (200 mg/kg) injections once weekly for 5 doses or once weekly for 26 doses. In addition to traditional Good Laboratory Practice toxicology study assessments, safety pharmacology assessments were performed during the 5-week monkey study, including the evaluation of body temperature, cardiovascular safety, observations for central nervous system (CNS) signs with neurological examination, and qualitative assessment of respiratory depth with quantitative estimates of respiratory rate. Cardiovascular assessment was also conducted in the 6-month monkey study on Day 8, 85, or 169 of the dosing phase. No drug-related changes occurred in any parameters. One monkey given the highest dose of 200 mg/kg IV for 5 weeks was observed with periorbital swelling after the last dose. The monkey was given diphenhydramine and the swelling was significantly reduced within 1 hour of diphenhydramine administration and resolved the following day. It is not clear if the periorbital swelling was compound-related; notably no observations of periorbital swelling were observed in the 6-month study. In the 6-month study, the only test article-related finding in animals administered 200 mg/kg IV was mildly increased globulin concentration, resulting in decreased albumin:globulin ratio, on Days 78 and 183. Evidence of inflammation was not observed in other clinical pathology data. In the absence of inflammation or evidence of immune stimulation, this increase in globulin concentration may have been due to the presence of the test article (Ig). In the 6-month study, spontaneous minimal liver changes were observed in 2 animals administered LY3303560. One female administered with 200 mg/kg had a minimally increased number of individual necrotic/apoptotic hepatocytes in 1 small subcapsular region in 1 of 2 examined liver sections; the liver sections were otherwise microscopically unremarkable. Based on the limited subcapsular distribution and lack of clinical chemistry changes, indicative of a more generalized

liver involvement, the change in this animal was considered spontaneous, rather than test article-related. One male administered with 20 mg/kg had a minimally increased number of individual necrotic/apoptotic hepatocytes scattered randomly in occasional microscopic fields in examined sections of liver; liver sections in this animal were otherwise microscopically unremarkable, and no differences in liver weight or in liver-related clinical chemistry parameters were noted compared with control. This less-restricted pattern of individual hepatocyte necrosis/apoptosis was limited to 1 animal and lacked evidence of a dose response; therefore, it was considered not test article-related. The NOAEL in both the 5-week and 6-month studies was 200 mg/kg/week (IV).

Comparable LY3303560 binding was observed in a standard panel of normal human and cynomolgus monkey tissues as evaluated by tissue cross-reactivity analysis. Thus, the monkey toxicology study is considered to have adequately assessed the potential for adverse effects that may have been associated with any binding to tissues in vivo.

The nonclinical safety profile of LY3303560 in monkeys and transgenic Tg4510 mice supports clinical development. Please see the Investigator's Brochure (IB) for details regarding nonclinical LY3303560 studies.

3.2.2. Phase 1 Studies

3.3. Benefit/Risk Assessment

3.3.1. Benefit

There is a large unmet medical need for disease-modifying treatments for AD. Animal models suggest that an anti-tau antibody will reduce progression/spread of the aggregated forms of tau. In addition to assessment of safety and tolerability of LY3303560, this study will also assess whether binding and clearance of extracellular aggregated tau can slow the progression of the disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration relative to placebo treatment.

3.3.2. Risks

The tolerability and safety of any new agent are unknown until sufficient clinical experience is obtained under controlled conditions. As of 08 February 2018, safety data have been reviewed for 63 subjects who have participated in a clinical trial examining LY3303560. Forty-eight healthy subjects have received LY3303560 as single IV doses (7 to 5600 mg) and 16 have received IV placebo. Six patients with AD have received between 6 and 9 doses of LY3303560 IV Q4W and 3 patients have received placebo. With any novel target or therapy there may be unforeseeable risks, and subjects should be monitored closely during clinical trials.

Potential AD pharmacological class effects for LY3303560 comprise of, but are not limited to: (1) LY3303560 – formation of anti-drug antibodies (ADAs), and (2) immediate hypersensitivity (immediate and nonimmediate, including infusion-related reactions).

LY3303560 – Anti-Drug Antibodies: Treatment-emergent anti-drug antibodies (TE-ADAs) may be observed in clinical studies with LY3303560. Anti-drug antibody levels may also affect PK and drug effect. Infusion reactions and ADAs are potential risks common to all large molecules. Although minimal ADAs have been observed in Study LMDA, a risk management plan for immune safety will be incorporated into the clinical trial including a protocol for management of infusion reactions, and standardized data collection for infusion reaction AEs. In Study LMDC,

ADAs will be assessed throughout the study and at a final safety visit 13 weeks after the final dose of LY3303560.

LY3303560 – Hypersensitivity (Immediate and Nonimmediate), including infusion-related reactions): There is a risk of an infusion-related reaction with LY3303560 therapy. In Study LMDA, single doses up to 5600 mg IV LY3303560 and multiple doses of 70 mg IV Q4W have been generally well tolerated in healthy subjects, and preliminary results show no infusion reactions. To mitigate the potential risk of hypersensitivity (immediate and nonimmediate), including infusion-related reactions, specific study exclusion criteria related to allergy are defined in the clinical protocol, and a protocol for management of infusion reactions is included in the trial Manual of Operations.

3.3.3. Benefit/Risk Assessment Summary

To mitigate the potential risks described in Section 3.3.2, the current study will include standard safety assessments: AEs, clinical laboratory tests, immunogenicity assessments, vital sign and body weight measurements, 12-lead ECGs, and physical examinations.

Additional safety assessments will include neurological examinations (as part of each physical examination), MRI examinations, and suicidality evaluations using the Columbia Suicide Severity Rating Scale (C-SSRS). The current study will use an independent external Data Monitoring Committee (DMC) to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study. The DMC will conduct an initial safety review when the first approximately 30 patients have completed 3 months of exposure to study treatment (that is, after completing 4 weeks following the third dose of study treatment). No new patients will be dosed until the DMC review has been completed and the recommendation is to continue the study.

In the current study, approximately 33% of the patients will be randomized to placebo. In addition, all patients participating in the study will have a designated study partner who will have regular contact with the patient, accompany the patient to study visits, and liaise with the study staff between visits as needed (see Section 6.1 for additional information about the role of the study partner).

In conclusion, the available nonclinical and clinical data support the IV administration of LY3303560 to the intended study population according to the proposed clinical investigation plan, and also provide a sufficient margin of safety for the proposed design and doses. There are currently no disease-modifying treatments for AD. The potential benefits of LY3303560 showing disease-modifying properties in patients with AD are considered to outweigh the potential risks.

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

4. Objectives and Endpoints

Table LMDC.4.1 shows the objectives and endpoints of the study.

Table LMDC.4.1. Objectives and Endpoints

Primary Objective	Primary Endpoint
To test the hypothesis that LY3303560 administered for 100 weeks will decrease the decline in cognitive and/or functional outcomes in patients with early symptomatic AD relative to placebo.	Change in cognition and function as measured by the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 104 weeks.
Secondary Objectives	**Secondary Endpoints**
To assess the effect of LY3303560 versus placebo on clinical progression in patients with early symptomatic AD.	Change in cognition and/or function from baseline to 104 weeks as measured by the change in: • Alzheimer's Disease Assessment Scale—Cognitive subscale ($ADAS\text{-}Cog_{13}$) score • Alzheimer's Disease Cooperative Study—instrumental Activities of Daily Living scale (ADCS-iADL) score • Clinical Dementia Rating Scale—Sum of Boxes (CDR-SB) score • Mini-Mental State Examination (MMSE) score
To assess the effect of LY3303560 versus placebo on brain aggregated tau deposition.	Change in brain aggregated tau deposition from baseline through 104 weeks as measured by flortaucipir F 18 PET scan.
To assess the effect of LY3303560 versus placebo on attenuating downstream markers of the neurodegenerative process in AD.	Change in brain volumetric measures from baseline through 104 weeks as measured by volumetric magnetic resonance imaging (vMRI).
Safety Objective	**Safety Endpoints**

To evaluate safety and tolerability of LY3303560.	• Safety assessments:
	  ○ Spontaneously reported AEs
	  ○ Clinical laboratory tests
	  ○ Vital sign and body weight measurements
	  ○ 12-lead ECGs
	  ○ Physical and neurological examinations
	  ○ Anti-drug antibodies
	• Magnetic resonance imaging (MRI) (treatment-emergent radiological findings)
	• Columbia Suicide Severity Rating Scale (C-SSRS)

Exploratory Objectives	Exploratory Endpoints
To assess the effect of LY3303560 versus placebo on clinical progression in patients with early symptomatic AD.	Change in dependence level derived from ADCS-ADL scale scores from baseline to 104 weeks.
To assess the effect of LY3303560 versus placebo on clinical progression in patients with early symptomatic AD.	Change in cognition from baseline to 104 weeks as measured by the change in: • CogState Brief Battery (CBB)
To assess peripheral PK and presence of anti-LY3303560 antibodies over 100 weeks.	• Maximum serum concentration of LY3303560 at steady state ($C_{max,ss}$). • Anti-drug antibodies (ADA) against LY3303560 including treatment-emergent ADA and neutralizing antibodies.
To assess the effect of LY3303560 versus placebo on clinical progression as measured by Digital Clock Drawing test (DCTClock) in patients with early symptomatic AD.	Change in DCTClock results from baseline through 104 weeks.
To assess time-dependent effects of LY3303560 versus placebo on plasma tau, phospho181tau, and neurofilament light (NfL) levels in patients with early symptomatic AD.	Change in plasma tau, phospho181tau, and NfL levels from baseline through 104 weeks.
To assess the utility of DCTClock and plasma phospho181tau in screening phase efficiency for trials of patients with early symptomatic AD.	Associations of DCTClock and plasma phospho181tau with MMSE, CBB, screen failure categories, and baseline data from enrolled subjects.

5. Study Design

5.1. Overall Design

Study LMDC is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of LY3303560 in patients with early symptomatic AD and low-to-medium cerebral tau burden.

The maximum possible duration of the study is 121 weeks that includes a screening period of up to 8 weeks, a treatment period of 100 weeks, a 4-week post last dose assessment, and an immunogenicity and safety follow-up period of up to 13 weeks, following the last dose of the study drug at Week 100. Subjects who meet entry criteria will be randomized in a 1:1:1 ratio to one of the following treatments:

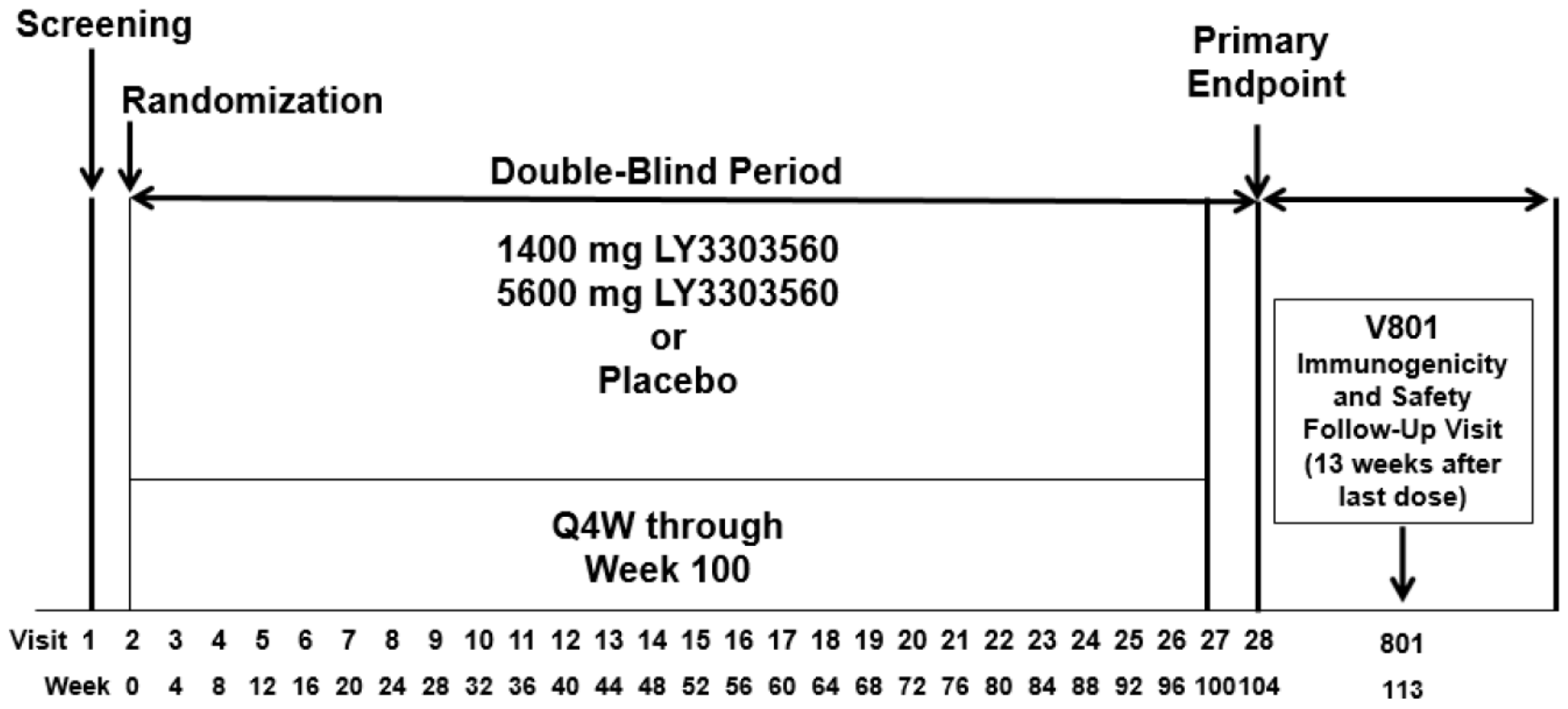
- **1400 mg LY3303560:** LY3303560 1400 mg IV infusion Q4W for 100 weeks (Visit 2 [Week 0] to Visit 27 [Week 100]).
- **5600 mg LY3303560:** LY3303560 5600 mg IV infusion Q4W for 100 weeks (Visit 2 [Week 0] to Visit 27 [Week 100]).
- **Placebo**: IV placebo infusion Q4W for 100 weeks (Visit 2 [Week 0] to Visit 27 [Week 100]).

