Protocol I7X-MC-LLCF(c)

Effect of LY3202626 on Alzheimer's Disease Progression as Measured by Cerebral 18F-AV-1451 Tau-PET in Mild Alzheimer's Disease Dementia

NCT02791191

Approval Date: 31-Jan-2018

Protocol I7X-MC-LLCF(c)
Effect of LY3202626 on Alzheimer's Disease Progression as Measured by Cerebral ^{18}F-AV-1451 Tau-PET in Mild Alzheimer's Disease Dementia

Confidential Information

LY3202626

Multicenter, randomized, double-blind, placebo-controlled, Phase 2 study comparing 3 mg and 12 mg of LY3202626 with placebo over 52 weeks in approximately 380 patients with mild Alzheimer's disease dementia.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly on 18 February 2016
Amendment (a) Electronically Signed and Approved by Lilly on 10 June 2016
Amendment (b) Electronically Signed and Approved by Lilly on: 06 July 2017
Amendment (c) Electronically Signed and Approved by Lilly
on approval date provided below.

Approval Date: 31-Jan-2018 GMT

Table of Contents

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

1. Synopsis

Title of Study:
Effect of LY3202626 on Alzheimer's Disease Progression as Measured by Cerebral ^{18}F-AV-1451 Tau-PET in Mild Alzheimer's Disease Dementia.

Rationale:
Eli Lilly and Company (Lilly) is developing LY3202626, a synthetic small molecule which is a potent inhibitor of β-site amyloid precursor protein (APP)-cleaving enzyme [BACE]1, for the treatment of Alzheimer's disease (AD). It is hypothesized that inhibition of BACE1 may slow or inhibit the progression of AD.

Study I7X-MC-LLCF (LLCF), a Phase 2 study, will assess if inhibiting the production of Aβ in the brain through BACE1 inhibition with LY3202626 can slow the progression of disease as assessed by biomarkers of neurodegeneration over 52 weeks of treatment. The ^{18}F-AV-1451 positron emission tomography (PET) scan is the primary outcome measure as a marker of disease progression for this study, to assess cerebral tau neurofibrillary tangle load and whether there are any changes with Aβ targeted BACE inhibitor treatment. The study will also assess LY3202626 pharmacokinetics (PK) and pharmacodynamics (PD; plasma Aβ), biomarkers of amyloid pathology (florbetapir PET) and neurodegeneration (volumetric magnetic resonance imaging [vMRI] and cerebral perfusion). In addition, LY3202626, Aβ, and tau in cerebrospinal fluid (CSF) will be collected in a substudy to assess the PK of LY3202626, PD (CSF Aβ), and neurodegeneration (CSF tau) within the central nervous system (CNS). Clinical outcomes including cognition, functional consequences of cognition, and safety will also be evaluated.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To assess the change from baseline in ^{18}F-AV-1451 positron emission tomography (PET) after treatment with LY3202626 3 mg or 12 mg per day compared with placebo for 52 weeks among patients with mild Alzheimer's disease (AD) dementia and evidence of brain amyloid.	The change in standardized uptake value ratio (SUVr) of ^{18}F-AV-1451 PET from baseline to 52 weeks. The change will be compared between the LY3202626 doses (3mg and 12mg) and placebo.
Secondary • To evaluate the safety and tolerability of LY3202626 (3 mg and 12 mg per day) compared with placebo.	• Standard safety assessments: o spontaneously reported adverse events (AEs) o clinical laboratory tests o vital sign and body weight measurements o 12-lead electrocardiograms (ECGs) o physical and neurological examinations • magnetic resonance imaging (MRI; amyloid-related imaging abnormality [ARIA] and emergent radiological findings) • Skin examination • Eye examination • Columbia-Suicide Severity Rating Scale (C-SSRS)

Objectives	Endpoints
• To assess peripheral pharmacokinetics (PK) and pharmacodynamics (PD) of LY3202626 (3 mg and 12 mg per day) over 52 weeks.	• Plasma PK of LY3202626 • Plasma Pharmacodynamics $A\beta_{1-40}$, $A\beta_{1-42}$, $A\beta_{1-x}$
• To assess change from baseline in cognition after 52 weeks of treatment among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo.	• 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog13)
• To assess change from baseline in function after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo.	• Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living inventory (ADCS-iADL)
• To assess change from baseline in a composite measure of cognition and function after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo.	• integrated Alzheimer's Disease Rating Scale (iADRS)

Summary of Study Design:

Study I7X-MC-LLCF is a multicenter, multi-region, randomized, double-blind, placebo-controlled study in patients with mild AD dementia and demonstration of amyloid pathology by florbetapir PET tracer. The study will test the effect of two oral doses of LY3202626, a potent BACE1 inhibitor, on ^{18}F-AV-1451 PET and evaluate the cognition, function, safety profile, PK and PD of LY3202626 in this population.

Treatment Arms and Duration:

Patients will initially be randomized into 1 of 3 treatment groups: 2 fixed dose levels of LY3202626 (3 mg and 12 mg per day) and placebo (1:1:1) until approximately 45 participants are enrolled in each arm; then randomization will change to 1:1 with subjects entering either the 12 mg or placebo arm. Treatment duration for all subjects will be 52 weeks.

Number of Patients:

Approximately 380 patients will be enrolled for approximately 320 completed evaluable patients, assuming approximately 15% drop out.

Statistical Analysis:

Patient Characteristics:

Standard baseline characteristics of gender, age, and race will be summarized for all patients. Treatment group comparisons will be made using Fisher's exact test for categorical data and an analysis of variance (ANOVA), with an independent factor for treatment for continuous data. Diagnosis, illness characteristics, and baseline efficacy and safety measures will be analyzed in a similar manner.

Efficacy:

The primary objective of this study is to assess the effect on neuropathological progression of 2 different LY3202626 doses in patients with mild AD dementia compared with placebo, measured by change in ^{18}F-AV-1451 PET standardized uptake value ratio (SUVr) at baseline and week 52. The primary measurement is change from

baseline ^{18}F-AV-1451 PET SUVr at Week 52. An analysis of covariance (ANCOVA) will be used to statistically evaluate change in ^{18}F-AV-1451 PET from baseline at 52 weeks post-dose.

Statistical analyses of mean change in efficacy and health outcome measures will be conducted. Generally, statistical assessment of the efficacy and health outcome measures will be a mixed model repeated measure (MMRM) or an ANCOVA. The primary comparison will be between LY3202626 12 mg versus placebo at endpoint.

Safety:

Safety will be assessed by summarizing and analyzing adverse events (AEs), laboratory analytes, vital signs, electrocardiograms (ECGs), skin examinations, and eye examinations during the treatment period. For continuous safety measurements, a change from baseline will be analyzed using MMRM or ANCOVA model. Safety analyses for the treatment period will include comparisons between LY3202626 dose groups and placebo. All hypotheses will be tested at a 2-sided 0.05 significance level. No adjustments for multiple comparisons will be made.

For analysis comparing proportion of treatment-emergent abnormalities between treatment groups for laboratory analytes, vital signs, weight, ECGs, skin examinations, and eye examinations, only patients who have both a baseline observation and a postbaseline observation will be included in the analysis for each analyte or parameter, respectively. The proportion of patients with abnormalities will be summarized and compared between treatment groups using Fisher's exact test.

Pharmacokinetics/Pharmacodynamics:

Plasma LY3202626 concentration data will be analyzed using a population approach. For each dose level and visit, plasma $A\beta_{1-40}$, $A\beta_{1-42}$ and $A\beta_{1-x}$ concentrations will be summarized and mean change from baseline will be calculated. If appropriate, a modeling approach may be used to describe the change in plasma Aβ. Additional exploratory analyses of the data will be conducted as suggested by the data. If appropriate, the data from this study may be combined with that from other studies in a meta-analysis.

Interim Analysis:

An interim analysis is planned for when data from approximately 105 qualified patients at 12 weeks (Study Visit 8) and 75 patients through 24 weeks (Study Visit 11) have been obtained. The interim analysis will be conducted for safety, and to support initial PK model development. An early lock of the PK/PD dataset will be conducted after all patients complete 24 weeks of treatment to prepare for final PK/PD model development.

2. Schedule of Activities

Study Procedure	**Screening Period**		**Double Blind Period**																	
Visit[a]	**V1**[b]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**Follow Up**	**ED**[c]
Week	**-60 to -1**[d]		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	
Tolerance Interval (days)				±5	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±10	±10	
Administrative																				
Subject Informed Consent	X																			
Subject number assigned	X																			
Study Partner Informed Consent[v]	X																			
Randomization			X																	
Clinical Assessments																				
Demographics	X																			
Medical/Psychiatric History	X																			
Inclusion/Exclusion Criteria	X	X	X																	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Habits	X																			
NIA-AA criteria review	X																			
Efficacy and Health Outcome Measures[e]																				
MoCA[f]	X										X							X		X
ADAS-Cog_{13}			X								X							X		X
ADCS-ADL			X								X							X		X
FAQ			X								X							X		X
MMSE[f]	X										X							X		X
ECog			X								X							X		X
NPI			X															X		X
BASQID			X															X		X
Imaging Measures[c,g]																				
MRI	X																	X		X
Florbetapir PET (including perfusion)	X																	X		X
^{18}F-AV-1451 PET		X																X[h]		X[h]
Laboratory Measures																				
Urinalysis	X		X					X			X			X				X		X
Blood sample for APOE genotyping		X																		
Blood sample for pharmacogenetics		X																		

Study Procedure	**Screening Period**		**Double Blind Period**																	
Visit[a]	**V1**[b]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**Follow Up**	**ED**[c]
Week	**-60 to -1**[d]		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	
Tolerance Interval (days)				±5	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±10	±10	
Blood sample for epigenetics		X																X		
Blood sample for RNA[i]		X																X		
Plasma LY3202626 (PK)[j]					X[k]	X[k]	X[l]	X[k]	X[l]		X[m]									X
Plasma peptides: $A\beta_{1-40}$, $A\beta_{1-42}$, $A\beta_{1-x}$ (PD)[n]		X			X	X	X	X	X		X							X		X
Plasma samples (EDTA) for storage and exploratory biomarker R&D		X				X	X	X	X	X	X			X				X		X
Clinical Chemistry, Hematology, Electrolytes[o]	X		X		X	X	X	X	X	X	X			X				X	X	X
Safety Measures																				
Eye Examination[p]	X							X					X					X		X
Skin Examination[q]	X							X			X							X		X
Physical/Neurological Examination	X		X		X		X			X				X				X		X
Vital Signs[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																			
Body weight	X							X			X							X		X
12-lead ECG(triplicate)	X[s]		X	X		X	X		X		X		X		X			X	X	X
C-SSRS[t]/Self Harm Supplement Form	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Drug			X[u]			X	X	X	X	X	X	X	X	X	X	X	X			
Assess Drug Compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: Aβ = amyloid beta peptide; ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory; APOE = apolipoprotein E; BASQID = Bath Assessment of Subjective Quality of Life in Dementia; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ECog = Everyday Cognition; ED = early discontinuation; EDTA = ethylenediaminetetraacetic acid; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental Status Examination; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NIA-AA = National Institute on Aging-Alzheimer's Association; NPI = Neuropsychiatric Inventory; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; R&D = research and development; RNA = ribonucleic acid; V = visit.

[a] Every effort should be made for visits to occur on the designated study days. The overall treatment period in the protocol should be maintained (that is, visits should be scheduled based on the baseline visit rather than the previous visit). Study procedures designated for a specific visit should be performed within 1 day whenever possible. If the time spent at the site needs to be minimized, the assessments can be completed over a longer period.

[b] Visit 1 takes place over more than 1 day. Clinical scales should be administered before imaging procedures are conducted.