The first safety review by a Data Monitoring Committee will be conducted after approximately 30 patients have received 3 doses and completed the 4-week assessment period (that is just prior to their 4th dose). Enrolment will halt after these patients have received one dose of study treatment, however those patients already dosed will continue their allocated treatment. If any of these patients discontinue from study treatment for reasons other than safety, they may be replaced, upon discussion between the investigators and Lilly.

The primary hypothesis being tested is that LY3303560 administered for 100 weeks will result in a significant slowing in cognitive/functional decline compared with placebo as measured by the change from baseline to the end of the double-blind period (Week 104) on the integrated Alzheimer's Disease Rating Scale (iADRS), in subjects with early symptomatic AD (where early symptomatic AD refers to the combination of 2 stages: prodromal AD [mild cognitive impairment (MCI)-AD] and mild dementia due to AD; Alaka et al. 2015) who have low-to-medium tau burden.

The overall study design is shown in Figure LMDC.5.1.

Abbreviations and definitions are provided in Appendix 1; clinical laboratory tests are described in Appendix 2; Study governance considerations are described in detail in Appendix 3; and Hepatic monitoring tests for treatment-emergent (TE) abnormality is provided in Appendix 4.



Abbreviations: Q4W = once every 4 weeks; Q13W = once every 13 weeks; V = visit.

Figure LMDC.5.1. Illustration of study design for Clinical Protocol I8G-MC-LMDC.

5.1.1. Screening Period (Visit 1)

At or before Visit 1, the study will be explained to the patient (and his or her legal representative, if applicable) and their study partner. Informed consent must be obtained before any study procedures are conducted. The screening period spans the time between Visit 1 to Visit 2. Study assessments are shown in the Schedule of Activities (Section 2).

A preliminary screening informed consent may be obtained to conduct initial screening to collect demographics data and administer the Mini-Mental State Examination (MMSE), the CogState Brief Battery (CBB), and the Digital Clock Drawing test (DCTClock). Patients who do not meet the MMSE screening criteria are not to have any other screening procedures performed, with the exception of the CBB and DCTClock. They may be rescreened for the MMSE 8 weeks or more after the first screen (see Section 6.4). Patients who screen failed on the CBB in the previous version of this protocol may be reconsented and immediately rescreened using the MMSE (see Section 6.4).

Patients who meet the MMSE screening criteria may proceed to the remaining screening procedures once they have given signed/dated informed consent for the full study and their study partner has given signed/dated informed consented to participate as a study partner.

Following signing of the full informed consent form (ICF), 56 days are allowed for completion of Visit 1 screening assessments, procedures, and evaluation of results from laboratory tests, ECGs, physical and neurological examinations, flortaucipir F 18 PET, and MRI.

Patients whose screening results are not available until after 56 days of signing the full ICF will remain eligible within Visit 1 until these results become available. **Note:** If a patient's screening results are received by the site after 56 days, it will not be considered as a protocol deviation, but clinical laboratory tests (blood hematology, chemistry, and urinalysis) are to be repeated for that patient. Results of the repeated laboratory tests are to be reviewed by the investigator or qualified designee for assessment of the patient's continued eligibility. Repeat screening for MMSE, CBB, DCTClock, C-SSRS, ECG, flortaucipir F 18 PET imaging, and MRI, sample collection for plasma tau, plasma phospho181 tau, and biomarker storage, laboratory testing for hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) ribonucleic acid (RNA) polymerase chain reaction (PCR) are not required.

Visit 1 is not considered complete until all screening procedures have been completed, results have been reviewed by the investigator or qualified designee, and the investigator or qualified designee has confirmed that the patient is eligible to be randomized. Only then can the patient proceed to Visit 2.

Current or planned use of concomitant medications, the effects of vacations or absences on protocol compliance, and general compliance with the protocol will be discussed at Visit 1. Patients must meet eligibility criteria (Section 6.1 and Section 6.2) to continue to Visit 2. Patients who do not meet all inclusion criteria or who meet any exclusion criterion may be discontinued from the study.

5.1.1.1. Screening Procedures

Screening, entry and administrative procedures, cognitive assessments, safety assessments, and laboratory assessments (see Schedule of Activities in Section 2) are to be performed at Visit 1 before the screening flortaucipir F 18 PET scan and MRI.

5.1.1.1.1. Mini-Mental State Examination

The MMSE will be administered to patients at Visit 1 to determine if the patient meets entry criteria for cognitive impairment. If a historical Lilly or Avid flortaucipir PET scan is deemed eligible for meeting entry criteria (see Section 5.1.1.1.6.1), then the MMSE, which is still to be administered at Visit 1, will serve as the baseline MMSE for data analysis, but will **not** be used for meeting entry criteria.

The MMSE is a brief instrument used to assess cognitive function in elderly patients (Folstein et al. 1975). The range for the total MMSE score is 0 to 30, with lower scores indicating greater level of impairment (see further description in Section 9.1.2.4. For entry into the study, patients must have an MMSE score of 20 to 28.

5.1.1.1.2. CogState Brief Battery

The CBB will be administered to patients at Visit 1, but is not an eligibility criterion. Patients should first perform a CBB practice round to familiarize themselves with the instrument, prior to actual administration of the CBB to be recorded for the study. The CBB is a brief (15- to 18-minute), computer-based cognitive test battery designed to measure psychomotor function, attention, working memory, and memory (see further description in Section 9.1.3.1).

5.1.1.1.3. Digital Clock Drawing Test

The DCTClock will be administered to subjects at Visit 1 to assess their performance in relation to the MMSE and CBB as well as other screening tests, but is not an eligibility criterion. The clock drawing test has been used for more than 50 years as a brief (3- to 5-minute) screening tool to differentiate normal individuals from those with cognitive impairment. The analysis will include data from subjects enrolled into the study as well as those who fail screening. The DCTClock uses a novel digitizing ballpoint pen that functions in the subject's hand as an ordinary ballpoint pen, but digitally records its position on the paper. These data can then be used along with the final result to assess the subject's cognitive status (Souillard-Mandar et al. 2016).

5.1.1.1.4. Columbia Suicide Severity Rating Scale—Adult Version

The C-SSRS will be administered to patients at Visit 1 to assess their psychological health. Patients at imminent risk of suicide (positive response to Question 4 or 5 on the C-SSRS) will be excluded from participating in the study. The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The C-SSRS, included here as a screening assessment, is described in detail in Section 9.4.6.1. The C-SSRS "Baseline" version will be used at screening, and the findings will constitute the baseline assessment.

The C-SSRS will be administered to the subject after the cognitive assessments. Responses from subjects will be considered when administering the scale. The Lilly Self-Harm Supplement form (SHSF) will be completed after each C-SSRS administration to enter the number of discrete events of suicidal behavior identified. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then completion of the Self-Harm Follow-Up (SHFU) form is required to collect additional information to allow for a more complete assessment of these behaviors.

5.1.1.1.5. Alzheimer's Disease Biomarkers

Blood-based biomarkers to screen for AD pathology are under development. A promising candidate is phospho181 tau, and samples will be collected during Visit 1. Results of the test may be used to improve the efficiency of the screening process through the identification of subjects who are likely to have tau pathology. A plasma tau and an additional biomarker storage sample will also be collected during Visit 1 and stored for future analysis to enable biomarker assay development and assessment of clinical utility for future trials.

5.1.1.1.6. Screening Positron Emission Tomography and Magnetic Resonance Imaging

All other screening criteria must be met in order for the patient to proceed with flortaucipir F 18 PET scan, followed by an MRI scan.

5.1.1.1.6.1. Screening Flortaucipir F 18 PET Scan

A screening flortaucipir F 18 PET scan will be performed as part of the study eligibility criteria (see Appendix 5). The flortaucipir F 18 PET scan will be submitted to a centralized PET imaging vendor designated by Lilly for assessment of patient's eligibility.

A historical Lilly or Avid flortaucipir F 18 PET scan result showing low to medium tau, within 6 months of V1, may be submitted to the PET imaging central reader to be considered for eligibility without requiring the screening MMSE to meet eligibility criteria. If the historical scan meets eligibility criteria but is performed more than 6 months prior to Visit 2, then another flortaucipir scan must be performed and used as the baseline scan for analysis.

The flortaucipir F 18 PET screening criteria should be met (scan results consistent with sponsor-derived eligibility limits for flortaucipir F 18 PET) before the patient can undergo the MRI.

Specific instructions for the flortaucipir F 18 PET scan itself will be provided in the PET Imaging Manual.

5.1.1.1.6.2. Screening MRI

A local screening MRI will be performed at Visit 1 as part of the study eligibility criteria. Training and specific instructions for the MRI protocol will be provided by a centralized MRI vendor designated by Lilly. The MRI scans will be reviewed by the investigator or qualified designee for immediate patient management. The scan is to be submitted to the centralized MRI vendor designated by Lilly for final determination of MRI eligibility. Results of centrally read

MRIs will be used for data analysis and report-writing purposes and patient safety and eligibility will be reported back to sites.

5.1.2. Double-Blind Period (Visit 2 through Visit 28)

The treatment period is a double-blind treatment phase beginning at Visit 2. At Visit 2, appointments should be made for all remaining visits and should be scheduled as close as possible to the target date, relative to Visit 2. Patients who meet entry criteria will be enrolled and randomized to receive 100 weeks of treatment with LY3303560 or placebo.

Every 4 weeks during this treatment period, all patients will be administered IV study medication (placebo or LY3303560) onsite as an IV infusion up to 250 mL over at least 90 minutes, and assessments will be performed.

A final assessment visit for the double-blind period will be performed at Visit 28 (Week 104), 4 weeks following the patient's last dose of study medication. See the Schedule of Activities (Section 2) for the timing of events and the measures to be assessed. Procedures for some visits may take more than 1 day.

The study investigator and site clinical study team will not have access to any flortaucipir F 18 follow-up PET scans, as the investigator and site clinical study team must remain blinded to any potential changes in tau deposition.

5.1.3. Immunogenicity and Safety Follow-Up Visit (Visit 801)

Patients should return to the site for immunogenicity and safety follow-up, Visit 801, at Week 113, or 13 weeks after their last dose of study drug if the patient discontinues the study early for collection of blood samples for anti-drug antibodies (ADA) (anti-LY3303560 antibody), PK measurement, assessment of AEs, concomitant medications, C-SSRS, and vital signs (see the Schedule of Activities in Section 2).

5.2. Number of Participants

Approximately 285 participants will be randomized.

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

Continuing Standard of Care. Patients may take AD symptomatic medications, such as concomitant AChEIs and/or memantine and/or Axona, if such medications are standard of care in the patient's country and stable dosing has been maintained for at least 2 months before Visit 2. During the double-blind period (V2 to V28), changes in doses of available symptomatic medications for MCI or AD will require reporting to the sponsor and these changes should occur only when necessary for the adequate overall care of the patient. The effect of LY3303560 treatment plus standard of care will be compared with placebo plus standard of care.