[c] Only capture imaging measures (MRI, florbetapir F 18 PET, and ^{18}F-AV-1451 PET) at the ED visit if at least 24 weeks have passed since the baseline measurement was obtained. Note: Patients should be encouraged to remain in the study after their ED Visit until Week 52 (Visit 18), even if study treatment has been discontinued. Patients who discontinue treatment, but remain in the study should continue to participate in all scheduled visits and assessments, as appropriate, with the exception of PK measurements and PET scans. The follow-up visit (Week 56) is not required for patients who discontinue study treatment early and continue in the study, unless the study drug was discontinued within that last 4 weeks of the study.

[d] Screening period exceeding 60 days will not be considered a protocol deviation. If the screening period exceeds 120 days, sites should contact the Lilly-designated medical monitor for guidance.

[e] If clinical scales are administered on the same day as medical procedures that could be stressful for the patient (for example, blood draws and imaging), the clinical scales should be administered first.

[f] The MoCA and the MMSE should not be administered in succession (that is, at least one other scale should be administered between them) and should be done by different raters.

[g] The baseline ^{18}F-AV-1451 scan should not be performed until a positive florbetapir F 18 PET result has been confirmed by central read and all other screening criteria have been confirmed. Florbetapir F 18 and ^{18}F-AV-1451 scans must be at least 16 hours apart.

[h] Before the Week 52 or ED ^{18}F-AV-1451 scan, 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 ^{18}F-AV-1451 scan should be considered by the investigator in consultation with the Lilly-designated medical monitor. Patients permanently discontinued from study treatment due to initiation of a prohibited medication known to prolong the QT-interval should not have an ED ^{18}F-AV-1451 scan unless the scan can be performed prior to initiation of the prohibited medication.

[i] Collect blood sample for RNA using PAXgene tube.

[j] Pharmacokinetic samples do not need to be collected for patients who discontinue study drug, but remain in the study for follow-up.

[k] At Visits 5, 6, and 8, patients are to hold their morning dose prior to the visit. After arriving at the site, a blood sample will be collected for LY3202626, and patients will receive their assigned dose of study drug. Prior to departing the site, a second blood sample will be collected for PK.

[l] At Visit 7 and 9, patients will take their morning dose at their usual time. After arriving at the site, a blood sample will be collected for PK. Prior to the patient departing the site, a second blood sample will be collected for PK.

[m] At Visit 11, patients will take their morning dose at their usual time. A single blood sample will be collected for PK after all cognitive testing has been completed.

[n] One blood sample for PD is to be taken at the same times as samples for PK. If multiple PK samples are taken at a visit, the PD sample is to be taken with the first PK sample. At Visit 18 the PD sample will be taken at the same time as the other clinical laboratory samples.

[o] See Appendix 2 for analytes to be collected by Visit.

[p] Eye examinations should be conducted under the supervision of an optometrist or ophthalmologist. Additional details are provided in Section 9.4.5.2.

[q] Skin examinations should be conducted by a dermatologist. Additional details are provided in Section 9.4.5.3.

[r] Vital signs to be collected are blood pressure, heart rate, and temperature.

[s] All ECGs are to be conducted in triplicate.

[t] The Baseline/Screen form of the C-SSRS will be administered at Visit 1. All subsequent measures will use the Since Last Visit form. 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 the Self-Harm Follow-Up (SHFU) form will be used to collect additional information to allow for a more complete assessment of these behaviors.

[u] Patients should be instructed to take the first dose of study drug in the morning on the day after dispensing of drug at Visit 3. For patients participating in the lumbar puncture addendum, Visit 3 LP must be performed before the first dose of study drug is administered and no later than the day after randomization.

[v] If the study partner changes at any time during the study, the new study partner must sign the study partner informed consent.

3. Introduction

3.1. Study Rationale

Lilly is developing LY3202626, a synthetic small molecule which is an inhibitor of β-site amyloid precursor protein (APP)-cleaving enzyme [BACE]1, for the treatment of mild Alzheimer's disease (AD) dementia. This small molecule, at the 12 mg dose, has a high level of BACE1 inhibition (resulting in 90% reduction in Aβ), which may be a differentiating characteristic for efficacy if the effects at an enzymatic level translate clinically. It is hypothesized that inhibition of BACE1 may slow the progression of AD.

Study I7X-MC-LLCF (LLCF), a Phase 2 study, will assess if inhibiting the production of Aβ in the brain through BACE1 inhibition with LY3202626 can slow the progression of disease as assessed by biomarkers of neurodegeneration over 52 weeks of treatment. The ^{18}F-AV-1451 positron emission tomography (PET) scan will be the primary outcome measure as a marker of disease progression for this study, to assess cerebral tau neurofibrillary tangle load and whether there are any changes with Aβ targeted BACE inhibitor treatment. The study will assess LY3202626 pharmacokinetics (PK) and pharmacodynamics (PD; plasma Aβ), biomarkers of amyloid pathology (florbetapir F 18 PET) and neurodegeneration (volumetric magnetic resonance imaging [vMRI] and cerebral perfusion). In addition, LY3202626, Aβ, and tau in cerebrospinal fluid (CSF) will be collected in a substudy to assess the PKs of LY3202626, PD (CSF Aβ), and neurodegeneration (CSF tau) within the central nervous system (CNS). Clinical outcomes including cognition, functional consequences of cognition, and safety will also be evaluated.

3.2. Background

Alzheimer's disease is a gradually progressive degenerative disease affecting older people that results in the slow decline of cognitive and behavioral functions with a characteristic early symptom of memory loss in patients (Takizawa et al. 2015). Currently available therapies for treatment of AD are able to variably reduce the symptoms without affecting the underlying pathology of the disease, so patients continue to decline clinically. Recent Phase 3 study failures in moderate AD (EPOCH study (press release [WWW]); Doody et al, 2014) suggest that treatment options may be limited once the disease has advanced. Thus, there is a significant need to develop a disease-modifying treatment that will slow the progression of this debilitating brain disorder, and a growing emphasis to move therapeutic trials for disease-modifying agents earlier in the disease.

After autopsy, patients with AD routinely display severe brain atrophy with neurofibrillary tangles and amyloid plaques (Cummings 2004). Although the definitive cause of the disease is not yet clearly understood, much evidence supports the hypothesis that amyloid β (Aβ) peptide aggregates to form amyloid plaques and acts as an initial trigger of the disease (Shankar et al. 2008). These plaques may be toxic to neurons and are believed to lead to synapse loss, neurofibrillary tangle formation, and neuronal cell death. Hence, inhibition of Aβ formation is a logical strategy towards developing a therapy for AD.

Amyloid β is part of the amyloid precursor protein (APP), which is a transmembrane protein widely expressed on the cell surface, particularly in neurons. The APP has been found to be cleaved through 2 cleavage pathways involving 3 secretase enzymes: α-secretase, γ-secretase, and β-secretase (now called β-site APP-cleaving enzyme [BACE]1). Cleavage of APP by α-secretase precludes the formation of Aβ as the site is located within the Aβ sequence. In the second pathway, β-secretase cleaves the APP molecule, generating membrane-associated C99 and releasing a larger secreted fragment called secreted APP (sAPP)β. γ-Secretase then cleaves C99 in a heterogeneous fashion within the membrane releasing a variety of Aβ species that aggregate in protofibrils, then fibrils, which seem to comprise the mass of Aβ plaques in AD brain tissue (Turner et al. 2003). While both γ- and β-secretase inhibition represent effective means of precluding the formation of Aβ, β-secretase inhibition may provide improved safety and tolerability (Doody et al. 2013).

LY3202626, a synthetic small molecule, potent BACE1 inhibitor is being developed for the treatment of AD dementia. LY3202626 has been shown to reduce plasma and CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ in mice, dogs, and humans. The Phase 1 clinical Study I7X-EW-LLCA (LLCA) investigated the safety, tolerability, PK, and PD of single- and multiple-ascending doses of LY3202626 given orally, in healthy subjects and patients with AD. In this study, single doses of LY3202626 from 0.1 mg to 45 mg were well tolerated, and demonstrated a robust, prolonged reduction in plasma Aβ concentrations. LY3202626 was also administered as single daily doses of 1 mg to 26 mg for 14 days. In this multiple dose portion of the trial, LY3202626 was well tolerated, and a dose-dependent reduction in both plasma and CSF Aβ concentrations was observed. At steady-state, 1 mg LY3202626 was associated with an approximate 50% reduction in CSF $A\beta_{1-40}$, while at 6 mg, reductions of approximately 75% were observed. At 26 mg, CSF $A\beta_{1-40}$ reductions exceeded 90%. These projected CSF $A\beta_{1-40}$ reductions will be verified in a mild AD dementia population in the lumbar puncture (LP) addendum to this study.

This Phase 2 study will assess if inhibiting the production of Aβ in the brain at doses projected to reduce CSF Aβ by 70% and 90%, can slow the progression of disease as assessed by biomarkers of neurodegeneration over 52 weeks of treatment. Data from the 12 mg dose arm will be used to assess the effect of greatest BACE inhibition on tau PET changes, other biomarkers of disease progression, and clinical outcomes. All outcomes will also be assessed for the 3 mg dose arm though the primary focus will be safety and tolerability of the 3 mg dose over 52 weeks of exposure in the mild AD population. Tau is a protein that accumulates in the brains of AD patients and is a defining pathology of the disease. The density and neuroanatomical localization of tau neurofibrillary tangles correlate strongly with neurologic symptoms and AD progression. Until recently, the only way to determine tau pathological changes in the brain was at autopsy. The recent development of the ^{18}F-AV-1451 PET tracer, has allowed for the first time, the ability to detect and measure tau protein in the brain of patients suspected of suffering from AD (Xia et al. 2013). Early use of this tracer shows increasing signal from healthy controls to mild cognitive impairment due to AD to mild to moderate AD. The anatomical distribution corresponds well to the pathological staging of Braak and Braak (Chien et al. 2013). The signal also increases with progression of disease, both in intensity and in spread to other cortical regions. The ^{18}F-AV-1451 PET scan will be the primary outcome measure as a marker of

neuropathological disease progression for this study, to assess for cerebral tau neurofibrillary tangle load and whether there are any changes with Aβ targeted BACE inhibitor treatment.

The biomarker florbetapir F 18 is a PET ligand that binds to fibrillar amyloid plaque. This biomarker can provide a qualitative and quantitative measurement of brain plaque load in patients with mild AD dementia. The absence of significant florbetapir F 18 signal indicates that those patients clinically manifesting dementia lack evidence of amyloid pathology. As such, implementation of florbetapir F 18 will provide a screening tool for entry into the clinical trials and provide a confirmation of amyloid pathology. Florbetapir F 18 PET also provides quantitative assessment of amyloid in the brain and can assess whether Aβ lowering by BACE inhibition can reduce amyloid deposition.

Alzheimer's disease progression is also associated with cerebral atrophy and hypoperfusion, which will be assessed by vMRI and the early post-injection data from the florbetapir F 18 PET scans, respectively.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3202626 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

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

Table LLCF.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess the change from baseline in ^{18}F-AV-1451 PET after treatment with LY3202626 3 mg or 12 mg per day compared with placebo for 52 weeks among patients with mild AD dementia and evidence of brain amyloid.	The change in SUVr of ^{18}F-AV-1451 PET from baseline to 52 weeks. The change will be compared between the LY3202626 doses (3mg and 12mg) and placebo.
Secondary • To evaluate the safety and tolerability of LY3202626 (3 mg and 12 mg per day) compared with placebo	• Standard safety assessments: o spontaneously reported AEs o clinical laboratory tests o vital sign and body weight measurements o 12-lead ECGs o physical and neurological examinations • MRI (ARIA and emergent radiological findings) • Skin examination • Eye examination • C-SSRS
• To assess peripheral PK and PD of LY3202626 (3 mg and 12 mg per day) over 52 weeks	• Plasma Pharmacokinetics of LY3202626 • Plasma Pharmacodynamics $A\beta_{1-40}$, $A\beta_{1-42}$, $A\beta_{1-x}$
• To assess change from baseline in cognition after 52 weeks of treatment among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo.	• ADAS-Cog_{13}
• To assess change from baseline in function after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo	• ADCS-iADL
• To assess change from baseline in a composite measure of cognition and function after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo	• iADRS

Objectives and Endpoints

Objectives	Endpoints
Exploratory	
• To assess change in cognition after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo	• MoCA
• To assess change in function after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo	• FAQ
• To assess change in cognition after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo	• MMSE
• To assess change in everyday functioning after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo	• ECog
• To assess change in neuropsychiatric symptoms after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo	• NPI
• To assess change in subjective quality of life after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo	• BASQID
• To assess change from baseline in rCBF after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo.	• SUVr cerebral perfusion from early post-injection florbetapir PET scan
• To assess change from baseline in brain amyloid after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo	• Florbetapir F 18 PET SUVr
• To assess change from baseline in brain and brain regional volumes after 52 weeks among patients treated with LY3202626 (3 mg and 12 mg per day) compared with placebo.	• Volumetric MRI

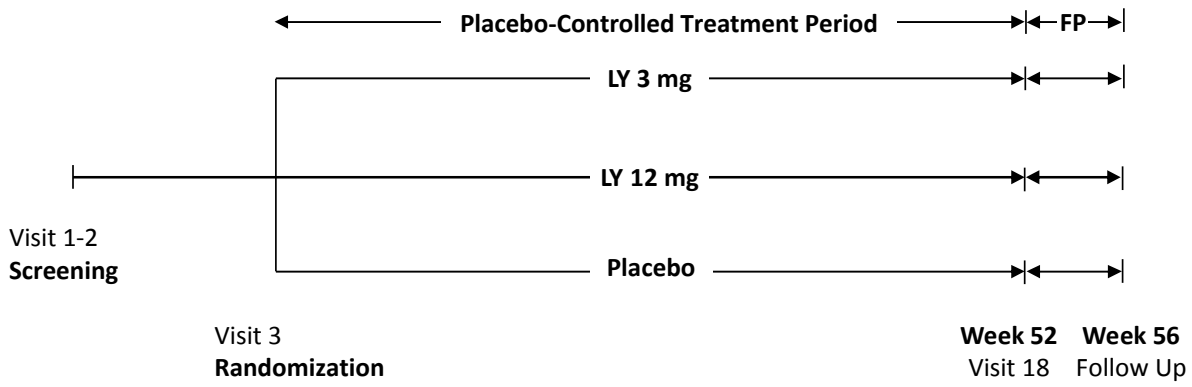
Abbreviations: AD = Alzheimer's disease; ADAS-Cog_{13} = Alzheimer's Disease Assessment Scale - Cognitive subscale, 13-item version; ADCS-iADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory, instrumental items; AE = adverse event; ARIA = amyloid-related imaging abnormality; BASQID = Bath Assessment of Subjective Quality of Life in Dementia; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ECog = Everyday Cognition; FAQ = Functional Activities Questionnaire; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini-Mental Status Examination; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic; rCBF = regional cerebral blood flow; SUVr= summary uptake value ratio.

5. Study Design

5.1. Overall Design

Study LLCF is a multicenter, randomized, double-blind, placebo-controlled study in patients with mild AD dementia. This study (Study LLCF) will enroll patients with mild AD dementia using National Institute on Aging-Alzheimer's Association (NIA-AA) work group consensus guidelines (McKhann et al. 2011) with amyloid deposition confirmed by florbetapir F 18 PET imaging. The treatment phase will be 52 weeks.

Figure LLCF.1 illustrates the study design.



Abbreviations: AD = Alzheimer's disease; FP = follow-up period; LY = LY3202626.
Note: This is a multicenter, randomized, parallel-group, 52-week-long double-blind, placebo-controlled, study of 2 fixed dose levels of LY3202626 (3 mg and 12 mg) in patients with mild AD dementia and evidence of amyloid pathology. Approximately 380 mild AD dementia patients will be enrolled (approximately 167 in the placebo and 12 mg groups, and approximately 45 in the 3 mg group).

Figure LLCF.1. Illustration of study design for Clinical Protocol I7X-MC-LLCF.

5.2. Number of Participants

Approximately 1000 participants will be screened to achieve approximately 380 randomized and approximately 320 completed evaluable participants, assuming approximately 15% drop out.

5.3. End of Study Definition

End of the trial 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

Please refer to Section 3.1.

5.5. Justification for Dose

The extent of Aβ reduction necessary to influence the spread of tau in the CNS is unknown. Thus, to maximize the likelihood of this study demonstrating an effect on tau, it was deemed reasonable to reduce CSF Aβ concentrations to near-minimal levels. Accordingly, doses of LY3202626 chosen for this study were based on a desire to reduce concentrations of CSF Aβ isoforms by 70-90% from baseline. Central and peripheral PK/PD data from healthy subjects collected in a previous single- and multiple-dose study were used to estimate the exposures necessary to achieve the desired levels of CSF Aβ reduction. These exposure targets were then used to select daily doses of 3 mg and 12 mg LY3202626 for this study. These doses are less than the highest doses previously evaluated in healthy subjects (45 mg as a single dose, or 26 mg once a day for 14 days), which were found to be well tolerated. LY3202626 was also found to be well tolerated in 2 patients with AD, when administered at a dose of 6 mg once a day, for 14 days (the only dose level tested to date in AD patients). Together, these data suggest that doses of 3 mg and 12 mg LY3202626 will be well tolerated in an AD population. To ensure patient wellbeing throughout the course of the trial, safety assessments and a safety interim are incorporated into the study design.

Protocol amendment (b) regarding stopping enrollment after 45 subjects have randomized into the lower 3 mg dose (70% lowering of Aβ by BACE1 inhibition) is based on the following: (1) We are prioritizing the opportunity, allowed by the molecular characteristics of LY3202626, to evaluate near maximal inhibition of Aβ production (90% reduction with the 12 mg dose); (2) The study will conclude approximately 6 months earlier to address the study objectives of safety, tolerability, clinical, and biomarker outcomes of 90% inhibition of the production of Aβ over 52 weeks in patients with mild AD; (3) Assessment of LY3202626 safety and tolerability remains a central objective; therefore, monitoring 45 subjects on 3 mg in parallel with approximately 150 subjects on 12 mg over 52 weeks exposure provides data to assess safety for further clinical development.

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 to be included in the study only if they meet all of the following criteria at screening:

Patient Characteristics and Diagnostic Criteria

[1] Present with mild AD dementia based on the NIA-AA disease diagnostic criteria as determined by a qualified clinician approved by the Sponsor or designee (McKhann et al. 2011).

[2] MMSE score of 20 to 26 inclusive at screening visit.

[3] Is ≥55 years of age and ≤85 years of age at the time of signing the informed consent

[4] Has a florbetapir F 18 PET scan, evaluated by central PET reader, with the presence of amyloid pathology at screening consistent with florbetapir eligibility criteria.

Patient Demographics

[5] 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 55 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.

[6] Patient must have a reliable study partner with whom he/she cohabits or has regular contact (combination of face-to-face visits and telephone contact is acceptable). If at all possible, the same study partner should be willing to participate in all study visits that require them to provide meaningful input into the rating scales administered in this study, for which study partner input is required, or be available by telephone and must have sufficient patient interaction. As guidance, the ability for a study partner to meet his/her expected responsibilities for this study would normally be possible when the study partner spends no less than 10 hours per week with the patient, divided over multiple days. The patient's study partner(s) must be willing to comply with protocol requirements, and in the investigator's opinion must have adequate literacy, vision, and hearing to complete the protocol-specified questionnaires.

Informed Consent

[7] Is able and willing to give signed informed consent

6.2. Exclusion Criteria

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

Medical Conditions

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

[9] 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)

[10] Current serious or unstable illnesses including retinal, cardiovascular (including unstable ischemic cardiovascular disease), hepatic, renal, gastroenterologic, respiratory, endocrinologic, 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 <12 months.

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

[12] 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 history of schizophrenia or other chronic psychosis are excluded.

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

[14] Ocular pathology that significantly limits ability to reliably evaluate vision or the retina.

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

[16] Congenital QT prolongation.

[17] Intermittent second- or third-degree atrioventricular (AV) heart block or AV dissociation or history of ventricular tachycardia.

[18] Has a cardiac pacemaker.

[19] History of vitiligo and/or current evidence of post-inflammatory hypopigmentation

[20] Severe drug allergy to 2 or more drugs classes

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

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

[22] Screening MRI which 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.

[23] A corrected QT (QTcF) interval measurement >450 msec (men) or >470 msec (women) at screening (as determined at the investigational site). The site may request a central read prior to making determination of this criterion.

[24] Patients with a past history (suspected or confirmed) of Hepatitis B should have HBsAg testing at screening and are excluded if HBsAg is positive.

Patients with a past history (suspected or confirmed) of Hepatitis C (resolved >6 months prior to enrollment) should have HCV RNA PCR testing at screening and are excluded if the HCV RNA PCR test is positive.

[25] Any clinically important abnormality at screening, as determined by 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.

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

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

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

1. Bilirubin is predominantly indirect (unconjugated) at screening (direct bilirubin within normal limits).
2. Absence of liver disease
3. ALT, AST, and ALP ≤1X ULN at screening
4. Hemoglobin is not significantly decreased at screening.

Prior/Concomitant Therapy

[28] Changes in concomitant medications that could potentially affect cognition and their dosing should be stable for at least 30 days 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).

[29] Current use of strong inducers of CYP3A. (See the Manual of Operations for a list of excluded drugs.)

[30] Prior treatment with an AD vaccine. Prior treatment with a passive anti-amyloid immunotherapy is allowed if completed at least 5 half-lives prior to randomization.

[31] Current use of drugs known to significantly prolong the QT interval. (See the Manual of Operations for a list of excluded drugs).

Procedural

[32] Sensitivity to florbetapir or ^{18}F-AV-1451.

[33] Contraindication to MRI or PET or poor venous access for blood draws.

[34] 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.

Prior/Concurrent Clinical Trial Experience

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

[36] Have participated, within the last 30 days (for Japan, 4 months) 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.

[37] Have previously completed or withdrawn from this study or any other study investigating LY3202626.

Other Exclusions

[38] 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.

[39] 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 which require exclusion of their employees.

6.3. Lifestyle Restrictions

1. Patients should refrain from donating blood or blood products from the time of their screening visit until 4 weeks following the last dose of study drug.
2. Patients should avoid use of tanning beds and self-tanning products.
3. Patients should wear a hat and appropriate clothing when exposed to sunlight; use a sunscreen with a skin protection factor (SPF) of at least 15; and protect their lips with a lip balm containing sunblock.
4. Patients should avoid excessive use of alcohol from the screening visit until the study ends. Excessive alcohol consumption is defined for men as consuming an average of more than 3 drinks per day, or more than 21 drinks per week. For women, excessive use of alcohol is defined as consuming an average of more than 2 drinks per day, or more than 14 drinks per week.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) for reasons deemed by the site investigator to be medically treatable (such as a serious UTI); and/or have issues that are correctable or reversible (for example, study partner status); or if the initial MMSE score is >26, but the investigator feels there has been further cognitive decline, may be rescreened. Patients may be rescreened up to 2 times. Each time rescreening is performed the patient must sign a new informed consent form (ICF) and will be assigned a new identification number.

6.5. Study Partners

Every patient in the study must have a study partner. An identification code will be assigned to each study partner and recorded for each efficacy measure for which the study partner provides input. Demographic data, including relationship to the patient, will be collected for every study

partner. Several of the efficacy measures require input from the study partner. The study partner should be willing to participate in every study visit that requires their input. The study partner is not required to attend all study procedures, including but not limited to MRI, PET, or lumbar procedures, skin or eye examinations. While every effort should be made to maintain the same study partner for a given patient throughout the study, in the event of an unavoidable change in study partner, the new study partner should be thoroughly oriented to the purpose and requirements of the study, sign consent, and be assigned a new identification code.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of 3 mg and 12 mg oral doses of LY3202626 administered daily against placebo. Study LLCF treatment regimens are:

- 3 mg LY3202626 orally once per day
- 12 mg LY3202626 orally once per day
- Placebo orally once per day.