Dosing. As described more fully in Section 7.1, LY3303560 (1400 mg or 5600 mg) or placebo will be administered every 4 weeks as an IV infusion of approximately 250 mL over at least 90 minutes.

Design. Study LMDC is a multicenter, randomized, patient, investigator and sponsor blinded, placebo-controlled study of LY3303560 in patients with early symptomatic AD (where early symptomatic AD refers to the combination of 2 stages: MCI-AD and mild AD dementia) (Alaka et al. 2015) and low-to-medium tau burden. The study is intended to characterize the benefits and risks of treatment with LY3303560 versus placebo in patients with early symptomatic AD.

Study LMDC includes a placebo treatment arm and allows all patients to continue their AD standard-of-care concomitant medications. Inclusion of a placebo treatment arm is acceptable in Study LMDC because there are no available disease-modifying treatments for AD; this approach is in agreement with the use of placebo described in the Declaration of Helsinki (World Medical Association 2013). The use of a placebo comparator in Study LMDC is needed to determine the efficacy and safety of LY3303560 therapy.

The study includes a screening visit, which can last up to 56 days from the time of signing the full ICF, at which patients are required to have flortaucipir F 18 PET imaging results consistent with low-to-medium tau in order to be randomized to the double-blind period. The duration of the double-blind period of the study is 104 weeks and includes 100 weeks of treatment with endpoint measures at the end of the double-blind period (Week 104), to assess the safety, tolerability, and efficacy of LY3303560 versus placebo.

In addition to AE reporting, safety measures such as laboratory assessments, immunogenicity testing, vital signs and weight monitoring, ECG monitoring, physical examinations, neurological examinations, MRI assessments, and assessments of suicidal ideation and behavior are included to facilitate a comprehensive safety evaluation.

5.5. Justification for Dose

In this study, patients will receive either 1400 mg or 5600 mg LY3303560 Q4W or placebo, for a total of 26 doses. All doses will be administered intravenously.

Suitable biomarkers to help select doses for this study are not currently available. Two doses were selected for use in this study. The 5600-mg dose corresponds with the highest dose tested in Phase 1, and is believed to be high enough to suppress soluble tau aggregate concentrations in the CNS by >95%. Given the high degree of suppression that is anticipated, it is thought that the 5600-mg Q4W dose level will provide proof of concept that an antibody targeting soluble tau aggregates can slow the progression of AD. To date, multiple doses of 5600 mg Q4W have not been administered clinically. However, based upon the PK observed in the single and multiple ascending dose studies, it is anticipated that little drug accumulation will be noted following a Q4W dosing regimen (maximum serum concentration of LY3303560 at steady state [$C_{max,ss}$] is anticipated to be approximately 26% higher than that following a single dose). Because the exposures in this study are expected to be relatively similar to those in the single-dose study, it is

anticipated that the tolerability of LY3303560 observed in this study will be similar to that observed in the single-dose study.

The lower dose level in this study (1400 mg) will evaluate LY3303560 safety and efficacy at exposures that have been tested in the single-dose study. The extent to which soluble tau aggregate concentrations will be suppressed at the 1400 mg Q4W dose level is unknown, but is believed to be >90%. Based on the 4-fold difference in the 2 active doses, little overlap in exposure between the dose levels is anticipated. Accordingly, the use of 2 doses is expected to provide an enhanced understanding of the exposure–response relationship with cognitive, functional, imaging, and safety endpoints, which will be useful in the selection of doses in subsequent studies. Additionally, the lower dose level will provide the opportunity to achieve the overall study objectives if the 5600-mg dose level is not tolerated in this study.

In toxicology studies, the highest dose level tested (200 mg/kg QW for 26 weeks) in both Tg4510 mice and cynomolgus monkeys was found to be the NOAEL dose. Based on toxicokinetics, the average serum concentration in Tg4510 mice at that dose level provides a 2.0 margin of safety to the anticipated average concentration in humans at 5600 mg Q4W, whereas the margin of safety determined with the cynomolgus data is 6.0. Based on these margins, the toxicology data do not suggest any potential safety concerns at the 5600 mg LY3303560 Q4W dose level.

6. Study Population

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

6.1. Inclusion Criteria

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

Type of Patient and Disease Characteristics

[1] Men or women (not of childbearing potential), at least 60 to 85 years of age.

a. Female patients: women must be of non-childbearing potential. Female patients are considered of non-childbearing potential if they have undergone surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation), have a congenital anomaly such as mullerian agenesis, or are postmenopausal as defined by either:

(i). Women aged 55 years or older not on hormone therapy, who have had at least 6 months of spontaneous amenorrhea; or

(ii). Women at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[2] Gradual and progressive change in memory function reported by patients or informants for ≥6 months.

[3] Criterion [#3] was replaced by criterion [#41].

[41] An MMSE score of 20 to 28 (inclusive) at Visit 1 or an acceptable historical flortaucipir PET scan within 6 months prior to Visit 1.

[4] Meets flortaucipir F 18 scan (central read) criteria.

Patient/Subject Characteristics

[5] Contraception

a. Male subjects

(i). Male subjects, regardless of their fertility status, with nonpregnant female partners of childbearing potential must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for 90 days after study drug dosing.

(ii). Men and their partners may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a 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.

(iii). Male subjects with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in women of childbearing potential, predicted to be 90 days following the last dose of study drug.

(iv). Male subjects should refrain from sperm donation for the duration of the study and until 90 days following the last dose of study drug.

(v). Male subjects who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

[6] Have a study partner who will provide written informed consent to participate, is in frequent contact with the patient (defined as at least 10 hours per week), and will accompany the patient to study visits or be available by telephone at designated times.

A second study partner may serve as backup. The study partner(s) is/are required to accompany the patient for signing consent. One study partner is requested to be present on all days the C-SSRS/Self-Harm Supplement Form and cognitive and functional scales are administered.

If a patient has a second study partner, it is preferred that 1 study partner be primarily responsible for the CDR and Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory (ADCS-ADL) assessments. If study partners are not able to accompany the patient in person, they must be available by telephone for the following assessments:

- AEs and concomitant medications
- relevant portions of the C-SSRS/Self-Harm Supplement Forms

If a study partner must withdraw from study participation, a replacement would be allowed at the investigator's discretion. The replacement(s) will need to sign a separate informed consent on the first visit that he/she accompanies the patient to participate.

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

[7] Have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site.

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

6.2. Exclusion Criteria

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

Medical Conditions

[9] Lack, in the investigator's opinion, of adequate premorbid literacy, adequate vision, or adequate hearing to complete the required psychometric tests.

[10] Significant neurological disease affecting the CNS, other than AD, that may affect cognition or ability to complete the study, including but not limited to other dementias, serious infection of the brain, Parkinson's disease, multiple concussions, or epilepsy or recurrent seizures (except febrile childhood seizures).

[11] Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic (including unstable diabetes), neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with the analyses in this study; or has a life expectancy of <24 months.

[12] History of cancer within the last 5 years, with the exception of nonmetastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, nonprogressive prostate cancer, or other cancers with low risk of recurrence or spread.

[13] Patients with any current primary psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the patient's ability to complete the study. (Patients with a history of schizophrenia or other chronic psychosis are excluded.)

[14] Are clinically judged by the investigator to be at serious risk for suicide as assessed by medical history, examination, or the C-SSRS.

[15] History of alcohol or drug use disorder (except tobacco use disorder) within 2 years before the screening visit.

[16] Have a history of clinically significant multiple or severe drug allergies or severe posttreatment hypersensitivity reactions (including but not limited to erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and/or exfoliative dermatitis).

[17] Known positive serologic findings for human immunodeficiency virus antibodies. Local laws and regulations may apply to whether testing is required.

Magnetic Resonance Imaging, Vital Signs, Electrocardiograms, Laboratory Tests, and Physical Examination

[18] Have any clinically important abnormality at screening, as determined by the investigator, in physical or neurological examination, vital signs, ECG, or clinical laboratory test results that could be detrimental to the patient, could compromise the study, or show evidence of other etiologies for dementia.

[19] Screening MRI that shows evidence of significant abnormality that would suggest another potential etiology for progressive dementia or a clinically significant finding that may impact the patient's ability to safely participate in the study.

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

[21] Patients with a history of hepatitis B should have HBsAg testing at screening and are excluded if HBsAg is positive.

[22] Patients who are hepatitis C virus (HCV) antibody positive should have follow-up HCV RNA PCR testing at screening and are excluded if HCV RNA PCR is positive.

[23] Calculated creatinine clearance <30 mL/min (Cockcroft–Gault formula; Cockcroft and Gault 1976) at screening.

[24] Alanine aminotransferase (ALT) ≥2× the upper limit of normal (ULN) of the performing laboratory, aspartate aminotransferase (AST) ≥2× ULN, total bilirubin level (TBL) ≥1.5× ULN, or alkaline phosphatase (ALP) ≥1.5× ULN at screening.

NOTE: Patients with TBL ≥1.5× ULN are not excluded if they meet all of the following criteria for Gilbert syndrome:

a. Bilirubin is predominantly indirect (unconjugated) at screening (direct bilirubin within normal limits).

b. Absence of liver disease.

c. ALT, AST, and ALP ≤1× ULN at screening

d. Hemoglobin is not significantly decreased at screening.

Prior/Concomitant Therapy

[25] If taking an acetylcholinesterase inhibitor (AChEI) and/or memantine, have received treatment with a stable dose of an AChEI and/or memantine for less than 2 months before randomization. [If a patient has recently stopped an AChEI and/or memantine, he or she must have discontinued treatment at least 2 months before randomization.]

[26] Changes in concomitant medications that could potentially affect cognition and their dosing should be stable for at least 1 month before screening, and between screening and randomization (does not apply to medications discontinued due to exclusions or with limited duration of use, such as antibiotics).

[27] Have received active immunization agents for the treatment of Alzheimer's disease.

[28] Have known allergies to LY3303560, related compounds, or any components of the formulation; or history of significant atopy.

[29] Have allergies to either monoclonal antibodies, diphenhydramine, epinephrine, or methylprednisolone.

[30] Are receiving IgG therapy (also known as gamma globulin or intravenous immunoglobulin [IVIG])

Procedural

[31] Sensitivity to flortaucipir F 18.

[32] Intend to use drugs known to significantly prolong the QT interval within 14 days or 5 half-lives, whichever is longer, of any scheduled flortaucipir F 18 PET scan, or have a medical history of a risk factor of Torsades de Pointes.

[33] Poor venous access.

[34] Contraindication to PET.

[35] Present or planned exposure to ionizing radiation that, in combination with the planned administration of study PET ligands, would result in a cumulative exposure that exceeds local recommended exposure limits.

Note: See Appendix 5 for additional flortaucipir F 18 Tau PET imaging inclusion/exclusion criteria.

Prior/Concurrent Clinical Trial Experience

[36] Are currently enrolled in any other interventional clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[37] Have participated within the last 30 days in a clinical trial involving an investigational product. If the previous investigational product is scientifically or medically incompatible with this study and has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to screening. (Participation in observational studies may be permitted upon review of the observational study protocol and approval by the sponsor.)

[38] Have previously discontinued LY3303560 treatment due to treatment-related AE. Prior treatment with LY3303560 in Phase 1 studies (LMDD) is allowed after 3 months of washout prior to screening.

Other Exclusions

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

[40] Are Lilly employees or are employees of third-party organizations (TPOs) involved in study who require exclusion of their employees, or have study partners who are Lilly employees or are employees of TPOs involved in a study that requires exclusion of their employees.

6.2.1. Rationale for Exclusion of Certain Study Candidates

The use of LY3303560 in older patients is anticipated, thus this study will specifically examine the efficacy and safety in an elderly population. Criterion [1] defines the population age range for the purposes of this study. Therefore, patients not meeting the age criterion are excluded.

6.3. Lifestyle Restrictions

Patients should refrain from donating blood or blood products from the time of their screening visit until 6 months following the last dose of study drug.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened if the screen failure is due to noneligible imaging results. If the screen failure is due to not meeting cognitive criteria on the MMSE, then 1 rescreen will be allowed after 8 weeks. Rescreens for other reasons may be considered, but will require sponsor approval.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of LY3303560 administered as an IV infusion of approximately 250 mL over at least 90 minutes compared with placebo. In the double-blind period, the treatment groups will be given either an IV infusion of LY3303560 or placebo for 100 weeks. Patients assigned to LY3303560 will receive either 1400 mg or 5600 mg, administered as an IV infusion Q4W. Patients will be randomized 1:1:1 to receive either placebo or 1 of the 2 dose levels of LY3303560.

Table LMDC.7.1 shows the treatment regimens during the double-blind period.