Both LY3202626 strengths and placebo will be identical capsules.

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

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

7.1.1. Packaging and Labelling

Study drug will be supplied as 3-mg and 12-mg capsules. The study drug and placebo will be identical in appearance and will be packaged in bottles. Clinical trial materials will be labeled according to the country's regulatory requirements.

7.1.2. ^{18}F-AV-1451 Dosage and Administration

A total of 2 ^{18}F-AV-1451 PET scans will be performed, approximately 52 weeks apart. The baseline ^{18}F-AV-1451 scan should not be performed until a positive florbetapir F 18 PET result has been confirmed by central read and all other screening criteria have been confirmed. The Visit 18 or early discontinuation florbetapir F 18 and ^{18}F-AV-1451 scans must be at least 16 hours apart. At each ^{18}F-AV-1451 PET scanning visit, patients will receive a single intravenous (IV) administration of approximately 370 MBq (10 mCi) of ^{18}F-AV-1451. A 30-minute scan, starting approximately 75 minutes following injection, will be acquired according to the procedure described in the technical operations manual provided by the designated imaging core laboratory.

Patients with a history of risk factors for Torsades de Pointes or taking prohibited medications known to prolong the QT interval should not have a ^{18}F-AV-1451 scan. Patients permanently discontinued from study treatment due to initiation of a prohibited medication known to prolong the QT-interval should not have an early discontinuation (ED) ^{18}F-AV-1451 scan unless the scan can be performed prior to initiation of the prohibited medication.

The following assessments will be performed for ^{18}F-AV-1451 imaging sessions:

- A physician or a licensed/credentialed medical professional (for example, a PET Technologist or an imaging center nurse) designated by the site Principal Investigator (PI), must assess or evaluate the patient to determine if the patient can safely undergo a ^{18}F-AV-1451 injection. If a designee performs this activity, a physician must be available to provide medical consultation or supervision.
- The patient will be requested to void after completion of the PET scan.
- A physician or a licensed/credentialed medical professional designated by the site PI must assess or evaluate the patient prior to discharge from the imaging center to evaluate the patient's readiness for discharge. If a designee performs the discharge evaluation, a physician must be available to provide medical consultation.
- Patients will be observed for signs of adverse events (AEs) or serious adverse events (SAEs) while at the imaging center. The injection site will be observed for evidence of inflammation or allergic reaction to the surrounding tissue where the dose was injected. All AEs and SAEs will be followed until resolution or stabilization and should be reported to Lilly or its designee via electronic case report form (eCRF) per Section 9.2. See Section 9.2.1 for details regarding SAE reporting requirements.

Information about the known and expected benefits, risks, and reasonably anticipated AEs of ^{18}F-AV-1451 may be found in the ^{18}F-AV-1451 IB.

7.1.3. Florbetapir F 18 Dosage and Administration

A total of 2 florbetapir F 18 scan visits will occur, approximately 52 weeks apart. The Visit 18 or early discontinuation florbetapir and ^{18}F-AV-1451 scans must be at least 16 hours apart. At each florbetapir F 18 PET scanning visit, the patient will receive a single IV administration of approximately 370 MBq (10 mCi) of florbetapir F 18, and will be scanned twice. First, a scan of approximately 6 minutes duration will be obtained immediately following injection of the tracer, which will be administered while the patient is in the scanner. This scan will capture the blood flow to the brain (perfusion PET, see Section 9.1.4 for more details). Second, starting approximately 50 minutes after the tracer injection, a scan lasting approximately 20 minutes will be acquired. The patient need not stay in the scanner between these 2 scans. The injection of the imaging agent will be followed by a saline flush according to the injection procedure described in the technical operations manual provided by the designated imaging core laboratory.

7.1.4. Radiation Doses Associated with PET Imaging

The estimated exposure to ionizing radiation per patient enrolled in this study (effective dose) is summarized in Table LLCF.2. This includes contributions from florbetapir F 18 and ^{18}F-AV-1451 scans, along with low-dose computed tomography (CT) scans required for attenuation correction.

For either florbetapir or ^{18}F-AV-1451 scans, if the image is not interpretable based on predetermined criteria outlined at the central PET core lab (for example, scanner failure, patient

motion, etc.), the patient may be asked to schedule an additional scan visit, requiring an additional injection of the radiotracer. Each patient will potentially only undergo up to 1 additional PET scan beyond those scheduled in this protocol. In this case, the patient would be exposed to up to an additional 9.1 mSv of ionizing radiation.

Table LLCF.2. Radiation Doses Associated with PET Imaging

	Injected Radioactive Dose per Scan, mCi*	Injected Radioactive Dose per Scan, MBq	Effective Dose (mSv) per Scan	Number of Scans in One Year (52 wks)	Total Effective dose (mSv)
^{18}F-AV-1451 scan	10	370	9.10	2	18.20
florbetapir F 18 scan	10	370	7.83[§]	2	15.66
Totals				4	33.86

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

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

[§] Dose includes an additional *non-clinical* CT scan (estimated at 0.4 mSv) for the patients undergoing the florbetapir perfusion scan.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). Randomization will be stratified by the following two factors: 1) patient participation of LP addendum (Y/N) and 2) type of perfusion (dynamic /static) of PET imaging center. The IWRS will be used to assign bottles containing double-blind investigational product to each patient. Sufficient study drug will be dispensed to supply the patient until the next visit. Site personnel will confirm that they have located the correct drug by entering a confirmation number found on the container into the IWRS.

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same time on each day, preferably in the morning. For patients who desire to regularly dose at another time of day, exceptions can be made in consultation with the Lilly medical monitor. The first dose should be taken the morning after the first dispensing of drug at Visit 3. Patients will be requested to record the actual date and time of the 2 dose administrations prior to each visit at which PK will be collected (for example, the date and time of the previous day's dose, as well as the date and time of the dose prior to that). If a dose is administered at the clinic, that date and time should also be recorded. The date and time of these dose administrations will be recorded in the patient's eCRF. If the patient fails to follow the dosing instructions for those visits where a dose is to be administered at the site, blood samples are still to be collected according to the Schedule of Activities (Section 2) and as described above. On those visits where the dose is to be administered at the site, if the patient fails to follow this instruction and is dosed prior to sample collection, an additional dose will not be administered at the visit.

7.3. Blinding

This is a double-blind study.

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

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event will be recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, patient, or study partner is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly-designated medical monitor for the patient 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. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly-designated medical monitor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

7.4. Dosage Modification

Dose adjustments are not allowed in this study.

7.5. Preparation/Handling/Storage/Accountability

Clinical trial material will be stored in a secure, locked location maintained at the conditions specified on the label. A record of inventory transactions will be maintained that will allow accountability of all study drug. Handling and storage instructions for patients will be included on labeling of clinical trial materials.

7.6. Treatment Compliance

The administration of all study medication should be recorded in the appropriate sections of the eCRF.

Compliance will be assessed at in-clinic visits via capsule counts when the study medication packaging and any unused study medication are returned at study visits. The patient should be instructed to bring all unused medication to the clinic at each visit so that the clinic staff can record the amount of medication used since the last visit.

Only patients who consume at least 80% of the prescribed daily dose (based on capsule count) during this study will be considered compliant. Similarly, patients will be considered significantly noncompliant if they are judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. Patients regarded as noncompliant may be discontinued at the investigator's discretion, in consultation with the Lilly-designated medical monitor.

Drug accountability will be emphasized at the start-up meeting, and drug accountability will be monitored throughout the study.

7.7. Concomitant Therapy

Concomitant medications with the potential to affect cognition will be permitted, provided the patient has been maintained on a stable dose regimen for at least 30 days before screening, and between screening and randomization. After randomization, attempts should be made to maintain stable doses of symptomatic AD medication, however, changes or additions will be permitted when clinically indicated and must be documented in eCRF.

The following concomitant therapies are prohibited:

- Use of any investigational drug or device not specified in this study judged to be scientifically or medically incompatible with this study
- Use of any drug of abuse, including but not limited to cannabis, illicit amphetamine, cocaine, illicit opiates, propoxyphene, methadone, methaqualone, phencyclidine, or illicit barbiturate
- Use of depigmenting agents, such as, hydroquinone
- Current use of strong inducers of CYP3A (See the Manual of Operations for a list of excluded drugs)
- Current use of drugs known to significantly prolong the QT interval (See the Manual of Operations for a list of excluded drugs)

The list of other excluded medications and procedures is provided in the Manual of Operations.

7.8. Treatment after the End of the Study

7.8.1. Continued Access

Investigational Product will not be made available to patients after conclusion of the study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a patient 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)
- alanine aminotransferase or AST >5X ULN for more than 2 weeks
- alanine aminotransferase or AST >3X ULN and total bilirubin level (TBL) >2X ULN or prothrombin time >1.5X ULN
- alanine aminotransferase 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
- alkaline phosphatase >2.5X ULN and TBL >2X ULN
- alkaline phosphatase >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

- Patient decision. The patient may discontinue treatment, without prejudice to further treatment, at any time.
- Adverse event or clinically significant laboratory value, ECG result, physical examination finding (including eye or skin examination), MRI finding (such as symptomatic vasogenic edema), C-SRSS 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 non-compliance 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 8.1.2).
- The patient develops a significant uncontrolled medical condition that meets one of the exclusion criteria that in the opinion of the investigator after appropriate medical assessment, would pose an unacceptable risk to the patient if they were to continue receiving study drug.

Patients who discontinue study treatment early should receive all early discontinuation procedures as described in Section 2. Patients should be encouraged to remain in the study until Week 52 (Visit 18), even if study treatment has been discontinued, and they should continue to participate in scheduled visits as described in Section 2. Patients who agree to remain in the study after discontinuing study treatment should continue to participate in scheduled visits and assessments, as appropriate, with the exception of PK measurements and PET scans, after completing the early discontinuation assessments described in Section 2, as appropriate. The follow-up visit (Week 56) is not required for patients who discontinue study treatment early and continue in the study, unless the study drug was discontinued within that last 4 weeks of the study. The Lilly-designated medical monitor may be consulted regarding the details of managing a specific patient who discontinues treatment but remains in the study.

8.1.2. Temporary Discontinuation from Study Treatment

Treatment can be temporarily discontinued (examples include short-term treatment using a prohibited drug, uncertain AE, and/or hospitalization). Re-starting investigational product is based on the PI's judgment. If temporary discontinuation is due to an AE, it should be reported to the Lilly-designated medical monitor. Temporary treatment discontinuation and re-starting should be documented. The maximum permissible treatment suspension is 4 weeks over the duration of the study. Exceptions may be considered to allow a subject to resume treatment when the temporary suspension period exceeds 4 weeks, after consultation with the Lilly medical monitor.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly-designated medical monitor and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly-designated medical monitor to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

8.2. Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include:

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

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

- patient or study partner decision: requests their withdrawal from the study
- an individual patient enrolled in the study may be discontinued based on a specific AE profile, as recommended by the Lilly-designated medical monitor or the Assessment Committee, in discussion with the PI

Patients who discontinue the study early will have end-of-study procedures performed at the early discontinuation visit as shown in the Schedule of Activities (Section 2) and should participate in the follow-up visit, 4 to 6 weeks after the last dose of study treatment.

8.3. Lost to Follow-Up

Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients 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 patient 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.

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the 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

9.1.1. Primary Outcome Assessments

^{18}F-AV-1451 PET. ^{18}F-AV-1451 PET scans provide an in vivo measurement of the anatomical distribution and load of paired-helical filament (PHF)-tau pathology in the brain (Xia et al. 2013). Along with amyloid plaques, tau PHF tangles are one of the defining pathological signatures of neuropathologically confirmed AD. Elevated ^{18}F-AV-1451 binding is increased in AD relative to control subjects and presents in an anatomical distribution consistent with neuropathological Braak staging (Chien et al. 2013). In contrast to amyloid, which becomes elevated many years before the onset of clinical symptoms, tau pathology is more closely associated in time with cognitive and functional decline. The ^{18}F-AV-1451 assessment involves 2 PET scans, one at baseline and another after 52 weeks of treatment (or upon early discontinuation). The change in ^{18}F-AV-1451 SUVr between the two PET scans will be the primary outcome measure. The change in ^{18}F-AV-1451 SUVr will be compared across the treatment groups and to total exposure to LY3202626.

9.1.2. Secondary Efficacy Assessments

Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog; Rosen et al. 1984). The ADAS 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. The cognitive subscale of the ADAS, the ADAS-Cog$_{13}$, consists of 13 items assessing areas of cognitive function most typically impaired in AD, for example, orientation, verbal memory, language, praxis, delayed free recall, and digit cancellation measures (Mohs et al. 1997). The ADAS-Cog$_{13}$ scale ranges from 0 to 85, with higher scores indicating greater disease severity.

Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory (ADCS-ADL; Galasko et al. 1997, 2004). 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. The ADCS-ADL subset of items (items 7 to 23) for instrumental activities of daily living (ADCS-iADL) will be used as a secondary efficacy measure. The focus in the mild AD dementia population is on

the instrumental activities of daily living (iADL) rather than the basic activities of daily living (bADL), which are thought to be affected in more severe stages of the disease. The range for the iADL score is 0 to 56, 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.

Integrated Alzheimer's Disease Rating Scale (iADRS). The iADRS comprises scores from the ADAS-Cog and the ADCS-iADL, 2 well-accepted measures in AD research. The iADRS is calculated as a linear combination of the total scores of the ADAS-Cog_{13} (score range 0 to 85 with higher scores reflecting worse performance) and the ADCS-iADL (score range 0 to 56 with higher scores reflecting better performance). To account for the opposite directionality of the scores, the ADAS-Cog score is multiplied by (-1) in the calculation of the integrated scale. Then a constant (85) is added to anchor the ADAS-Cog at 0. The iADRS score is then calculated by summing the transformed ADAS-Cog_{13} and the ADCS-iADL, as shown below:

$$\text{iADRS score} = [-1(\text{ADAS-Cog}_{13})+85]+\text{iADL}$$

The iADRS score ranges from 0 to 141 with lower scores indicating worse performance (Wessels et al. 2015).

9.1.3. Screening and Exploratory Efficacy Assessments

Montreal Cognitive Assessment (MoCA). The MoCA is a brief 30-point cognitive screening test developed with high sensitivity and specificity for detecting mild cognitive impairment (MCI) in patients who perform in the normal range on the MMSE. Compared to the MMSE, the MoCA uses more numerous and demanding tasks to assess executive function, higher level language abilities, memory, and complex visuospatial processing (Nasreddine et al. 2005). The MoCA has also demonstrated utility in diagnosis and classification of AD dementia (Roalf et al. 2013).

Functional Activities Questionnaire (FAQ). A growing literature supports the FAQ as a measure sensitive to changes in milder AD populations (Teng et al. 2010; Tabert et al. 2002). The FAQ (Pfeffer et al. 1982) is a rater-administered instrument directed at the study partner that is aimed to assess perceived ability in performing instrumental everyday activities thought to be especially cognitively complex (for example, financial management, shopping, playing games, food preparation, traveling, keeping appointments, keeping track of current events, and understanding media). Each of the 10 items offers 6 response alternatives, varying in level of dependence and familiarity of the task, which are recorded so that each item receives a score ranging from 1 (*complete independence*) to 4 (*complete dependence*). The sum of 10 items provides an overall assessment of perceived functional ability.

Mini-Mental State Examination (MMSE; Folstein et al. 1975). The MMSE is a brief instrument used to assess cognitive function in elderly patients. 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.

Everyday Cognition (ECog). The ECog measures functional abilities that are mediated by cognition in older adults through an informant-rated questionnaire. Study partners are asked to compare the patient's current level of functioning with the level of functioning 10 years earlier (or for as long as the study partner has known the patient) with 4 response options from 1 (better or no change compared with 10 years earlier) to 4 (consistently much worse) on each of 7 factors. The ECog comprises 1 global factor and 6 domain-specific factors, including everyday memory, language, semantic knowledge, visuospatial abilities, planning, organization, and divided attention (Farias et al. 2008).

Neuropsychiatric Inventory (NPI). The NPI is a tool for assessing psychopathology in patients with dementia and other neurologic disorders. Information is obtained from a study partner familiar with the patient's behavior. A screening question assays each subarea of the NPI—delusions, hallucinations, agitation, apathy, anxiety, depression, euphoria, irritability, disinhibition, and aberrant motor behavior. Two questions inquire about neurovegetative changes, including alterations in appetite and nighttime behavior disturbances. If the answer to the screening question is no, no further questions are pursued. If the answer is yes, subquestions are asked and ratings of the frequency and severity of the behavior are made by the study partner through the use of scales with anchor points. The distress induced in the study partner by each behavior is also rated by the study partner. Scores for each subscale, the total tool, study partner distress associated with each behavior, and total study partner distress are computed. The NPI standard version consists of 10 items with study partner distress scale and 2 neurovegetative questions. Validity and reliability of the instrument have been demonstrated (Cummings et al. 1994). Four subscales can be defined based on a previously reported factor analysis: Mood (depression, anxiety, nighttime behavior, appetite, irritability); Psychosis (delusions, hallucinations, agitation); Frontal (euphoria, disinhibition); and Other (apathy, aberrant motor behavior) (Frisoni et al. 1999).

Bath Assessment of Subjective Quality of Life in Dementia (BASQID). The BASQID is a 14-item, patient-reported outcome assessing a range of quality of life issues, including satisfaction with physical, psychological, social, and environmental aspects of living, as well as abilities to perform activities and feelings of autonomy, usefulness, and happiness. Each item is scored from 0 to 4, with low scores indicating poor quality of life. The BASQID is intended to complement objective measures to provide a more complete assessment of dementia patients, including quality of life from their own perspectives (Trigg et al. 2007).

9.1.4. Exploratory Biomarker Assessments

Florbetapir F 18 (amyloid) PET. Florbetapir F 18 amyloid PET scans provide an in vivo measurement of deposited amyloid plaques in the brain. Florbetapir F 18 cortical composite SUVr correlates with post-mortem assessments of amyloid plaque load (Clark et al. 2012). Scans will be performed twice, once at screening and again after 52 weeks of treatment (or upon

early discontinuation). The change in whole grey matter standardized uptake value ratio (SUVr) between baseline and follow-up scans will be compared across treatment groups and to total exposure to LY3202626.

Perfusion PET. An additional perfusion-weighted image will be acquired at each florbetapir F 18 PET scanning visit, with no additional tracer injection, by utilizing the initial wash-in of florbetapir to the brain (Section 7.1.3). These images will provide a perfusion (or blood flow) map of the brain at each florbetapir F 18 PET time point. In AD, cerebral perfusion is reduced, especially in temporal and parietal areas, and this pattern of hypoperfusion closely mirrors the hypometabolism pattern observed using 18F-fluorodeoxyglucose (FDG)-PET. As such, the florbetapir F 18 perfusion PET images provide a biomarker of resting brain function. Changes in florbetapir F 18 perfusion PET between the baseline and follow-up scans will be compared across treatment groups and to total exposure to LY3202626.

Volumetric MRI. Brain atrophy is one of the signature biological changes associated with AD, with shrinkage of the medial temporal lobe (including the hippocampus) and ventricular enlargement particularly prominent. The volume of different brain structures and measures of atrophy can be accurately quantified from vMRI scans. Magnetic Resonance Imaging changes in brain volume from baseline to after 52 weeks of treatment (or early discontinuation) will be quantified. Measurements of brain structural changes, including, but not limited to, whole brain, ventricles and hippocampus will be evaluated. Brain structural changes will be compared across treatment groups and to total exposure to LY3202626.

9.1.5. Appropriateness of Assessments

As described above, this Phase 2 study will assess whether inhibition of production of Aβ in the brain can slow the progression of disease as assessed by biomarkers of neurodegeneration over 52 weeks of treatment. The ^{18}F-AV-1451 PET scan will be the primary outcome measure as a marker of disease progression for this study, to assess for cerebral tau neurofibrillary tangle load and whether there are any changes with Aβ targeted BACE inhibitor treatment. More details on the appropriateness of ^{18}F-AV-1451 PET as primary outcome are provided in Section 3.2.

The ADAS-Cog and the ADCS-iADL are well recognized as measures of cognitive and functional abilities, respectively, in this patient population. The iADRS is a newly developed measure combining scores from the ADAS-Cog and ADCS-iADL.

Additional clinical and biomarker endpoints are included as exploratory measures.

9.1.6. Scheduling of Cognitive and Functional Assessments

Assessments should be scheduled to allow the cognitive testing to be performed at approximately the same time of the day (±4 hours) at all the visits to avoid the known circadian variation of cognitive performance (Higuchi et al. 2000). Patients and study partners should be assessed separately, because the presence of the other person may potentially contaminate the results of an assessment. When necessary, patients should be allowed a rest break between cognitive tests. Based on rater judgment, other nonstressful study procedures may be conducted during these breaks.

9.1.7. Rater Qualifications

There should be at least two independent, trained, qualified raters at each site. The raters that perform screening/baseline should also be the same as those who perform the longitudinal post-screening assessments for each patient. The ADAS-Cog_{13} must have a different rater than the rater who performs the ADCS-ADL for each patient. For all outcome measures, every effort should be made to have the raters remain consistent throughout the duration of the trial.

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, 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 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 eCRF 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 and investigational product via eCRF.

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

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, PET tracers, 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 eCRF clarifying if possible, the circumstances leading to 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
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

Although all AEs occurring after signing the ICF are recorded in the eCRF, SAE reporting begins after the patient has signed the ICF and has received investigational product or PET imaging. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product or PET imaging, it needs to be reported ONLY 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 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.

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 summary eCRF 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 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

Refer to the IB for LY3202626.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, triplicate ECGs should be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study specific recommendations included in the Manual of Operations for the study.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment or PET tracers should be reported to Lilly or its designee as an AE via eCRF per Section 9.2.

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. Patients must meet eligibility criteria with respect to cardiac inclusion/exclusion criteria at the time of the screening. The triplicate ECGs then must be transmitted for central reading.

Note that new findings on ECG after enrollment that do not meet entry criteria do not automatically indicate that subject should be discontinued. In some cases, discontinuation may not be necessary and will depend on clinical significance and implications. The investigator should refer to the Manual of Operations for guidance should a patient's QTcF interval exceed 450 msec (male) or 470 msec (female) or if >30 msec change from baseline while receiving study drug. Unscheduled ECGs may be obtained at the discretion of the investigator.

9.4.2. Vital Signs

For each patient, vital sign measurements (blood pressure, heart rate, and temperature) must be conducted according to the Schedule of Activities (Section 2) and following the study specific recommendations included in the Manual of Operations for the study. Blood pressure and heart rate will be measured supine and standing.

Any clinically significant findings from vital signs measurements that result in a diagnosis and that occur after the patient receives the first dose of investigational treatment or PET tracers should be reported to Lilly or its designee as an AE via eCRF per Section 9.2.

9.4.3. Laboratory Tests

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

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational treatment or PET tracers should be reported to Lilly or its designee as an AE via eCRF per Section 9.2.

9.4.4. Physical Examinations and Neurologic Examination

Physical and neurological examinations will be conducted as specified in the Schedule of Activities (Section 2) and as clinically indicated.

Physical examinations will include assessment of general appearance, skin, head and neck, lymph nodes, thyroid, abdomen (bowel sounds and liver and spleen palpation), back (costovertebral angle tenderness), and musculoskeletal, cardiovascular, and respiratory systems. Neurological examinations will include assessment of cranial nerves, motor and sensory systems, muscle stretch reflexes, balance and coordination, and gait. The physical and neurological examination will be performed by a physician, nurse practitioner, or physician's assistant (for Japan, physician only).