The study also includes the use of the investigational diagnostic product, flortaucipir F 18, for the determination of aggregated tau deposition. Information regarding the use of flortaucipir F 18 in the study is provided in Appendix 5.

Table LMDC.7.1. Treatment Regimens, Double-Blind Treatment Period

Regimen	Dose Visit 2 (Week 0) through Visit 27 (Week 100)
1400 mg LY3303560	LY3303560: 1400 mg IV infusion Q4W for 100 weeks (Visit 2 [Week 0] – Visit 27 [Week 100]).
5600 mg LY3303560	LY3303560: 5600 mg IV infusion Q4W for 100 weeks (Visit 2 [Week 0] – Visit 27 [Week 100]).
Placebo	IV placebo infusion Q4W for 100 weeks (Visit 2 [Week 0] – Visit 27 [Week 100]).

Abbreviations: IV = intravenous; Q4W = once every 4 weeks.

Investigational product will be prepared at the site by unblinded pharmacists or other trained personnel. Investigational product will be administered at the site by blinded nurses or other trained infusion personnel.

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

- explaining the correct use of the investigational agent(s) to the subject and/or legal representative
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study, returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed that all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labeling

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

The drug product (LY3303560) is supplied for clinical trial use as lyophilized powder formulation in vials. The vial is reconstituted/diluted with sterile reconstitution solution.

The lyophilized drug product LY3303560 is composed of LY3303560 and the excipients CCI [redacted]. The vial is manufactured to deliver 600 mg of LY3303560 per vial. Reconstituting/diluting the vial contents with 20 mL of sterile reconstitution solution gives a clear/lightly opalescent solution containing 30 mg/mL of LY3303560 at a pH of 6.0. For clinical administration, the reconstitution volume for the vial may be adjusted to facilitate delivery of doses requiring a higher drug product concentration. Further dilution may also be made using sterile saline. Substitution for 0.9% normal saline may be permitted if allowed in the pharmacy manual.

Placebo is to be administered with 250 mL of 0.9% normal saline.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be assigned a study (patient) number at Visit 1 and randomized to double-blind treatment at Visit 2. Patients will be randomized to LY3303560 or Placebo in a 1:1:1 ratio. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web response system (IWRS). For the first, approximately, 30 patients, the IWRS will be programmed to guarantee balance between the arms for the first interim analysis for safety; this is referred to as the burn-in period. After the burn-in period, patient randomization will then follow the dynamic allocation (minimization) method of Pocock and Simon (1975) to balance the treatment arms using investigative site as a factor. This is to ensure balanced patient assignment between treatment arms within each site at the end of the study.

The IWRS will be used to assign a dosing regimen to each patient. Site personnel will confirm that they have located the correct packages by entering a confirmation number found on the label into the IWRS, prior to dosing the patient.

The IWRS will be used to assign a dosing regimen to each patient. Site personnel will confirm that they have located the correct packages by entering a confirmation number found on the label into the IWRS, prior to dosing the patient.

7.2.1. Selection and Timing of Doses

Assessment of LY3303560 safety and tolerability is a central objective; therefore, monitoring approximately 232 patients on LY3303560 (116 per 1400-mg and 5600-mg dose groups, respectively) over 104 weeks in parallel with approximately 116 patients on placebo over 104 weeks provides data to assess safety for further clinical development.

The actual time of LY3303560 dose administrations on the day of study visits will be recorded in the subject's case report form (CRF).

Note that at visits at which cognitive assessments are to be performed, all cognitive scales are to be administered before IV study medication (LY3303560 or IV placebo) is administered.

Intravenous study medication (that is, IV placebo or LY3303560) is to be administered Q4W. Based on the permitted visit window (see Section 2), although IV study medication could theoretically be administered at a 2-week interval, IV study medication must not be given at a dosing interval of less than 21 days at any time during the study. Intravenous study medication given at a dosing interval of less than 21 days at any time during the study will be considered a protocol deviation. The dose of LY3303560 was chosen based on nonclinical and clinical PK/PD and safety from Study LMDA (See Section 5.5).

Infusions should occur over the course of at least 90 minutes. If a patient demonstrates an infusion reaction to LY3303560, medications to manage the infusion reaction may be administered at the discretion of the investigator (see Section 7.7). In the event of infusion reactions, refer to the operations manual. Patients should be observed for a minimum of 2 hours following each infusion of LY3303560 for the first 3 infusions. After the first 3 doses, a minimal post-infusion observation time of at least 60 minutes will be required for all subsequent infusions.

Sites must have resuscitation equipment available.

7.3. Blinding

This is a patient, investigator and sponsor blinded study, with design to maintain blinding to LY3303560 treatment. To preserve the blinding of the study, a minimal number of Lilly personnel, and personnel external to the study team, will have access to the randomization table and treatment assignments before the study is complete. Only a study site pharmacist or other trained person will be unblinded at the site for investigational product preparation. The independent external DMC will be unblinded for any safety or efficacy assessments.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All unblinding events are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or subject is unblinded, the subject must be discontinued from the study. In cases where there are ethical reasons to have the subject remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) for the subject to continue in the study.

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. The patient's safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

A list of all those who are unblinded to study treatment as the study progresses will be maintained and stored with the final documentation of the study.

7.4. Dosage Modification

Dosage modifications will not be made by investigators.

7.5. Preparation/Handling/Storage/Accountability

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

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

The administration of all study medication should be recorded in the appropriate sections of the electronic case report form (eCRF).

Because dosing occurs at study visits, patients who attend all visits and successfully receive LY3303560 or placebo infusions are automatically compliant with this treatment. Any infusion at which 75% (approximately 190 mL) or more of the infusion solution is given will be considered a complete infusion.

If a patient attends a visit but does not receive a complete infusion (for example, due to technical complications), every effort should be made to complete the infusion within 24 hours if possible. If less than 75% of the infusion solution is given, this must be recorded as an incomplete infusion on the CRF.

Missed infusions should be recorded on the CRF.

7.7. Concomitant Therapy

All concomitant medications taken during the study must be recorded on the Concomitant Medication CRF. Patients and their study partners will be instructed to consult the investigator or other appropriate study personnel at the site before initiation of any new medications or supplements and before changing the dose of any current concomitant medications or supplements.

To ensure standard of care for AD, use of approved and/or standard-of-care treatments for AD is permitted in this study, and no medications are explicitly excluded from use. The section below provides additional guidance on managing concomitant medication use.

Allowed Medications. Use of approved and/or standard-of-care treatments for AD is permitted during the study, provided that such medications dose has been unchanged for 2 months before Visit 2. Doses of these medications should remain constant throughout the double-blind period (Visit 2 to Visit 28).

If a patient has recently stopped AChEIs and/or memantine, he or she must have discontinued treatment at least 2 months before Visit 2.

Other vitamins, medical food, or nutraceuticals given for their possible effects on AD may be continued on stable doses beginning 2 months before Visit 2.

Prior to V28, before a patient starts, stops, or changes doses of AChEIs and/or memantine or other treatments for their AD, the Sponsor or designee must be contacted to determine whether or not the patient should continue in the study and whether or not clinical outcome measures should be performed. Failure to notify Lilly or its designee regarding starting, stopping, or changing doses of AChEIs and/or memantine or other treatments for their AD prior to V28 will be considered a protocol violation.

Nonmedication treatments for AD such as behavioral management are permitted but are subject to the same restrictions as medication treatment taken for AD. Changes in therapies that may potentially affect the patients' AD should be encouraged to be stable; changes will be allowed and should be captured in patients' notes at the site.

Use of benzodiazepines for treatment on an as-needed basis for insomnia or daily dosing as anxiolytics is permitted. Use of sedatives or hypnotics should be avoided for 8 hours before the cognitive and functional tests are conducted unless they are given chronically.

If an infusion reaction occurs, medications to manage reactions such as, but not limited to, diphenhydramine, epinephrine, and/or methylprednisolone may be administered at the discretion of the investigator (see Section 9.4.7.1 and the clinical trial Manual of Operations for additional information). Administration of medications prior to an infusion to prevent a reaction does not cause a discontinuation of the patient from the study. If the need for concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the investigator after consultation with a Lilly CRP. Concomitant therapy administered to treat an infusion reaction or as premedication for infusions should be documented.

If it becomes necessary for a patient to start taking a medication known to prolong QT interval prior to performance of any postbaseline flortaucipir F 18 scan, do not perform the scan or wait until the QT-prolonging medication has been stopped for the longer of 14 days or 5 half-lives. The patient may, however, remain in the study. Nonperformance of postbaseline flortaucipir F 18 PET scans in patients taking a medication known to prolong QT interval will not be considered a protocol violation.

Excluded Medications

Concomitant therapies that are prohibited during treatment with LY3303560: IgG therapy (also known as gamma globulin or intravenous immunoglobulin [IVIG]) is not allowed during the study.

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

Patients who complete this study through Visit 28 may be eligible to participate in an active treatment extension, if available.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of study treatment:

- Subject Decision
  - the subject or the subject's designee, for example the legal guardian, requests to discontinue the investigational product.
- Discontinuation due to a hepatic event or liver test abnormality

Subjects who are discontinued from the investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via CRF/electronic data entry.

Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a subject meets one of the following conditions after consultation with the Lilly designated medical monitor:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X upper limit of normal (ULN)
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio (INR) >1.5
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

In addition, subjects will be discontinued from the investigational product in the following circumstances:

- Severe acute infusion reaction (for example, not responsive to medication such as antihistamines, nonsteroidal anti-inflammatory drugs, and/or narcotics and/or brief interruption of infusion).
- An AE including symptoms or clinically significant laboratory value, ECG result, physical examination finding, MRI finding (such as symptomatic ischemic stroke), C-SSRS result, or vital sign measurement of such severity that, in the opinion of the investigator or Lilly-designated medical monitor, continued treatment is not in the best interest of the patient.
- Severe noncompliance to the study protocol that results in a safety concern, in the judgment of the investigator.

- The patient, for any reason, requires a treatment with an excluded therapeutic agent and temporary discontinuation criteria cannot be met (see Section 8.1.1).

Subjects discontinuing from the study treatments prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.1. Temporary Discontinuation from Study Treatment

Temporary discontinuation from LY3303560 treatment is allowed if a short-term treatment with an excluded medication is necessary, secondary to hospitalization, personal circumstances, or to evaluate the study drug impact on an uncertain AE. Study drug may be restarted at the investigator's discretion. If temporary discontinuation is due to an AE, it should be reported to the Lilly CRP. Temporary treatment discontinuation and restarting should be documented. Restarting treatment after a discontinuation period that is greater than 12 weeks should be discussed between the investigator and Lilly CRP.

8.1.2. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, then the subject should be considered for discontinuation from study treatment. If the investigator and the sponsor CRP/clinical research scientist (CRS) agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled subject to continue in the study.

Safety follow-up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.2. Discontinuation from the Study

Patients who do not meet entry criteria or who are excluded by exclusion criteria from Visit 1 tests and procedures should be discontinued from the study before randomization as an entry failure.

Subjects will also be discontinued from the study in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged by sponsor not to be scientifically or medically compatible with this study.
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- investigator decision
  - the investigator decides that the subject should be discontinued from the study.

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

- subject decision
  - the subject or the subject's legal representative requests to be withdrawn from the study.
- subject requires a ferromagnetic implant or insertion of a cardiac pacemaker that is not MRI-compatible.

Subjects discontinuing from the study prematurely for any reason must complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol. In addition, subjects discontinuing from the study prematurely should be encouraged to return to the site 13 weeks after their early discontinuation (ED) visit for a follow-up visit (V801).

8.3. Lost to Follow-Up

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

Site personnel, or an independent third party, will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the subject will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

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

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

Unless otherwise stated in the 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.

9.1. Efficacy Assessments

Screening measures used for diagnosis and establishment of study eligibility are described elsewhere (Section 5.1.1.1).

Cognitive and functional testing will be administered using an eCOA tablet. The audio voice recordings of the rater's questions and the patient's and study partner's responses will also be collected via the eCOA tablet during administration of the cognitive and functional testing for central monitoring of rater scale administration (Section 2). Cognitive and functional testing for each patient should be performed at approximately the same time on each day that testing occurs to reduce potential variability. Note that the ADAS-Cog and MMSE should be administered by a different rater than the ADCS-ADL and CDR. These 2 raters should continue doing the same scale with the same patient throughout the study. If possible, each assessment should be performed on a given patient by the same rater at each visit. The principal investigator (PI) has the responsibility of selecting who will administer the instruments at the site, as long as all training requirements have been met by those raters (Appendix 3, 3.1.5).