Body weight and height will be recorded according to the Schedule of Activities (Section 2).

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

Any clinically significant change from baseline on follow-up physical and neurological examinations should be reported to Lilly or its designee as an AE via eCRF per Section 9.2.

9.4.5. Other Tests

9.4.5.1. C-SSRS

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 Columbia Suicide Severity Rating Scale (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 C-SSRS is available in an adult's and a children's version. There is no version of the C-SSRS designed for use in a cognitively impaired population such as patients with AD; therefore,

the children's version will be used. Terms captured by the use of the C-SSRS children's version can be mapped to Columbia Classification Algorithm for Suicide Assessment (Posner et al. 2007), to facilitate future pooling of data.

The first time the scale is administered in this study (at Visit 1), the C-SSRS "Baseline/Screening" version will be used. The C-SSRS "Since Last Visit" scale will be used for all subsequent assessments. If, in the opinion of the investigator or C-SSRS administrator, the patient's responses to the C-SSRS may not be reliable, the C-SSRS may be administered to the patient with the study partner present in person or by phone. In this instance, responses from both the study partner and the 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.

Any clinically significant findings from the C-SSRS should be reported to Lilly or its designee as an AE via eCRF per Section 9.2.

9.4.5.2. Eye Examination

All patients will undergo comprehensive eye examinations performed under the supervision of an optometrist or ophthalmologist to assess visual function and morphology. Scheduled examinations will include the following: visual acuity, intraocular pressure, dilated funduscopic exam (dilation only performed in patients without contraindication to mydriatics), slit lamp exam, color photography of the retina, and optical coherence tomography (OCT) or equivalent; examinations may also include color vision assessment where feasible. Assessments will be performed at times shown in the Schedule of Activities (Section 2), preferably supervised by the same optometrist or ophthalmologist for each patient's visit. Patients who complain of vision disturbance, such as change in field of vision, color, acuity or anything potentially localizable to the retina, during the clinical trial should be referred to the optometrist or ophthalmologist for unscheduled evaluation.

Data from the eye examination visits will be provided from the local optometrist or ophthalmologist to the Investigator. Based on the morphological and functional results, the investigator will include or exclude the patient in consultation with the performing eye examiner, if applicable.

The local optometrist or ophthalmologist will review the color photography and OCT to aid in the investigator's assessment of study eligibility and for immediate patient management. Additionally, the color photography of retina and OCT will be analyzed by a central reader.

Unblinded results of the eye safety data will be reviewed by the Assessment Committee (AC) with the participation of an ophthalmologist, as specified in Section 10.3.7.

Any clinically significant findings that result in a diagnosis should be reported to Lilly or its designee as a pre-existing condition or AE via eCRF per Section 9.2. The PI will make all final determinations of AEs in consultation with performing eye examiner, if applicable.

9.4.5.3. Skin Examination

A complete skin examination will be performed at the times shown in the Schedule of Activities (Section 2), preferably by the same dermatologist for each patient's visit. All skin examinations must be performed by a dermatologist who will inspect the patient's unclothed full body using a ultraviolet (UV) light. The initial examination will include Fitzpatrick skin-type classification scale.

At each examination, abnormal hypopigmentation will be assessed by location, percentage of body surface area involvement, degree (partial/decreased pigmentation to complete depigmentation), and other findings in or around the hypopigmented area (such as redness or induration). A static physician's global assessment (sPGA) will be used to determine the patient's overall hypopigmentation severity at a given time point using a visual analog scale (VAS) ranging from 0 to 100. In addition, patients noted to have evidence of hypopigmentation will be asked to record how bothersome they find the hypopigmentation on a VAS ranging from 0 to 100. Skin photographs may be taken as appropriate for generating supporting documentation, but not for the purpose of primary clinical dermatologic evaluation or for data generation or analysis. A punch biopsy may be obtained at the discretion of the dermatologist.

Any clinically significant findings that result in a diagnosis should be reported to Lilly or its designee as a pre-existing condition or AE via eCRF per Section 9.2. The principal investigator will make all final determinations of AEs in consultation with the dermatologist.

9.4.5.4. Magnetic Resonance Imaging

Magnetic resonance imaging of the brain will be performed according to the Schedule of Activities (Section 2) to screen patients for eligibility to participate in the study and for secondary efficacy assessment. Magnetic resonance imaging screening scans should be performed during the screening period, after the patient has met most other screening criteria, as outlined in the Schedule of Activities (Section 2). The central radiologist review of the screening MRI scan must be available before randomization to evaluate the inclusion/exclusion criteria. Any clinically significant findings that result in a diagnosis should be recorded as a pre-existing condition or AE per Section 9.2.

Magnetic resonance imaging scanning will be conducted under the management of a central vendor. The scans will be reviewed by the investigator or qualified designee for immediate patient management. The MRI scans will be acquired at the imaging sites using a standardized protocol. The MRI scans will be transmitted to the imaging vendor for evaluation.

If a patient develops an acute neurological change such as symptoms suggestive of vasogenic edema during the study, an unscheduled MRI should be obtained. Potential symptoms of ARIA-E could include headache, gait instability, dizziness, tremor, worsening cognitive function, alteration of consciousness, seizures, unsteadiness, and vomiting (Ostrowitzki et al. 2012; Sperling et al. 2012). The abnormality is best detected by fluid attenuation inversion recovery

(FLAIR) sequences on the MRI and ARIA-H is detected with the T2* gradient-recalled echo on the MRI. It is recommended to repeat the MRIs with these sequences every 2 to 4 weeks until resolution of ARIA-E is documented. For asymptomatic or mild symptoms, the patient can be observed; for moderate symptoms, the use of oral or IV steroids can be considered. In the case of severe symptoms, it is recommended to hospitalize the patient for close observation and consider the use of IV steroids such as high-dose dexamethasone or a similar agent. Study treatment should be discontinued if clinically symptomatic vasogenic edema, clinical symptomatic superficial siderosis, or clinically symptomatic incident microhemorrhage is seen.

Magnetic resonance imaging findings believed to have potential clinical significance will be reported to the investigator and sponsor. Any new or aggravated clinically relevant abnormal MRI finding as compared with the baseline MRI should be reported to Lilly or its designee as an AE via an eCRF per Section 9.2. If a clinically meaningful change in MRI is noted during the study, an additional, full neurological exam will be performed as soon as possible, along with any other medical follow-up deemed necessary by the investigator (Section 9.4.4).

9.4.6. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. An AC will be designated for at least one interim evaluation of unblinded safety data from Study LLCF (Section 10.3.7).

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, hepatic laboratory tests (Appendix 4) must 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 improving or worsening. If the abnormality persists or worsens, clinical and laboratory monitoring must be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP must continue until levels normalize or return to approximate baseline levels.

Additional safety data must be collected via the case report form (CRF) 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 a SAE

See Appendix 4, for hepatic eCRFs that must be completed for these patients.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of LY3202626.

A maximum of 2 samples 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. The actual date and time (24-hour clock time) of each sampling will be recorded.

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

Bioanalytical samples collected to measure LY3202626 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 analyses such as metabolism and/or protein binding work.

9.6. Pharmacodynamics

The peripheral dose-dependent PD activity of LY3202626 and placebo administration will be evaluated by analysis of plasma $A\beta_{1-40}$, $A\beta_{1-42}$, $A\beta_{1-x}$ as measured using validated immunoassays. These plasma based biomarkers will provide an assessment of target engagement and the data will inform dose optimization. Central PD will be assessed in a substudy in which CSF is collected from participating patients.

Biological samples collected to measure PD parameters will be identified by the patient number (coded) and retained for a maximum of 15 years following last patient visit for the study at a facility selected by Lilly or its designee.

9.7. 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 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 Sample 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 LY3202626 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 for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/investigational review boards (IRBs) impose shorter time limits, at a facility selected by Lilly. 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 LY3202626 or after LY3202626 become(s) 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, exome or directed next-generation 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 Research & Development

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 (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Plasma and whole blood samples for RNA and epigenetic analyses will be collected for non-pharmacogenetic biomarker research 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 LY3202626, pathways associated with AD, mechanism of action of LY3202626, and/or research methods 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 for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3202626 or after LY3202626 becomes commercially available.

9.9. Medical Resource Utilization and Health Economics

Health Economics and Medical Resource Utilization parameters were not evaluated in this study.

10. Statistical Considerations

10.1. Sample Size

Approximately 380 patients will be enrolled so that approximately 320 patients will complete the study.

Patients who are randomized but not administered treatment may be replaced to ensure that enough subjects complete the study.

10.1.1. Sample size calculation

The sample size was determined based on internal, 9-month, longitudinal ^{18}F-AV-1451 data. ^{18}F-AV-1451 SUVr values were calculated from these images using the CCI as the reference region (CCI), and the CCI. The map providing the CCI s (MUBADA) (Abdi 2012) and corresponds to an intensity map that reflects the cross-sectional difference in ^{18}F-AV-1451 signal between AD subjects and healthy controls. This map is most CCI CCI ; CCI .

Approximately 380 patients will be randomized into the trial according to a treatment ratio 1:1:1 for LY3202626 3 mg, LY3202626 12 mg, and placebo, until approximately 45 participants are enrolled into each arm, then 1:1 in the LY3202626 12 mg and placebo arms until 380 total have been randomized. CCI

A sensitivity analysis was performed on drop-out rates as high as 30%, and the power for the primary outcome was no worse than 79%.

CCI .

With respect to CCI . Based on research by Schott and colleagues (2010), CCI CCI

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

10.2. Populations for Analyses

Analysis populations for Study LLCF are defined below (Table LLCF.3).

Table LLCF.3. Analysis Populations

Population	Description
Enrolled	All participants who have been assigned to treatment (randomized).
Efficacy	All randomized participants who take at least 1 dose of double-blind study treatment and have at least 1 postdose efficacy measurement.
Safety	All randomized participants who take at least 1 dose of double-blind study treatment.

Note: Participants will be included in the treatment group to which they were randomized.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Unless otherwise specified, all safety analyses will be conducted on the safety population and all efficacy and PD analyses will be conducted on the efficacy population as defined above (Table LLCF.3).

No adjustments will be made for multiple comparisons.

All total and subscale scores will be derived from individual items. If any individual item is missing, the corresponding total and subscale scores will be considered missing, except for the ADAS-Cog_{13}, which will be imputed. The imputation algorithm will be specified in the statistical analysis plan (SAP).

All tests of treatment effects of biological efficacy or clinical efficacy will be conducted at a 1-sided α=.10, unless otherwise stated. Safety assessments will be conducted at a 2-sided α=.05.

A repeated measures analysis refers to a restricted maximum likelihood (REML)-based, mixed effects repeated measures analysis using all the longitudinal observations at each post-baseline

visit. A repeated measures analysis model will include the fixed, categorical effects of treatment group, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and the baseline-by-visit interaction, unless otherwise noted. Unless otherwise specified, when an ANOVA model is used to analyze a continuous efficacy variable, the model will contain the main effects of treatment. Similar logic is applied to an ANCOVA model, which in general, refers to the ANOVA model with baseline value added as a covariate. Type III sum-of-squares for the least squares (LS) LS Means will be used for statistical comparisons using an ANOVA or ANCOVA. Categorical comparisons between treatment groups will be performed using Fisher's exact tests, where appropriate.

Any change to the data analysis methods described in the protocol will require an amendment to the protocol 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 clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

SAS® software will be used to perform most or all statistical analyses.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

Reasons for discontinuation for all patients will be tabulated for treatment groups, and comparisons between treatment groups will be assessed by Fisher's exact test. Additionally, the median time to all-cause discontinuation will be compared between the treatment groups. The null hypothesis is that the median time to discontinuation estimated using the Kaplan-Meier product limit method will be identical for the LY3202626 dose groups and placebo. The log-rank test will be used to test the null hypothesis against the alternate hypothesis that the median time to discontinuation is not the same between the groups. A detailed description of patient disposition will be provided at the end of the study.