When administered, cognitive and functional testing should be performed first, before medical procedures that could be stressful for the patient (for example, blood draws). Note that some procedures (MRI and flortaucipir F 18 PET tau imaging) can be conducted on other days within the visit window.

9.1.1. Primary Efficacy Assessments

Integrated Alzheimer's Disease Rating Scale (iADRS; Wessels et al. 2015). The iADRS represents a composite that was developed using both a theory-driven approach (incorporating measures of both cognition and function) and a data-mining approach (identifying the most sensitive combination of scales through analysis of data from the Alzheimer's Disease Neuroimaging Initiative and the LY2062430 EXPEDITION and EXPEDITION2 studies). The iADRS is a simple linear combination of scores from 2 well-established, therapeutically sensitive, widely accepted measures in AD, the Alzheimer's Disease Assessment Scale—Cognitive subscale ($ADAS\text{-}Cog_{13}$) and the Alzheimer's Disease Cooperative Study—instrumental Activities of Daily Living Inventory (ADCS-iADL), measuring the core domains of AD. All items of these 2 scales are included without additional weighting of items, yielding face validity and ease of interpretation of the composite relative to its components.

The iADRS score will be derived from the ADAS-Cog$_{13}$ and the ADCS-iADL and will be the primary efficacy measure. The ADAS-Cog$_{13}$ and the ADCS-ADL will be the actual scales administered to patients.

9.1.2. Secondary Efficacy Assessments

Immediately following administration of the ADAS-Cog$_{13}$ and ADCS-ADL, additional clinical outcome measures should be administered in the same order at every visit. To minimize missing data, the rater should verbalize the questions for each measure with the patient or study partner (as designated in instructions), recording responses appropriately.

One study partner is requested to be present on all days the C-SSRS/Self-Harm Supplement Form and cognitive and functional scales are administered. If a patient has a second study partner, it is preferred that 1 study partner be primarily responsible for the CDR and ADCS-ADL assessments.

9.1.2.1. Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog$_{13}$)

The ADAS-Cog$_{13}$ is a rater-administered instrument that was designed to assess the severity of the dysfunction in the cognitive and noncognitive behaviors characteristic of persons with AD (Rosen et al. 1984). The ADAS-Cog$_{13}$ should be administered by the same rater from visit to visit to reduce potential variability. The cognitive subscale of the ADAS, the ADAS-Cog$_{13}$, consists of 13 items assessing areas of cognitive function most typically impaired in AD: orientation, verbal memory, language, praxis, delayed free recall, digit cancelation, and maze-completion measures (Mohs et al. 1997). The ADAS-Cog$_{13}$ allows for better discrimination of differences among mild patients than the ADAS-Cog$_{11}$. The ADAS-Cog$_{13}$ scale ranges from 0 to 85, with higher scores indicating greater disease severity.

9.1.2.2. Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory (ADCS-ADL)

The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire that is to be answered by the patient's study partner (Galasko et al. 1997, 2004). The ADCS-ADL should be administered by the same rater from visit to visit to reduce potential variability. The ADCS-ADL subset of items (Items 6a, 7 to 23) for instrumental activities of daily living (ADCS-iADL) will be used as a secondary efficacy measure. The focus in the early symptomatic AD population is on the instrumental activities of daily living (iADLs) rather than the basic activities of daily living (bADLs), which are thought to be affected in more severe stages of the disease. The range for the iADL score is 0 to 59, with lower scores indicating greater disease severity. For each of the specific items, the study partner is first asked if the patient attempted the ADL during the past 4 weeks. If the patient did attempt the ADL, the study partner is asked to rate the patient's performance level based on a set of performance descriptions. Scores for each item and the overall score for the tool are calculated. The range for the total ADCS-ADL score is 0 to 78, with higher scores indicating greater level of impairment. Separate scores for the bADLs (0 to 19) will also be computed.

9.1.2.3. Clinical Dementia Rating Scale—Sum of Boxes (CDR-SB)

The CDR is a semi-structured interview performed with the patient and study partner (informant) that provides an index of global functioning (Berg e al. 1992). The CDR should be administered by the same rater from visit to visit to reduce potential variability. The informant is queried about the patient's memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The patient's memory, orientation, judgment, and problem-solving ability are assessed. Higher scores indicate greater disease severity. By assigning a severity score for each of the 6 domains, a total score known as sum of boxes is obtained—hence the abbreviation, CDR-SB.

9.1.2.4. Mini-Mental State Examination (MMSE)

The MMSE is a brief instrument used to assess cognitive function in elderly patients (Folstein et al. 1975). The MMSE should be administered by the same rater from visit to visit to reduce potential variability. The instrument is divided into 2 sections. The first section measures orientation, memory, and attention. The maximum score for the first section is 21. The second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures. The maximum score for the second section is 9. The range for the total MMSE score is 0 to 30, with lower scores indicating greater level of impairment.

9.1.2.5. Biomarker Efficacy Measures

9.1.2.5.1. Flortaucipir F 18 PET Scan

Change in aggregated tau deposition (as assessed by flortaucipir F 18 PET signal) will be compared in LY3303560- and placebo-treated patients for those patients who undergo flortaucipir F 18 PET scans as described in the Schedule of Activities (Section 2).

9.1.2.5.2. Volumetric MRI

Magnetic resonance imaging of the brain will be performed according to the Schedule of Activities (Section 2). LY3303560- and placebo-treatment effects on volumetric MRI will be assessed and compared to evaluate brain atrophy.

9.1.3. Exploratory Efficacy Measures

9.1.3.1. CogState Brief Battery (CBB)

The CBB is a brief (15- to 18-minute), computer-based cognitive test battery designed to measure psychomotor function, attention, working memory, and memory (Maruff et al. 2009, 2013; Fredrickson et al. 2010; Darby et al. 2012). The CBB has been shown to be sensitive to AD-related cognitive decline in healthy older adults and in adults with amnestic MCI (Darby et al. 2002, 2012; Lim et al. 2013a,b) as well as to improvement in cognition arising from treatment with cognitive enhancing drugs (Davison et al. 2011; Jaeger et al. 2011; Nathan et al. 2013). The CBB will be administered as described in the Schedule of Activities (Section 2).

9.1.3.2. Digital Clock Drawing Test (DCTClock)

The clock drawing test in manual form has been used for more than 50 years as a brief (3- to 5-minute) screening tool to differentiate normal individuals from those with cognitive

impairment. The DCTClock test uses a novel digitizing ballpoint pen that functions in the subjects' hand as an ordinary ballpoint pen, but digitally records its position on the paper. The DCTClock will be administered to subjects at Visit 2 prior to their first dose and similarly at each subsequent dosing visit to assess their performance in relation to the other efficacy measures and biomarkers. These data can then be used along with the final result to assess the subjects cognitive status (Souillard-Mandar et al. 2016).

9.1.3.3. Plasma Tau, Phospho 181 Tau, and Neurofilament Light

Samples for the measurement of plasma tau, phospho181 tau, and NfL will be collected at the times specified in the Schedule of Activities (Section 2) to evaluate the time-dependent effects of LY3303560 compared with placebo over 104 weeks in patients with early symptomatic AD.

9.1.4. Appropriateness of Efficacy Assessments

The iADRS, the primary efficacy measure, is a simple linear combination of scores from 2 well-established, therapeutically sensitive, widely accepted measures in AD, the ADAS-Cog_{13} and the ADCS-iADL, measuring the core domains of AD. It represents a composite that was developed using both a theory-driven approach (incorporating measures of both cognition and function) and a data-mining approach (identifying the most sensitive combination of scales through analysis of data from the Alzheimer's Disease Neuroimaging Initiative and the LY2062430 EXPEDITION, EXPEDITION2, and EXPEDITION3 studies). Composite endpoints have been increasingly used as primary endpoints in clinical trials (Freemantle et al. 2003). Liu-Seifert et al. (2017) demonstrated that the treatment effect size of the iADRS composite is greater than the minimum treatment effect size of its components and that above certain thresholds of correlations of components and ratios of component effect sizes the composite may outperform its components.

The secondary efficacy measures described in Section 9.1.2 are established measures of cognitive and functional outcomes, as well as behavioral symptoms associated with AD dementia, and considered appropriate assessments for the early symptomatic AD population.

In addition, the primary target engagement outcome is the reduction of cerebral aggregated tau deposits as measured by quantitative tau PET imaging (flortaucipir F 18 PET standardized uptake value ratio [SUVr]) assessed as specified in the Schedule of Activities (Section 2).

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.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following up, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient [patient/subject] to discontinue the investigational product before completing the study. The patient should be followed until the event resolves,

stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the informed consent form (ICF) is signed, study site personnel will record via CRF/electronic data entry the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via CRF/electronic data entry.

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

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

The investigator answers yes/no when making this assessment.

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

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF/electronic data entry, clarifying if possible the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the CRF/electronic data entry and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received an investigational product, including PET tracers. However, if an SAE occurs after signing the ICF, but prior to receiving the investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

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 up 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. Patients with a serious hepatic AE should have additional data collected using the CRF/electronic data entry.

Pregnancy (during maternal or paternal exposure to investigational product) 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.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient disposition 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.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, 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 investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

9.3. Treatment of Overdose

There is no known antidote to LY3303560. In case of overdose, use appropriate monitoring and supportive therapy.

9.4. Safety

9.4.1. Physical and Neurological Examinations

As indicated in the Schedule of Activities (Section 2), complete physical examinations will be performed at the beginning and end of the double-blind period or at ED; and brief physical examinations will be performed at 3- to 6-month intervals.. The complete physical examination will include assessment of the following: general appearance; skin, head and neck; lymph nodes; thyroid; abdomen (bowel sounds, liver and spleen palpation); back (costovertebral angle tenderness); and musculoskeletal, cardiovascular, and respiratory systems. The brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen.

Complete neurological examinations will be performed as indicated in the Schedule of Activities (Section 2). The examinations will include a thorough assessment of gait, balance, coordination, cranial nerves, sensory and motor systems, and reflexes. If necessary, given the training of the principal investigator, a neurologist will be consulted in the event of significant new findings.

If a clinically meaningful change in an MRI is noted during the study, an additional full neurological examination will be performed as soon as possible, along with any other medical follow-up deemed necessary by the investigator.

9.4.2. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected as triplicates during the double-blind period according to the Schedule of Activities (Section 2). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

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

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

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

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

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

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

9.4.3. Vital Signs

Vital signs, including body temperature, will be measured at all visits.

9.4.3.1. Blood Pressure

Sitting blood pressure and pulse will be measured after 5 minutes in the sitting position at **all** visits. In addition, orthostatic blood pressure and pulse will be measured in the supine and standing positions at designated visits, as detailed in the Schedule of Activities (Section 2).

Orthostatic Blood Pressure Monitoring: For orthostatic blood pressure monitoring, subjects should be supine for at least 5 minutes and stand for at least 3 minutes prior to taking the respective measurements. If the subject feels unable to stand, only supine vital signs will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via CRF/electronic data entry.

9.4.3.2. Height, Weight, and Body Temperature

Height and body weight will be measured, with shoes removed at least for the height measurement at the screening visit. The same scale should be used for all measurements. Body mass index (BMI) will be calculated from the height and body weight. Temperature will be recorded using an oral or tympanic (or other acceptable route) thermometer.

Body weight will be collected on the laboratory requisition for creatinine clearance calculations. Any body weight data entered into the eCRF will be used for the overall data analysis.

9.4.4. Laboratory Tests

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

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via CRF/electronic data entry.

9.4.5. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against LY3303560. To interpret the results of immunogenicity, a venous blood sample will be collected, if warranted, at the same time points to determine the serum concentrations of LY3303560. All samples for immunogenicity should be taken predose when applicable.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3303560 at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize 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 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.

9.4.6. Other Tests

9.4.6.1. Columbia Suicide Severity Rating Scale

Consistent with Food and Drug Administration (FDA) regulatory guidance (FDA 2012), any occurrence of suicide-related thoughts and behaviors will be assessed as indicated in the Schedule of Activities (Section 2). The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The scale includes suggested questions to elicit the type of information needed to determine if a suicide-related thought or behavior occurred.

The first time the scale is administered in this study, the C-SSRS "Baseline" version will be used, and the findings will constitute the baseline assessment. The C-SSRS "Since Last Visit" scale will be used for all subsequent assessments.

The C-SSRS will be administered to the patient with the study partner/study informant present or available by telephone, after the cognitive and functional assessments. Responses from both the study partner/study informant and patient will be considered when administering the scale. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

9.4.6.2. Magnetic Resonance Imaging

Magnetic resonance imaging of the brain will be performed according to the Schedule of Activities (Section 2) and as clinically indicated. These images will be used to check for evidence of clinically relevant exclusion criteria and safety findings. (The MRI data will also be used to calculate brain volumetric measures, as noted in Section 9.1.2.5.)