10.3.2.2. Patient Characteristics

Standard baseline characteristics of gender, age, and race will be summarized for all patients. Treatment group comparisons will be made using Fisher's exact test for categorical data and an ANOVA, with an independent factor for treatment for continuous data. Diagnosis, illness characteristics, and baseline efficacy and safety measures will be analyzed in a similar manner.

10.3.2.3. Concomitant Therapy

Stable doses of standard-of-care (SOC) AD medications will be permitted in this study as described in Section 6.2. Exploratory analyses stratified by use of SOC medications at baseline will be conducted.

10.3.2.4. Treatment Compliance

The proportion of patients who are significantly noncompliant as noted in Section 7.6 of this protocol will be summarized and compared among all treatment groups using Fisher's exact test.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective of this study is to assess the PD effect of 2 different LY3202626 doses (3 mg and 12 mg) in patients with mild AD dementia compared with placebo, measured by change in ^{18}F-AV-1451 PET SUVr at baseline and Week 52. The primary measurement is change from baseline ^{18}F-AV-1451 SUVr. The method for calculating the SUVr will be provided in the SAP. ANCOVA will be used to statistically evaluate change in SUVr from baseline at 52 weeks post-dose. The ANCOVA will include the fixed, categorical effects of treatment dose, and the continuous, fixed covariate of baseline ^{18}F-AV-1451 SUVr.

10.3.3.2. Secondary Analyses

Statistical analyses of mean change in the ADAS-Cog$_{13}$, ADCS-iADL, and iADRS will be conducted. Generally, statistical assessment of the efficacy and health outcome measures will be an MMRM or an ANCOVA. The primary comparison will be between LY3202626 12 mg versus placebo at endpoint.

10.3.3.3. Exploratory Analyses

Statistical analyses of mean change in the exploratory endpoints will be conducted. Generally, statistical assessment of the efficacy and health outcome measures will be an MMRM or an ANCOVA. The primary comparison will be between LY3202626 12 mg versus placebo at endpoint.

In addition, changes from baseline in the vMRI and the florbetapir F 18 PET will be assessed.

10.3.4. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, ECGs, skin examinations, and eye examinations during the treatment period. For continuous safety measurements, a change from baseline will be analyzed using an MMRM or an ANCOVA model.

Safety analyses for the treatment period will include comparisons between LY3202626 dose groups and placebo. All hypotheses will be tested at a 2-sided α=.05 significance level. No adjustments for multiple comparisons will be made.

For analysis comparing proportion of treatment-emergent abnormalities between treatment groups for laboratory analytes, vital signs, weight, ECGs, skin examinations, and eye examinations, only patients who have both a baseline observation and a postbaseline observation will be included in the analysis for each analyte or parameter, respectively. The proportion of patients with abnormalities will be summarized and compared between treatment groups using Fisher's exact test.

Suicide-related thoughts and behaviors, based on the C-SSRS, will be listed by patient and visit. Only patients that show suicidal ideation/behavior will be displayed (that is, if a patient's answers are all "no" for the C-SSRS, then that patient will not be displayed). However, if a

patient reported any ideation or behavior at any time point, then all their ideation and behavior will be displayed, even if not positive.

Additional safety analyses may be performed if warranted.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Plasma LY3202626 concentration data will be analyzed using a population approach implemented with the program nonlinear mixed-effect modeling (NONMEM) on a computer that meets or exceeds the minimum system requirements. The version of any software used for the analysis will be documented, and the program will meet or exceed the Lilly requirements of software validation. It is possible that other validated software programs may be utilized if appropriate, warranted, and approved by Global PK/PD management. Basic PK parameters, including clearance and distribution volume, will be characterized, and covariate relationships will be explored as appropriate.

For each dose level and visit, plasma $A\beta_{1-40}$, $A\beta_{1-42}$ and $A\beta_{1-x}$ concentrations will be summarized and mean change from baseline will be calculated. If appropriate, a modeling approach may be used to describe the change in plasma Aβ. Additional exploratory analyses of the data will be conducted as suggested by the data. If appropriate, the data from this study may be combined with that from other studies in a meta-analysis.

It is planned that two interim locks of the PK dataset will be conducted during the course of this study. The first lock will occur after 75 patients complete 24 weeks of treatment (Study Visit 11) and will be used to support initial PK model development and will be conducted by the AC. The second lock will be conducted after all patients complete 24 weeks of treatment, and will be used by pre-specified individuals from Lilly to prepare for final model development.

10.3.6. Other Analyses

10.3.6.1. Subgroup Analyses

All subgroup analyses will be exploratory (post hoc) in nature. The details of these analyses will be described in the SAP.

10.3.7. Interim Analyses

Only the AC and Internal Review Committee (IRC) are authorized to evaluate unblinded interim safety and efficacy analyses, respectively. Study sites will receive information about interim results ONLY if results are clinically relevant for the safety of their patients. Membership of the AC and IRC will be documented in the AC charter and IRC plan. Unblinding details are specified in the unblinding plan section of the SAP or a separate document.

Details of the timing and decision criteria of the interim analyses by the AC and IRC are documented in a separate interim analysis plan and/or AC charter in order to maintain study blind, for the primary study team. If an LY3202626 dose is recommended to be dropped at the interim analysis because of safety, then randomization will be modified accordingly; in this instance, the percentage of patients receiving placebo will not be reduced.

An initial safety interim analysis will be conducted by the AC when data from approximately 130 qualified patients at 12 weeks and 40 patients through 24 weeks have been obtained. The AC may be asked to conduct additional safety interim analyses if safety concerns are observed during blinded safety monitoring. In the event that blinded safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the AC can conduct additional analyses of the safety data.

Efficacy reviews of data by an IRC may occur during the course of the study and will be documented in the IRC plan. At the times specified in Section 10.3.5, a limited number of pre-identified individuals may gain access to the unblinded PK/PD data, as specified in the unblinding plan, prior to the interim or final database lock. 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.

11. References

Abdi H, Williams LJ, Beaton D, Posamentier MT, Harris TS, Krishnan A, Devous MD Sr. Analysis of regional cerebral blood flow data to discriminate among Alzheimer's disease, frontotemporal dementia, and elderly controls: a multi-block barycentric discriminant analysis (MUBADA) methodology. *J Alzheimer Dis.* 2012;31(suppl 3):S189-201.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.

Chien DT, Bahri S, Szardenings AK; Walsh JC, Mu F, Su MY, Shankle WR, Elizarov A, Kolb HC. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. *J Alzheimer Dis.* 2013;34(2):457-468.

Clark CM, Pontecorvo MJ, Beach TG, Bedell BJ, Coleman RE, Doraiswamy PM, Fleisher AS, Reiman EM, Sabbagh MN, Sadowsky CH, Schneider JA, Arora A, Carpenter AP, Flitter ML, Joshi AD, Krautkramer MJ, Lu M, Mintun MA, Skovronsky DM, for the AV-45-A16 Study Group. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: a prospective cohort study. *Lancet Neurol.* 2012;11:669–678.

Cockcroft DW, Gault MH. Prediction if creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-2314.

Cummings JL. Alzheimer's disease. *N Engl J Med*. 2004;351(1):56-67.

Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, He F, Sun X, Thomas RG, Aisen PS; Alzheimer's Disease Cooperative Study Steering Committee, Siemers E, Sethuraman G, Mohs R; Semagacestat Study Group. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*. 2013;369(4):341-350.

Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E, Liu-Seifert H, Mohs R; Alzheimer's Disease Cooperative Study Steering Committee; Solanezumab Study Group. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. 2014 Jan 23;370(4):311-21.

Farias ST, Mungas D, Reed BR, Cahn-Weiner D, Jagust W, Baynes K, Decarli C. The measurement of everyday cognition (ECog): Scale development and psychometric properties. *Neuropsychology.* 2008;22:531–544.

[FDA] United States Food and Drug Administration. Guidance for Industry. Suicide ideation and behavior: prospective assessment of occurrence in clinical trials [draft guidance] 2012. Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM225130.pdf. Accessed 8 February 2016.

Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(13):189-198.

Frisoni GB, Rozzini L, Gozzetti A, Binetti G, Zanetti O, Bianchetti A, Trabucchi M, Cummings JL. Behavioral syndromes in Alzheimer's disease: description and correlates. *Dement Geriatr Cogn Disord*. 1999;10(2):130-138.

Galasko D*,* Bennett D*,* Sano M, Ernesto C, Thomas R, Grundman M, Ferris S. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Diasese Cooperative Study. *Alzheimer Dis Assoc Disord.* 1997*;***11**(Suppl 2)*:*S33-S39*.*

Galasko D, Kershaw PR, Schneider L, Zhu Y, Tariot PN. Galantamine maintains ability to perform activities of daily living in patients with Alzheimer's disease. *J Am Geriat Soc*. 2004;52(7):1070-1076.

Higuchi S, Liu Y, Yuasa T, Maeda A, Motohashi Y. Diurnal variation in the P300 component of human cognitive event-related potential. *Chronobiology international.* 2000;17(5):669-678.

Landau SM, Harvey D, Madison CM, Koeppe RA, Reiman EM, Foster NL,Weiner MW, Jagust WJ, the Alzheimer's Disease Neuroimaging Initiative. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging*. 2011;32:1207–18.

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

Merck Announces EPOCH Study of Verubecestat for the Treatment of People with Mild to Moderate Alzheimer's Disease to Stop for Lack of Efficacy. Merck.com. http://investors.merck.com/news/press-release-details/2017/Merck-Announces-EPOCH-Study-of-Verubecestat-for-the-Treatment-of-People-with-Mild-to-Moderate-Alzheimers-Disease-to-Stop-for-Lack-of-Efficacy/default.aspx. Published [February 14, 2017]. Accessed [June 28, 2017].

Mohs RC, Knopmann D, Petersen RC, Ferris SH, Ernesto C, Grundman M, Sano M, Bieliauskas L, Geldmacher D, Clark C, Thal LJ. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11(Suppl 2):S13-S21.

Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Amer Geratr Soc.* 2005;53(4):695-699.

Ostrowitzki S, Deptula D, Thurfjell L, Barkof F, Bohrmann B, Brooks, DJ, Klunk WE, Ashford E, Yoo K, Xu ZX, Loetscher H, Santarelli, L. Mechanism of amyloid removal in patients with Alzheimer's disease treated with Gantenerumab. *Arch Neurol*. 2012;69(2):198-207.

Pfeffer RI, Kurosaki TT, Harrach CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol*. 1982;37(3):323-329.

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

Roalf DR, Moberg PJ, Xie SX, Wolk DA, Moelter ST, Arnold SE. Comparative accuracies of two common screeninginstruments for classification of Alzheimer's disease, mild cognitive impairment, and healthy aging. *Alzheimer Dementia*. 2013;9(5):529–537.

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356-1364.

Schott JM, Bartlett JW, Barnes J, Leung KK, Ourselin S, Fox NC, Alzheimer's Disease Neuroimaging Initiative investigators. Reduced sample sizes for atrophy outcomes in Alzheimer's disease trials: baseline adjustment. *Neurobiology Aging*. 2010;31(8):1452–1462.

Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, Regan CM, Walsh DM, Sabatini BL, Selkoe DJ. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat Med.* 2008;14(8):837-842.

Sperling R, Salloway S, Brooks DJ, Tampieri D, Barakos J, Fox NC, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Lieberburg I, Arrighi HM, Morris KA, Lu Y, Liu E, Gregg KM, Brashear HR, Kinney GG, Black R, Grundman M. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. *Lancet Neurol*. 2012;11(3):241-249.

Tabert MH, Albert SM, Borukhova-Milov L, Camacho Y, Pelton G, Liu X, Stern Y, Devanand DP. Functional deficits in patients with mild cognitive impairment: prediction of AD. *Neurology*. 2002;58(5):758-764.

Takizawa C, Thompson PL, van Walsem A, Faure C, Maier WC. Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America. *J Alzheimers Dis*. 2015;43(4):1271-1284.

Teng E, Becker BW, Woo E, Knopman DS, Cummings JL, Lu PH. Utility of the functional activities questionnaire for distinguishing mild cognitive impairment from very mild Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2010;24(4):348-353.

Trigg R, Skevington SM, Jones RW. How can we best assess the quality of life of people with Dementia? The Bath Assessment of Subjective Quality of Life in Dementia (BASQID). *Gerontologist.* 2007;47(6):789-797.

Turner PR, O'Connor K, Tate WP, Abraham WC. Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. *Prog Neurobiol.* 2003;70(1):1-32.

Wessels AM, Siemers ER, Yu P, Andersen SW, Holdridge KC, Sims JR, Sundell K, Stern Y, Rentz DM, Dubois B, Jones RW, Cummings J, Aisen PS. A Combined Measure of Cognition and Function for Clinical Trials: The Integrated Alzheimer's Disease Rating Scale (iADRS). *J Prev Alz Dis.* 2015;2(4):227-241.

Xia C-F, Arteaga J, Chen G, Gangadharmath U, Gomez LF, Kasi D, Lam C, Liang Q, Liu C, Mocharla VP, Mu F, Sinha A, Su H, Szardenings K, Walsh JC, Wang E, Yu C, Zhang W,

Zhao T, Kolb HC. [18F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease. *Alzheimer Dementia.* 2013;9(6):666-676.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
Aβ	amyloid beta peptide
AC	Assessment Committee
AD	Alzheimer's disease
ADAS-Cog$_{13}$	13-item Alzheimer's Disease Assessment Scale-Cognition
ADCS-ADL **ADCS-iADL**	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living Inventory (instrumental ADL items sub-score)
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.
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APOE	apolipoprotein E
APP	amyloid precursor protein
ARIA-E	amyloid-related imaging abnormality–edema/effusions (also known as vasogenic edema)
ARIA-H	amyloid-related imaging abnormality–hemosiderin deposition (also known as microhemorrhage)
AST	aspartate aminotransferase
BACE	Beta-site amyloid precursor protein cleaving enzyme
BASQID	Bath Assessment of Subjective Quality of Life in Dementia
blinding	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.

CIOMS	Council for International Organizations of Medical Sciences
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CRF	Case report form (sometimes referred to as clinical report form). A printed or electronic form for recording study patients' data during a clinical study, as required by the protocol.
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP3A	cytochrome P450 3A
ECG	electrocardiogram
ECog	Everyday Cognition
eCRF	electronic case report form (see CRF)
ED	Early discontinuation
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result under controlled conditions.
Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
Enter	patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
FAQ	Functional Activities Questionnaire
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
florbetapir	[18F]-AV-45 (chemical name (E)-4-(2-(6-(2-(2-(2-[18F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-Nmethylbenzenamine)
GCP	good clinical practice
HCV	Hepatitis C virus
HDL	High-density lipoproteins
iADRS	integrated Alzheimer's Disease Rating Scale

IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference for Harmonisation
IgG/IgM	immunoglobulin G/immunoglobulin M
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.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB/ERB	Institutional Review Board/Ethical Review Board: a board or committee (institutional, regional, or national) composed of medical professional and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
IRC	Internal Review Committee
IWRS	interactive web-response system
LDL	Low-density lipoproteins
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
Lilly	Eli Lilly and Company
LP	lumbar puncture
MCI	Mild cognitive impairment
MMRM	mixed-model repeated-measures
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NIA-AA	National Institute on Aging (NIA) and the Alzheimer's Association (AA)
NPI	Neuropsychiatric Inventory

PCR	polymerase chain reaction
PET	positron emission tomography
PK/PD	pharmacokinetics/pharmacodynamics
QTcF	Fridericia's corrected QT interval
RBC	Red blood cells
rCBF	regional cerebral blood flow
RNA	ribonucleic acid
ULN	Upper limit of normal
SAE	serious adverse event
SAP	statistical analysis plan
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.
SHFU	Self-Harm Follow Up Forms
SUSARs	suspected unexpected serious adverse reactions
SUVr	standard uptake value ratio
TBL	total bilirubin level
TPO	third-party organizations
VAS	visual analog scale
vMRI	volumetric magnetic resonance imaging
WBC	White blood cells

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology	**Clinical Chemistry**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Chloride
Mean cell volume	Phosphate
Mean cell hemoglobin concentration	Potassium
Leukocytes (WBC)	Total bilirubin
Neutrophils, segmented	Direct bilirubin
Lymphocytes	Alkaline phosphatase (ALP)
Monocytes	Alanine aminotransferase (ALT)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine
	Uric acid
Urinalysis	Calcium
Specific gravity	Glucose, nonfasting
pH	Albumin
Protein	
Glucose	Creatine kinase (CK)
Ketones	Screening Visit 1 only
Blood	Folic acid
Urine leukocyte esterase	Vitamin B12
	Hepatitis B surface antigen (HBsAg)[a]
	Hepatitis C virus (HCV) PCR[b]
	Screening Visit 1 and Visit 18 or ED only
	Hemoglobin A1c
	Creatinine clearance
	Thyroid stimulating hormone
	Total T3
	Free T4
	Cholesterol (total, HDL, LDL) and triglycerides
	Other Tests
	HIV (optional, at screening only[c])

Abbreviations: ED = early discontinuation; HIV = human immunodeficiency virus; HDL = High-density lipoproteins; LDL = Low-density lipoproteins; PCR = polymerase chain reaction; RBC = red blood cells; WBC = white blood cells.

[a] Hepatitis B surface antigen (HBsAg) should be collected at screening Visit 1 only in patients with a suspected or past history of hepatitis B.

[b] Hepatitis C virus (HCV) PCR should be collected at screening Visit 1 only in patients with a suspected or past history of hepatitis C.

[c] Tested at the discretion of the investigator or if mandated by local regulatory authorities.

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

Appendix 3.1.2. 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 International Conference on 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 current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- relevant curricula vitae

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- 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 3.1.4. Investigator Information

Investigators in this clinical trial will include neurologists, geriatricians, psychiatrists, or other clinicians approved by the Sponsor or designee.

Appendix 3.1.5. Protocol Signatures

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

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

Appendix 3.1.6. Final Report Signature

The 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.

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

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

Case report form data collected by a third-party will be encoded by the third-party and stored electronically in the third-party's database system. Validated data will subsequently be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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 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
PK for LY3202626	**antibody)[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; PK = pharmacokinetics; 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. Sampling Summary

This table summarizes the approximate number of samples (venipunctures and lumbar punctures) and volumes for all sampling (screening, standard laboratory, drug concentration, pharmacogenetic, biomarker, and exploratory) and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment. Lumbar punctures are only collected for patients participating in the optional substudy.

Protocol I7X-MC-LLCF Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Screening tests[a]	Blood	3.5 mL	5	14 mL
Standard laboratory tests[a]	Blood	2.5 mL	23	52 mL
Drug, Aβ isoforms, tau	CSF	20 mL	2	40 mL
Drug concentration	Blood	3 mL	12	36 mL
Pharmacogenetic samples	Blood	10 mL	3	27 mL
Other exploratory samples	Blood	10 mL	22	120 mL
Total Blood and CSF				289 mL
Hepatic Monitoring[b]	Blood	3 - 30 mL	-	-

Abbreviation: CSF = cerebrospinal fluid.

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

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Lilly-designated Medical Monitor.

Appendix 6. Protocol Amendment I7X-MC-LLCF(c) Summary Effect of LY3202626 on Alzheimer's Disease Progression as Measured by Cerebral ^{18}F-AV-1451 Tau-PET in Mild Alzheimer's Disease Dementia

Overview

Protocol I7X-MC-LLCF Effect of LY3202626 on Alzheimer's Disease Progression as Measured by Cerebral ^{18}F-AV-1451 Tau-PET in Mild Alzheimer's Disease Dementia has been amended. The new protocol is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The protocol has been amended to include the performance of additional interim analyses and unplanned data reviews by the AC and IRC.

The overall changes and rationale for the specific changes made to this protocol are described in the following table:

Amendment Summary for Protocol I7X-MC-LLCF Amendment (c)

Section # and Name	Description of Change	Brief Rationale
Section 10.3.7 Interim Analyses	Only the AC and Internal Review Committee (IRC) are ~~is~~ authorized to evaluate unblinded interim ~~efficacy and~~ safety and efficacy analyses, respectively. Study sites will receive information about interim results ONLY if results are clinically relevant for the safety of their patients. Membership of the AC and IRC will be documented in the AC charter and IRC plan. Unblinding details are specified in the unblinding plan section of the SAP or a separate document.	Added Interim Review Committee to permit review of efficacy data
Section 10.3.7 Interim Analyses	Details of the timing and decision criteria of the interim Details of the timing and decision criteria of the interim ~~analysis~~ analyses by the AC and IRC are documented in a separate interim analysis plan and/or AC charter in order to maintain	Added for clarification

	study blind, for the primary study team. If an LY3202626 dose ~~may~~ is recommended to be dropped at the interim analysis because of safety ~~and the~~, then randomization will be modified accordingly; in this instance, the percentage of patients receiving placebo will not be reduced.	
Section 10.3.7 Interim Analyses	An initial safety interim analysis will be conducted by the AC when data from approximately ~~105~~ 130 qualified patients at 12 weeks and ~~75~~ 40 patients through 24 weeks have been obtained.	The data from approximately 105 qualified patients at 12 weeks is the data that was intended for safety review by the AC. The data obtained for 75 patients through 24 weeks was intended to support initial pharmacokinetic (PK) model development. As the data from 75 patients with 24 weeks of treatment was not needed to perform the safety review to meet the primary objective, the decision was made to proceed with the data lock with approximately 130 patients with 12 weeks of treatment and 40 patients with 24 weeks of treatment.
Section 10.3.7 Interim Analyses	Efficacy reviews of data by an IRC may occur during the course of the study and will be documented in the IRC plan. At the times specified in Section 10.3.5, a limited number of pre-identified individuals may gain access to the unblinded PK/PD data, as specified in the unblinding plan, prior to the interim or final database lock.	Added to describe efficacy analyses by the IRC
Appendix 1 Abbreviations and Definitions	ICH - International Conference ~~on~~ for Harmonisation	Definition added to the Abbreviations and Definitions Appendix
Appendix 1 Abbreviations and Definitions	IRC – Independent Review Committee	Definition added to the Abbreviations and Definitions Appendix

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

10.3.7. Interim Analyses

Only the AC and Internal Review Committee (IRC) are ~~is~~ authorized to evaluate unblinded interim ~~efficacy and~~ safety and efficacy analyses, respectively. Study sites will receive information about interim results ONLY if results are clinically relevant for the safety of their patients. Membership of the AC and IRC will be documented in the AC charter and IRC plan. Unblinding details are specified in the unblinding plan section of the SAP or a separate document.

Details of the timing and decision criteria of the interim ~~analysis~~ analyses by the AC and IRC are documented in a separate interim analysis plan and/or AC charter in order to maintain study blind, for the primary study team. If an LY3202626 dose ~~may~~ is recommended to be dropped at the interim analysis because of safety ~~and the~~, then randomization will be modified accordingly; in this instance, the percentage of patients receiving placebo will not be reduced.

An initial safety interim analysis will be conducted by the AC when data from approximately ~~105~~ 130 qualified patients at 12 weeks and ~~75~~ 40 patients through 24 weeks have been obtained. The AC may be asked to conduct additional safety interim analyses if safety concerns are observed during blinded safety monitoring. In the event that blinded safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the AC can conduct additional analyses of the safety data.

Efficacy reviews of data by an IRC may occur during the course of the study and will be documented in the IRC plan. At the times specified in Section 10.3.5, a limited number of pre-identified individuals may gain access to the unblinded PK/PD data, as specified in the unblinding plan, prior to the interim or final database lock. 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.