The MRI scans will be reviewed by the investigator or qualified designee for immediate patient management. Any clinically significant findings noted at baseline that result in a diagnosis should be recorded as a preexisting condition or AE. The MRI scans will be sent for analysis to a centralized MRI vendor designated by Lilly. Final MRI eligibility at screening will be determined by the centralized MRI vendor designated by Lilly and the MRI results will be reported to the site along with a determination as to whether the scan meets MRI eligibility criteria. Specific analyses of the scans and calculations of brain volumetric measures will be performed by the centralized MRI vendor for data analysis and report-writing purposes. Results of centrally read MRIs regarding patient care/safety will be reported back to sites.

9.4.7. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

Lilly will review SAEs within time frames (see Section 9.2.1) mandated by company procedures. The Lilly CRP or scientist will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and conduct blinded trial level safety reviews, including assessment of the following:

- trends in safety data
- laboratory analytes including blood hematology, chemistry, and urinalysis
- AEs including monitoring of hypersensitivity and infusion reactions, ECG findings, neurological findings, as identified by investigator, and suicide-related thoughts and behaviors.

This approach will allow for the early assessment of safety and tolerability.

If safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC (an advisory group for this study formed to protect the integrity of data; refer to Interim Analyses section [Section 10.3.6]) can conduct additional analyses of the safety data.

9.4.7.1. Infusion Reactions

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

Management of the infusion reaction should proceed according to the severity of the reaction.

Additional data should also be collected via the CRF/electronic data entry; please refer to the Operations Manual for more details.

Additional, unscheduled stored serum samples for possible immune safety laboratory testing (including but not limited to β tryptase, total IgE, and immune complex testing) should also be collected approximately 60 to 120 minutes and 4 to 6 weeks after moderate or severe infusion reactions. Results of these samples will remain blinded to the investigator until the end of the study.

9.4.7.2. Immunogenicity

Patients are to return to the site for immunogenicity and safety follow-up visit, with Visit 801 at Week 113 (or 13 weeks after their last dose of study drug) for collection of blood samples for ADA (anti-LY3303560 antibody), PK measurement, assessment of AEs, concomitant medications, C-SSRS, and vital signs. See the Schedule of Activities (Section 2) for the timing of events and the measures to be assessed.

Treatment-emergent ADAs are defined in Section 10.3.4.5. A PK sample may be collected at the follow-up immunogenicity assessment if warranted and agreed upon between both the investigator and sponsor.

In the event of drug hypersensitivity reactions during the infusion or during monitoring afterwards, additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. 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.

9.4.7.3. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in

consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection
Additional safety data should be collected via the CRF/electronic data entry if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥ 2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE

9.4.8. Appropriateness of Safety Assessments

The clinical safety measurements (AE reporting, physical examinations, neurological examinations, vital signs, ECGs, and clinical safety laboratory tests [including immunogenicity]; Section 9.2 and Section 9.4) are well-established methods in drug development research and are standard procedures for clinical trials.

Regular MRIs will assess for any emergent radiographic abnormalities during treatment with LY3303560.

LY3303560 is an antibody therapy. Therefore, immunogenicity analyses are indicated. Blood samples for the assessment of immunogenicity will be taken at regular intervals throughout the study.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the serum concentrations 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. Any samples that are to be collected following an infusion must not be collected from the same site that was used to infuse study drug (for example, sample should be collected from the arm that did not receive the 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.

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

Bioanalytical samples collected to measure LY3303560 concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory purposes such as bioanalytical method development/validation work.

9.6. Pharmacodynamics

9.6.1. Change in Aggregated Tau Deposition as Estimated by Flortaucipir F 18

The flortaucipir F 18 PET provides a measure of tau deposition in the brain, expressed as an SUVr, and can serve as a PD biomarker of change in extracellular soluble aggregated tau deposition. Details of the analysis methods will be provided in the PET Imaging Manual.

Change from screening in flortaucipir F 18 signal will be compared in LY3303560- and placebo-treated patients for those patients who undergo flortaucipir F 18 PET scans as described in the Schedule of Activities (Section 2).

9.7. Pharmacogenomics [OR] Genetics

9.7.1. Apolipoprotein E Genotyping

Apolipoprotein E (APOE) genotyping is a mandatory part of this study, unless country-specific laws and regulations prohibit this type of testing. Blood sampling for APOE genotyping will be performed as shown in the Schedule of Activities (Section 2). Neither patients nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results. Failure to collect samples for APOE will not be considered a protocol deviation if country-specific regulations prohibit the testing of genetic material or transportation of such material outside of the country.

9.7.2. Whole Blood Samples for Pharmacogenetic Research

A whole 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 used to investigate variable response to LY3303560 and to investigate genetic variants thought to play a role in AD. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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 investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards (IRBs) impose shorter time limits. 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 becomes 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, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

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

Samples for the measurement of plasma tau, phospho181tau, NfL, and biomarker storage will be collected at the times specified in the Schedule of Activities (Section 2).

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

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

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 investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. 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 becomes commercially available.

9.9. Medical Resource Utilization and Health Economics

Dependence, or the level of assistance required by a patient, has been suggested as a construct for assessing the effect of AD treatment. The process of increasing dependence on others is intended as a complementary measure to existing clinical measures in order to help explain the impact of AD on economic issues such as the risk of institutionalization and caregiver burden (McLaughlin et al. 2010; Spackman et al. 2013). Recently, the ADCS-ADL scores were used to map individuals into 1 of 6 dependence levels (0 to 5): Level 0 – No iADL/bADL impairment; Level 1 – Some supervision needed on isolated iADLs; Level 2 – Supervision on multiple iADLs or loss of at least 1 household activity; Level 3 – Supervision on all types of iADLs or homebound; Level 4 – Supervision on some bADLs; and Level 5 – Impaired transfer or complete incontinence (Kahle-Wrobleski et al. 2015). An approach to transforming continuous

functional scale scores into discrete levels of dependence was examined previously in a longitudinal observational study, with preliminary results suggesting acceptable validity and progression in dependence level over time (Kahle-Wrobleski et al. 2017). At baseline, 49.6% of those with mild AD dementia had dependence level 2 and 42.7% were at levels 3 or 4. At 18 months, the proportion of patients at level 2 declined to 31.2% whereas those at levels 3 and 4 rose to 58.8%. Analyses will be conducted to examine changes in dependence levels across the trial population as well as potential differences on dependence level by treatment group assignment.

10. Statistical Considerations

10.1. Sample Size Determination

Study LMDC was powered using a mixed-model repeated measures (MMRM) analysis. Additional power calculations using DPM are described below.

Originally, approximately 285 subjects were planned to be enrolled and randomized in a 1:1:1 ratio to the 2 LY3303560 treatment arms and placebo. Because of an unexpected increase in patients entering screening and a drop in the screen fail rate at the end of the enrollment period, approximately 350 participants will be randomized. Assuming a dropout rate of 20%, it is expected that approximately 280 subjects will complete the double-blind treatment period of the study (approximately 93 per treatment arm). This sample size will provide approximately 87% power to demonstrate that at least 1 of the active treatment arms has a ≥0.6 posterior probability of slowing of iADRS progression over placebo by at least 4 points (that is, 25% slowing relative to placebo, based on a mean change from baseline in the placebo group of 16 points and mean change from baseline on at least one of the active treatment arms of at most 12 points) after 104 weeks (approximately 24 months) on study treatment. The assumption for the power calculation is that the mean change from baseline in iADRS levels in placebo and LY3303560 arms are approximately 16, 11, and 8 points (that is, 33% slowing on 1400 mg LY3303560 and 50% slowing on 5600 mg LY3303560 relative to placebo) at approximately 104 weeks, respectively, with a common standard deviation of the change from baseline of 20 points. If both active treatment arms are placebo-like with no efficacy, the probability of passing the efficacy criterion specified above (that is, false positive) is approximately 8%. The simulation for the power calculation and sample size determination was carried out in FACTS Version 5.5.

Based on the DPM, 360 enrolled patients, a 30% dropout rate, and a 3-month delay of treatment effect onset, this sample size will provide more than 95% power to demonstrate that at least one of the active treatment arms has slowed cognitive/functional decline. This claim of slowing cognitive/functional decline is based on showing that at least one of the active treatment arms has a ≥0.6 posterior probability of slowing of iADRS progression over placebo by at least 4 points (that is, 25% slowing relative to placebo, based on a mean change from baseline in the placebo group of 16 points and mean change from baseline on at least one of the active treatment arms of at most 12 points) after 104 weeks (approximately 24 months) on study treatment. This power calculation comes from simulations using a placebo decline of 19.56 points and 33% slowing on 1400 mg LY3303560 and 50% slowing on 5600 mg LY3303560 relative to placebo at 104 weeks. The variance-covariance matrix in the simulations had a variance at Week 104 of 436.85 (equal to a standard deviation of 20.9). If both active treatment arms are placebo like with no efficacy, the probability of passing the efficacy criterion specified above (that is, false positive) is approximately 2.5%. To test the hypothesis of a disease progression benefit, we calculate the posterior probability of superiority in cognitive/functional slowing, and if it is above a pre-specified threshold (which controls the experiment-wise type I error at 2.5%), then a claim of cognitive slowing will be made.

10.2. Populations for Analyses

For purposes of analysis, in general, the following populations are defined unless otherwise specified:

For primary efficacy analysis, the Full Analysis Set will group patients according to randomized treatment assignment, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. This is the intent-to-treat (ITT) population. When change from baseline is assessed, patients will be included in the analysis only if both a baseline and at least 1 valid postbaseline measure are available.

For safety analysis (safety population), all patients who received at least 1 dose of study treatment (LY3303560 or placebo) will be included in the safety analysis set. In safety data presentations, erroneously treated patients (for example, those randomized to "Treatment A" but actually given "Treatment B") will be accounted for in their actual treatment groups.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Unless otherwise noted, all pairwise frequentist tests of treatment effects will be conducted at a 2-sided alpha level of 0.05; 2-sided confidence intervals (CIs) will be displayed with a 95% confidence level. All tests of interactions between treatment and other factors will be conducted at an alpha level of 0.05. Details on the graphical approach and testing strategy will be specified in the statistical analysis plan (SAP).

All efficacy analyses will follow the ITT principle unless otherwise specified. An ITT analysis is an analysis of data by the groups to which subjects are assigned by random allocation, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol.

When change from baseline is assessed, subjects will be included in the analysis only if both a baseline and a postbaseline measure are available. Unless otherwise defined, a baseline measure is the last nonmissing observation collected prior to the first administration of study medications.

For efficacy analyses described in the Efficacy Analysis section (10.3.3), observations collected at nonscheduled visits will not be included in the analyses.

A database lock is expected to occur after all randomized subjects have had a chance to complete the double-blind period of the study. Efficacy and safety analyses will be conducted based on data collected during double-blind period. Data collected at the follow-up visit will be summarized and analyzed separately.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the SAP and clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Details of the statistical methods are specified in the SAP for Study LMDC.

10.3.1.1. Handling of Missing Items for Scales

If any of the individual items for ADAS-Cog or ADCS-ADL are missing or unknown, every effort will be made to obtain the score for the missing item or items.

For ADAS-Cog_{13}, if 3 or fewer of a total of 13 items are missing, the total score (maximum =85) will be imputed as follows: the total from the remaining items will be multiplied by a factor that includes the maximum score for the missing items. For example, if the first item, "Word-Recall Task," which ranges from a score of 0 through 10 (maximum = 10), is missing, and the second item "Commands," which ranges from a score of 0 to 5 (maximum = 5), is missing, then the multiplication factor = 85/(85 - [10 + 5]) = 85/70 = 1.21. Thus, the total score for this example will be the sum of the remaining 11 items multiplied by 1.21. The imputed number will be rounded up to the nearest integer. If more than 3 items are missing, the total score for ADAS-Cog_{13} at that visit will be considered missing.

For the ADCS-iADL, if <30% of the items are missing, the total score will be imputed. The sum of the nonmissing items will be prorated to the sum of total items. The imputed number will be rounded up to the nearest integer. If the nearest integer is greater than the maximum possible score, the imputed score will be equal to the maximum score. If >30% of the items are missing, the total score for ADCS-iADL at that visit will be considered missing. The same imputation technique will be applied to the ADCS-ADL total score. Note that, depending on the specific item responses that are missing, it is possible to have an imputed total score for both the ADCS-iADL and the ADCS-ADL, an imputed total score for one but not the other, or both total scores missing.

The same imputation technique will be applied to the CDR-SB. If only 1 box (of 6) of the CDR is missing, the sum of the boxes will be imputed by prorating the sum from the other 5 boxes. If the score from more than 1 box is not available, the CDR-SB at that visit will be considered missing.

The iADRS score is calculated as follows: iADRS score = [−1(ADAS - Cog_{13}) + 85] + ADCS-iADL (Wessels et al. 2015). If either ADAS-Cog_{13} or ADCS-iADL is missing, iADRS score will be considered missing.

For all other scales, if any item is missing, any total or sum involving that item will be considered missing.

10.3.2. Treatment Group Comparability

10.3.2.1. Subject Disposition

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

The reasons for discontinuation will be collected when the patient's participation in the study ends and will be summarized by treatment group for all randomized subjects. The percentage of subjects discontinuing from each treatment group will be compared between groups using Fisher's exact test. The comparisons will be done for the overall percentage of patients who discontinue and also for select specific reasons for discontinuation.

10.3.2.2. Subject Characteristics

The patient's age, gender, race, height, body weight, BMI (weight (kg)/[height (m)]2), tobacco use, alcohol use, caffeine use, years of education, work status, time since onset of first AD symptoms, tau PET burden (various measures), time since diagnosis, MMSE score at Visit 1, APOE genotype (E4 carrier vs noncarrier), having 1 or more first-degree relatives with AD, and AChEI and/or memantine use at baseline will be recorded.

Baseline characteristics will be summarized by treatment group and overall. Summaries will include descriptive statistics for continuous and categorical measures. Fisher's exact test or Pearson's chi-square test will be used for treatment-group comparisons of categorical data. For continuous data, analysis of variance, with independent factors for treatment and investigator (pooled as necessary), will be used.

10.3.2.3. Prior and Concomitant Therapy

Prior medications are defined as those that stop before randomization (Visit 2). Concomitant medications are defined as those being taken on or after randomization (Visit 2). A summary of concomitant medications will be presented as frequencies and percentages for each treatment group. Fisher's exact test will be used to test for treatment differences between groups.

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

Prior and concomitant medications will be listed.

Summary tables will also be provided for concomitant anticholinergics that affect cognitive function and AChEI/memantine medications.

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

10.3.2.4. Treatment Compliance

Summary statistics for LY3303560 treatment compliance will be provided for the total number of complete infusions received, duration of complete infusion, and volume of complete infusion by treatment group.

Frequencies and percentages of reasons why infusion was stopped will also be presented.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective of this study is to test the hypothesis that IV infusion of LY3303560 will slow the cognitive and/or functional decline of AD as measured by the composite measure

iADRS compared with placebo in patients with early symptomatic AD. This will be assessed using a disease progression model (DPM) as the primary analysis.

The DPM is as follows:

$$Y_{ij} = \gamma_i + e^{\theta_{T_i}} \sum_{v=0}^{j} \alpha_v + \varepsilon_{ij}, i = 1, 2, \ldots k; j = 1, 2, \ldots l$$

where Y_{ij} denotes the clinical outcome at Visit j for participant i, clinical outcome score at baseline (prior to treatment) is Y_{i0}. γ_i (i=1, 2, …, k), which represents the random participant effects. T_i denotes the treatment arm for participant i. e^{θ_T} is the disease progression ratio (DPR) for treatment T and $e^{\theta_T} = 1$ for placebo. Furthermore, α_v is the change in mean cognitive score for placebo from visit v-1 to v. ε_{ij} is the error term. Additional covariates such as age, APOE4 status, concomitant use of approved prescription AD medications at baseline (yes/no) may be added to the model and specified in the SAP. A DPR less than 1 favors LY3303560 and corresponds to a slowing of disease progression with LY3303560 in comparison to placebo; a DPR greater than 1 favors placebo. The DPM will be fitted to the data and Bayesian inferences will be summarized including posterior distribution of DPR and posterior probabilities of various DPR thresholds of interest (for example, 0.75 which translates to 25% slowing of disease progression with LY3303560 group versus placebo). To test the hypothesis of a disease progression benefit, we calculate the posterior probability of superiority in cognitive/functional slowing and if it is above a pre-specified threshold (which controls the experiment-wise type I error at 2.5%), then a claim of cognitive/functional slowing will be made. Details describing the pre-specified threshold will be included in the SAP. The null hypothesis is that the DPR between the LY3303560 group versus placebo equals 1. Bayesian inferences for the primary analyses using DPM will use non-informative prior distributions and will be further detailed in the SAP.

10.3.3.2. Secondary Efficacy Analyses

The MMRM analysis will also be assessed for the iADRS as a sensitivity analysis. The change from baseline score on the iADRS at each scheduled post-baseline visit (according to the SoA in Section 2) during the treatment period will be the dependent variable. The model for the fixed effects will include the following terms: baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. Visit will be considered a categorical variable. The null hypothesis is that the contrast between the zagotenemab group versus placebo at the last visit equals 0. An unstructured covariance matrix will be used to model the within-subject variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence:

- heterogeneous Toeplitz covariance structure
- heterogeneous autoregressive covariance structure
- heterogeneous compound symmetry covariance structure

- compound symmetry covariance structure

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The primary time point for treatment comparison will be at Week 104. The treatment group contrast in least-squares mean progression and its associated p-value and 95% CI will be calculated for the treatment comparison of zagotenemab versus placebo using the MMRM model specified above.

In addition to the DPM and MMRM models described above, the mean for each treatment group over the entire double-blind duration of the study can be modeled using natural cubic splines (Bates and Chambers 1992). The natural cubic spline (NCS) model provides a type of smoothing function to the data and can adequately estimate longitudinal trajectories under a variety of shapes (for example, linear and quadratic) for each treatment group. The degrees of freedom of the model can be prespecified to establish the level of smoothing of the data. The number and location of the "knots" is utilized to parse out different time periods where the data may transition from one shape to another to provide an adequate fit.

Each of the secondary efficacy outcomes will be assessed using DPM (similar to the primary analyses), MMRM, and NCS analyses. These secondary efficacy outcomes include ADAS-Cog_{13}, ADCS-iADL, CDR-SB, and MMSE. iADRS will also be assessed using MMRM and NCS analyses. Additional details are described in the SAP.

The change from baseline to endpoint in tau SUVr (as calculated from flortaucipir F 18 PET scans) will be analyzed using an analysis of covariance model with terms of baseline value and treatment. Longitudinal changes from baseline in vMRI parameters will be analyzed using MMRM including the following terms in the model: baseline parameter value, treatment, visit, treatment-by-visit interaction, and baseline-by-visit interaction.

Any additional analyses of secondary efficacy outcomes and biomarkers will be specified in the SAP.

10.3.4. Safety Analyses

All subjects who receive at least 1 dose of LY3303560 will be evaluated for safety and tolerability. Safety parameters (AEs, laboratory analytes, vital signs, ECGs, and MRIs) will be summarized using descriptive statistics for continuous variables and frequencies along with percentages for categorical variables during the treatment period.

10.3.4.1. Adverse Events

Treatment-emergent adverse events will be defined as events that first occurred or worsened on or after randomization (Visit 2). Should there be insufficient data for AE start date and stop date, the AE will be considered TE.

Treatment-emergent adverse events will be calculated based on AE identifier and coded according to established Medical Dictionary for Regulatory Activities (MedDRA) terms and summarized by MedDRA System Organ Class and Preferred Term.

An overview of AEs, including the number and percentage of subjects who died, had SAEs, discontinued due to AEs, and who had TEAEs, will be summarized by treatment group.

10.3.4.2. Vital Signs and Weight

Vital sign measurements and weight will be analyzed using continuous data (change from baseline) and categorical data (proportion of TE abnormalities).

Summary statistics will be presented for observed values at baseline and each scheduled postbaseline visit and for change from baseline results at each scheduled postbaseline visit. Systolic and diastolic blood pressure and pulse (collected in sitting position), body temperature, and weight will be summarized.

The incidence of TE abnormal high or low vital signs and weight will be summarized by treatment groups. Treatment-emergent vital sign evaluations are defined for evaluations collected after the initiation of study medication. Criteria for abnormal vital signs and weight will be identified prospectively and provided in the SAP. Any vital sign or weight outside the criterion values will be considered abnormal.

10.3.4.3. Laboratory Analyses

Laboratory measurements will be analyzed as continuous data (change from baseline) measured as International System Units (SI) or as categorical data (proportion of TE abnormalities).

If there are multiple records of laboratory measurements at baseline or postbaseline visits, the last record will be used.

Change from baseline to postbaseline visits at which laboratory measurements are taken will be summarized using descriptive statistics.

For all laboratory analytes, frequencies of subjects with notable changes (that is, increases or decreases of a prespecified amount unique to each analyte) from baseline to each postbaseline visit will also be summarized for all subjects and stratified by low, normal, or high at baseline.

10.3.4.4. Electrocardiograms

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

Since ECG is measured in triplicates during the double-blind period, the average of triplicates will be used at baseline and each double-blind period visit. If there are multiple records after averaging ECG triplicates within a visit, the last record of averages will be used.

The analysis will be done for the following ECG measurements: heart rate, PR, QT, QTc, and RR intervals, and QRS duration. All analyses of QTc will be carried out using the Fridericia correction (QTcF) method. These summaries will include data from each visit at which ECG measures are performed.

Change from baseline to each postbaseline visit at which ECG measurements are taken will be assessed using an Analysis of covariance (ANCOVA) model. This analysis will be done separately for each ECG parameter.

Incidence of TE abnormal ECGs will be assessed by comparisons at (1) anytime and (2) each postbaseline visit between treatment groups with Fisher's exact test. For analyses of TE abnormal ECGs, baseline will be considered as all visits before the initiation of drug dose.

Criteria for abnormal ECGs and QTcF prolongation will be identified prospectively and provided in the SAP.

Treatment-emergent high ECG parameters (heart rate, PR interval, QRS duration, and QT and QTcF intervals) are the values that are low or normal at all baseline visits and fall into high abnormal categories postbaseline. Similarly, TE low ECG parameters (heart rate, PR interval, and QRS duration) are the values that are high or normal at all baseline visits and fall into low abnormal categories.

For each TE high ECG parameter, only subjects who were low or normal at baseline and have at least 1 postbaseline value will be included in the denominator when computing the proportion of subjects with TE high values. Similarly, only subjects who were high or normal at baseline and have at least 1 postbaseline value will be included in the denominator when computing the proportion of subjects with TE low values.

For prolonged QTcF interval assessments, when computing the proportion of subjects with TE high abnormalities, only subjects who were normal at baseline and had a nonmissing result at that postbaseline visit will be included in the denominator.

In addition, treatment differences in the proportion of subjects who have normal baselines with a change to abnormal high or abnormal low values at any postbaseline visits will be summarized. Treatment-emergent qualitative ECG findings will also be summarized.

10.3.4.5. Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting (baseline) ADA, ADA at any time after baseline, and TE-ADAs to LY3303560 will be tabulated. If no ADAs are detected at baseline, TE-ADAs are defined as those with a titer 2-fold (1 dilution) greater than the MRD of the assay. For samples with ADA detected at baseline, TE-ADA are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. For the TE-ADA subjects, the distribution of maximum titers will be described. The frequency of neutralizing antibodies may also be tabulated. The relationship between the presence of antibodies to LY3303560 and PK, PD, safety and/or efficacy assessment may be assessed.

10.3.4.6. Suicidal Ideation and Behavior

Suicide-related thoughts and behaviors, based on the C-SSRS, will be listed by subject and visit. Only subjects who show suicidal ideation/behavior will be displayed (that is, if a subject's answers are all "no" for the C-SSRS, then that subject will not be displayed). However, if a subject reported any ideation or behavior at any time point, then all their ideation and behavior will be displayed, even if not positive.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Compartmental modeling of LY3303560 PK data using nonlinear mixed effects modeling or other appropriate methods may be explored, and population estimates for clearance and central volume of distribution may be reported. Depending on the model selected, other PK parameters may also be reported. Exploratory graphical analyses of the effect of dose level or demographic factors on PK parameters may be conducted. If appropriate, data from other studies of LY3303560 may be used in this analysis.

The PK/PD relationships between plasma LY3303560 concentration and SUVr, cognitive endpoints, or other markers of PD activity may be explored graphically. The relationship between the presence of antibodies to LY3303560 and PK, PD, safety, and/or efficacy may be assessed graphically. If warranted, additional analysis may be explored to evaluate potential interactions for ADA, PD, and other endpoints (PET scan, safety, etc.).

Additional modeling may be performed based on the results of the graphical analyses.

10.3.6. Interim Analyses

An external DMC is authorized to evaluate results from unblinded interim analyses to

- assess safety,
- assess efficacy to inform future development as needed, and
- recommend any modifications to the study (such as stopping the study or dropping an arm).

Operational details and the decision rules will be provided in the DMC charter and DMC SAP.

Study sites will receive information about interim results ONLY if relevant for the safety of their patients.

Unblinding details will be specified in a separate unblinding plan document.

First DMC Review. An unblinded DMC review for safety will be conducted once approximately 30 patients have completed 3 months of exposure to study treatment (that is, after completing 4 weeks following the third dose of study treatment). No patients beyond this initial group of approximately 30 patients will be dosed until the DMC review has been completed and the recommendation is to continue the study. This initial group will continue treatment during the assessment period.

Second DMC Review. A second unblinded DMC review will be conducted to evaluate efficacy results from unblinded interim analyses to inform future development, as well as to evaluate safety. It will be conducted after a proportion of patients, for example approximately 100% of patients, have completed 12 months of exposure to study treatment (that is, 4 weeks after the 12^{th} dose at Visit 15 [Week 52]). The efficacy review will not affect the operation of the study. However, to control for the remote possibility that the study will be stopped for efficacy, a Haybittle-Peto adjustment (Haybittle 1971; Peto et al. 1976) will be used if efficacy is tested at this review. A significance level of α=0.00025, accounting for the Bonferroni adjustment and a similar potential analysis at the third DMC review, would be used for comparisons between each

LY3303560 treatment group and the placebo group. Because of the small alpha used in this review, the final analysis at the conclusion of the study would not adjust alpha as a result of this review. Enrollment and/or treatment will continue during the second interim analysis.

Third DMC Review. A third unblinded DMC review will be conducted to evaluate safety after a proportion of patients, for example, approximately 100% of patients, have completed 18 months of exposure to study treatment (that is, 4 weeks after the 18th dose at Visit 21 [Week 76]).

Additional unblinded interims may be requested by the Sponsor or DMC, and if needed, would be conducted by the DMC. Any efficacy review would not affect the operation of the study.

To facilitate PK/PD interim analyses and to initiate the final population PK/PD model development processes, a limited number of preidentified individuals may also gain access to the unblinded data, as specified in the unblinding plan. This will be conducted at the same time as the second DMC review. In preparation for the final analysis, access may also be granted after all patients complete 64 weeks of treatment (that is, Visit 18). Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

Quarterly, blinded trial level safety reviews will be carried out as documented in the trial level safety review plan.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
Aβ	amyloid beta
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADA	anti-drug antibodies
ADAS-Cog13	Alzheimer's Disease Assessment Scale—Cognitive subscale 13
ADCS-ADL	Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory
ADCS-bADL	Alzheimer's Disease Cooperative Study—basic Activities of Daily Living
ADCS-iADL	Alzheimer's Disease Cooperative Study—instrumental Activities of Daily Living
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
APOE	apolipoprotein subtype E
AST	aspartate aminotransferase
blinding/masking	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 patients 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
CBB	CogState Brief Battery
CDR-SB	Clinical Dementia Rating Scale—Sum of Boxes

CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
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.
CRS	clinical research scientist
C-SSRS	Columbia Suicide Severity Rating Scale
DCTClock	Digital Clock Drawing Test
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form
ED	early discontinuation
End of study	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.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FDA	Food and Drug Administration
GCP	good clinical practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus

IAC	internal assessment committee
iADRS	integrated Alzheimer's Disease Rating Scale
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study 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.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IVIG	intravenous immunoglobulin
IWRS	interactive web response system
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NCS	natural cubic spline
NfL	neurofilament light
NFT	neurofibrillary tangle

NOAEL	no-observable-adverse-effects level
PCR	polymerase chain reaction
PET	positron emission tomography
PI	principal investigator
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
PSP	progressive supranuclear palsy
Q4W	once every 4 weeks
QT	QT interval on the ECG
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
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 study.
SHSF	Self-Harm Supplement form
SUSAR	suspected unexpected serious adverse reaction
SUVr	standardized uptake value ratio
TBL	total bilirubin level
TE	treatment-emergent
TEAE	treatment-emergent adverse event: An 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 organization
ULN	upper limit of normal
V	visit
vMRI	volumetric magnetic resonance imaging

WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry[a,b,c]**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase (ALP)
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose, nonfasting
Urinalysis[a,b]	Albumin
Specific gravity	Cholesterol
pH	Creatine kinase (CK)
Protein	**Other Tests**
Glucose	APOE genotyping[a,c,d]
Ketones	High sensitivity C-reactive protein[c]
Blood	Calculated creatinine clearance (Cockcroft and Gault 1976)
Urine leukocyte esterase	HBsAg[e]
	HCV antibody
	HCV RNA PCR[f]
	Immune Safety Labs[g]
	B tryptase
	Total Immunoglobulin E
	Immune complex testing

Abbreviations: APOE = apolipoprotein subtype E; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; PCR = polymerase chain reaction; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cells.

[a] Assayed by Lilly-designated (central) laboratory.

[b] Results will be confirmed by the Lilly-designated (central) laboratory at the time of initial testing.

[c] Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

[d] Neither patients nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results. Failure to collect samples for APOE genotyping will not be considered a protocol violation if country-specific regulations prohibit the testing of genetic material or transportation of such material outside of the country.

[e] Laboratory test to be performed only for patients with a history of hepatitis B.

[f] Laboratory test to be performed only for patients who are hepatitis C antibody positive.

[g] Laboratory tests to be performed only for patients with moderate-to-severe infusion reaction (see Section 9.4.7.1 for timing of sample collection). Investigators will remain blinded to the immune safety lab results until the end of study.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the subject/subject's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject 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 subject/subject's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's/subject's legal representative's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the subject or the subject's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Study partners will also sign the informed consent. If it is not known that the study partner will change, the new study partner would need to sign the ICF when he/she takes over the care for the subject and study participation. The change in study partner would also need to be documented on the eCRF.

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

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by the International Council for Harmonisation (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, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

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

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- 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
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.5. Investigator Information

For this clinical trial, the following qualifications are required for the principal investigator (PI):

- Physician with a specialty in neurology, geriatrics, or psychiatry
- Experience in conducting clinical trials in the treatment of AD

If the PI does not meet these qualifications, then the site must have a subinvestigator who meets these qualifications and the PI must be a licensed clinician with experience in conducting clinical trials in the treatment of AD.

Cognitive assessments must be administered by an individual trained in the use of these instruments. Investigators and site personnel who will perform ratings will be trained and approved by Lilly or its designee prior to participating in the study. In most cases, evaluation and notification will occur via online training sessions. Note that the ADAS-Cog and MMSE should be administered by different rater than the ADCS-ADL and CDR. The PI has the responsibility of selecting who will administer the instruments at the site, as long as all training requirements have been met by those raters. However, it is a best practice that the measurements be performed on a given patient by the same rater at each visit.

Appendix 3.1.6. 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 PI will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.7. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR 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 qualified subjects will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

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

Appendix 3.2. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- sponsor investigator study site trainings 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 eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, 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 original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic Clinical Outcome Assessment (eCOA) measures (for example, a rating scale, including audio voice recordings of the rater's questions and the patient's and study partner's responses) are entered into an eCOA instrument (at the time that the information is obtained). The eCOA tablet has both keyboard entry and audio voice recording capabilities. In these instances where there is no prior written or electronic source data at the site, the eCOA instrument record will serve as the source.

If eCOA records are stored at a third party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the eCOA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as audio voice recordings, laboratory test data or ECG data, will be stored electronically in the central vendor's database system. With the exception of the audio voice recordings, which are only used for central monitoring purposes, data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the subject will serve as the source document will be identified and documented by each site in that site's study file.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. 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.

Appendix 3.3.2. 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 3.4. Publication Policy

The publication policy for Study LMDC is described in the Clinical Trial Agreement.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Flortaucipir F 18 Tau PET Imaging

A screening flortaucipir F 18 PET scan will be performed as part of the study eligibility criteria. Additional flortaucipir F 18 PET scans will be performed at Visit 15 and Visit 28, and at early discontinuation (ED) if ED occurs after the patient has at least completed Visit 11. Specific instructions for the flortaucipir F 18 PET scan itself will be provided in the PET Imaging Manual.

Inclusion Criteria for Flortaucipir F 18 PET Scans

A patient must meet all other Visit 1 eligibility criteria before having a flortaucipir F 18 PET scan with the exception of the MRI.

[42] Criterion [#42] has been deleted.

Exclusion Criteria for Flortaucipir F 18 PET Scans

A patient will be excluded from participation in flortaucipir F 18 imaging if he or she meets any of the criteria below:

[43] Has any condition that, in the investigator's opinion, could increase risk to the patient, limit the patient's ability to tolerate the experimental procedures, or interfere with analysis of the data (for example, patients with chronic back pain might not be able to lie still during the scanning procedures).

[44] Has abnormal findings on physical examination, laboratory screening tests, or screening ECGs that suggest the patient might have a condition that could, in the opinion of the investigator, affect his or her response to the radiopharmaceutical and related testing procedures.

[45] Is deemed likely to be unable to complete the imaging procedure for any reason.

[46] Is receiving other radiation exposure that, when added to the flortaucipir F 18 PET scan, would exceed local or national regulatory limits for a patient.

Site investigators, patients, and study partners will not be informed of the results of PET scans obtained following randomization, as they relate to the study. Any findings that may be of potential medical concern will be provided for appropriate follow-up.

PET Scan-Specific Information

PET Scan Procedures

Specific imaging acquisition protocols designed to ensure consistency across sites will be provided in the PET Imaging Manual. The scanning technologists will be blinded to patients' treatment assignments.

Scan Safety

The primary risk related to flortaucipir F 18 is radiation exposure. Details on the amount of exposure estimated to occur on each imaging occasion and cumulatively are shown in Table APP.5.1. In addition, the tau ligand flortaucipir F 18 continues to be in clinical evaluation, and risks from the agent are not fully known. Details on the clinical information to date regarding flortaucipir F 18 exposure will be provided in the ICF. More detailed information about the known and expected benefits and risks of flortaucipir F 18 may be found in the Investigator's Brochure.

Patients must minimize movement during each PET procedure, which can last 10 to 30 minutes for each scan. Most state-of-the-art imaging systems are designed to reduce head motion and patient discomfort.

Table APP.5.1. Effective Radiation Dose (mSv)

	Effective Dose (mSv) per Scan[a]	Number of Scans in First Year[b]	Effective Dose (mSv) for Scans in First Year	Number of Scans in Second Year[b]	Effective Dose (mSv) for Scans in Second Year	Effective Dose (mSv) for Years 1 and 2
Flortaucipir F 18 Scan (10 mCi IV)	9.10	1	9.10	2	18.20	27.30
Totals		1	9.10	2	18.20	27.30

Abbreviations: CT = computerized tomography; IV = intravenous infusion; PET = positron emission tomography.

[a] Dose shown includes radiation exposure from the radiotracer and also assumes a nonclinical CT scan is obtained (estimated at 0.4 mSv) as part of the PET scan attenuation correction process when the scan is performed on a PET/CT scanner. A clinical CT scan is not needed during the PET scan session and because it will add additional radiation exposure it is not recommended.

[b] If the patient is discontinued from Study LMDC, the subject will be asked to participate in a discontinuation visit. Patients who discontinue from the study early will have a flortaucipir scan performed at the ED visit only if they discontinue the study after they have at least completed V11.

Visits that include imaging should be completed over adjacent days. Note that flortaucipir F 18 PET tau imaging can be performed 1 or 2 days after cognitive and functional testing.

With respect to other compound-related risks, AV-1451 was positive in the in vitro human ether-à-go-go-related gene (hERG) assay. Although the margin of safety appears high, and in vivo cardiovascular assessments in dogs showed no evidence of QT prolongation, subjects with a history of risk factors for Torsades de Pointes and patients taking drugs known to prolong the QT interval will be excluded from this study.

If clinically meaningful abnormalities are noted on the ECG, the advisability of the flortaucipir scan should be considered by the investigator in consultation with the Lilly-designated medical monitor.

If it becomes necessary for a patient to start taking a medication known to prolong QT interval prior to performance of any postbaseline flortaucipir F 18 scan, do not perform the scan or wait until the QT-prolonging medication has been stopped for the longer of 14 days or 5 half-lives. The patient may, however, remain in the study. Nonperformance of postbaseline flortaucipir F 18 PET scans in patients taking a medication known to prolong QT interval will not be considered a protocol violation.

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