

I7X-MC-LLCE

Relative Bioavailability and Food Effect Study in Healthy
Subjects Administered Two Different Formulations of
LY3202626

NCT03023826

Approval Date: 10 Sep 2016

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LY3202626

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Approval Date: 10-Sep-2016 GMT

Table of Contents

Relative Bioavailability and Food Effect Study in Healthy Subjects Administered Two Different Formulations of LY3202626

Section	Page
Protocol I7X-MC-LLCE Relative Bioavailability and Food Effect Study in Healthy Subjects Administered Two Different Formulations of LY3202626.....	1
Table of Contents.....	2
1. Protocol Synopsis.....	8
2. Schedule of Activities	10
3. Introduction	12
3.1. Study Rationale.....	12
3.2. Background.....	12
3.3. Benefit/Risk Assessment	13
4. Objectives and Endpoints.....	15
5. Study Design.....	16
5.1. Overall Design	16
5.2. Number of Participants.....	17
5.3. End of Study Definition	17
5.4. Scientific Rationale for Study Design.....	17
5.5. Justification for Dose	18
6. Study Population.....	19
6.1. Inclusion Criteria.....	19
6.2. Exclusion Criteria	20
6.3. Lifestyle and/or Dietary Requirements	21
6.3.1. Meals and Dietary Restrictions.....	21
6.3.2. Xanthine, Alcohol, and Tobacco	22
6.3.3. Activity	22
6.4. Screen Failures.....	23
7. Treatment.....	24
7.1. Treatment Administered.....	24
7.1.1. Packaging and Labeling	24
7.2. Method of Treatment Assignment	24
7.2.1. Selection and Timing of Doses.....	24
7.3. Blinding	24

7.4. Dose Modification.....	24
7.5. Preparation/Handling/Storage/Accountability.....	24
7.6. Treatment Compliance	25
7.7. Concomitant Therapy.....	25
8. Discontinuation Criteria	26
8.1. Discontinuation from Study Treatment.....	26
8.1.1. Discontinuation of Inadvertently Enrolled Subjects	26
8.2. Discontinuation from the Study	26
8.3. Subjects Lost to Follow-up.....	26
9. Study Assessments and Procedures	27
9.1. Efficacy Assessments.....	27
9.2. Adverse Events	27
9.2.1. Serious Adverse Events.....	28
9.2.1.1. Suspected Unexpected Serious Adverse Reactions.....	28
9.2.2. Complaint Handling.....	28
9.3. Treatment of Overdose.....	29
9.4. Safety.....	29
9.4.1. Laboratory Tests	29
9.4.2. Vital Signs	29
9.4.3. Body Weight.....	29
9.4.4. Electrocardiograms	29
9.4.5. Safety Monitoring	30
9.5. Pharmacokinetics	30
9.5.1. Bioanalysis.....	31
9.6. Pharmacodynamics	31
9.7. Genetics	31
9.8. Biomarkers.....	32
9.9. Health Economics	32
10. Statistical Considerations and Data Analysis	33
10.1. Sample Size Determination	33
10.2. Populations for Analyses.....	33
10.2.1. Study Participant Disposition	33
10.2.2. Study Participant Characteristics	33
10.3. Statistical Analyses	33
10.3.1. Safety Analyses.....	34
10.3.1.1. Clinical Evaluation of Safety	34
10.3.1.2. Statistical Evaluation of Safety	34
10.3.2. Pharmacokinetic Analyses.....	34

10.3.2.1. Pharmacokinetic Parameter Estimation.....	34
10.3.2.2. Pharmacokinetic Statistical Inference	34
10.3.3. Pharmacodynamic Analysis	35
10.3.3.1. Pharmacodynamic Parameter Estimation	35
10.3.3.2. Pharmacodynamic Statistical Inference.....	35
10.3.4. Interim Analyses	35
11. References	36

List of Tables

Table	List of Tables	Page
Table LLCE.1.	Objectives and Endpoints	15
Table LLCE.2.	Dose Administration Sequences.....	16
Table LLCE.3.	High-Fat Meal Composition	22

List of Figures

Figure	List of Figures	Page
Figure LLCE.1.	Illustration of Study Design for Protocol I7X-MC-LLCE.....	17

List of Appendices

Appendix		Page
Appendix 1.	Abbreviations and Definitions	37
Appendix 2.	Clinical Laboratory Tests.....	40
Appendix 3.	Study Governance, Regulatory and Ethical Considerations	41
Appendix 4.	Blood Sampling Summary	44

1. Protocol Synopsis

Title of Study:

Relative Bioavailability and Food Effect Study in Healthy Subjects Administered Two Different Formulations of LY3202626

Rationale:

This study will explore the rate and extent of LY3202626 absorption when administered using a pilot tablet formulation, as compared to the drug-in-capsule formulation of LY3202626 that was used in previous studies. The effect of a high fat meal on the rate and extent of LY3202626 absorption will also be explored. The results of this study will be used when selecting doses for future clinical evaluations using a tablet formulation of LY3202626 and to understand whether the tablet formulation may be administered without regard to food. The change from baseline of amyloid beta (A β) isoforms (A β 1-40 and A β 1-42) will be evaluated at the 12-mg LY3202626 dose level for both tablet and capsule formulations.

Objective(s)/Endpoints:

Objectives	Endpoints
<p><u>Primary</u></p> <ul style="list-style-type: none"> To evaluate the relative bioavailability of a single 12-mg dose of LY3202626 as a tablet formulation (test formulation [T1-12]) compared to the capsule formulation (reference formulation [R]) 	<p>The ratio of geometric least square means and corresponding 90% confidence interval (CI) between T1-12 and R will be calculated for: maximum observed drug concentration (C_{max}), area under the concentration versus time curve (AUC) from time zero to infinity (AUC_{0-∞}), and AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC_{0-t}last).</p>
<p><u>Secondary</u></p> <ul style="list-style-type: none"> To evaluate the effect of a high-fat meal on the bioavailability of LY3202626 when administered as a single 12-mg dose of the test tablet formulation (T1-12) To assess the tolerability of LY3202626 when administered as a single 12-mg dose to healthy subjects 	<p>The ratio of geometric least square means and CI between LY3202626 T1-12 fed versus fasted will be calculated for: C_{max}, AUC_{0-∞}, and AUC_{0-t}last.</p> <p>Incidence of treatment-emergent adverse events.</p>
<p><u>Exploratory</u></p> <ul style="list-style-type: none"> To evaluate plasma Aβ1-40 and Aβ1-42 after a single 12-mg dose of LY3202626 as a tablet formulation (test formulation [T1-12]) and capsule formulation (reference formulation [R]) 	<p>Plasma concentrations of Aβ1-40 and Aβ1-42 will be summarized for each treatment based on the nadir concentration (C_{nadir}), and the time to reach C_{nadir} (t_{nadir}). The percent change from baseline in Aβ1-40 and Aβ1-42 will be summarized for each treatment.</p>

Summary of Study Design:

Study I7X-MC-LLCE is a single-center, open-label, single-dose, randomized, 3-period, crossover study in healthy subjects.

Subjects will be admitted to the clinical research unit (CRU) on Day -1 of each period. In each period, subjects will be fasted overnight for at least 10 hours, and a single dose of 12 mg LY3202626 will be administered on the morning of Day 1. Blood sampling for assessment of LY3202626 PK and for pharmacodynamic assessments of A β 1-40 and A β 1-42 will be performed up to 168 hours postdose (Day 8). Subjects may be discharged from the CRU following completion of all 24-hour or 36-hour procedures on Day 2. Subjects will return to the CRU daily for outpatient visits for PK sample collections Days 3 through 8. The washout period between dosing in 2 consecutive periods will be at least 10 days. A follow-up telephone call will be performed approximately 5 to 8 days after Period 3, Day 8.

Study completion is defined as completing all 3 study periods. Tolerability will be explored by assessment of clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms, and recording of adverse events.

Treatment Arms and Duration:

Subjects will receive single doses of 12 mg LY3202626 on 3 separate occasions as a tablet formulation (1 administration under fed conditions and 1 administration under fasted conditions) and as a capsule formulation under fasted conditions, with sequence determined by randomization. Screening will occur up to 28 days prior to Day 1 of Period 1 and each period will last approximately 8 days. A follow-up telephone call will be performed approximately 5 to 8 days after Period 3, Day 8.

Number of Subjects:

A maximum of 30 subjects may be enrolled in order that approximately 20 subjects complete the study.

Statistical Analysis:

Pharmacokinetic parameter estimates will be evaluated to delineate effects of LY3202626 formulation and effect of food on LY3202626. Log-transformed C_{max}, AUC_{0- ∞} , and AUC_{0-t_{last}} estimates will be evaluated in a linear mixed-effects model with fixed effects for formulation or fed/fasted state, period, and a random effect for subject. The treatment differences for T1-12 compared to R formulation and for T1-12 under fed conditions versus fasted conditions will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CI.

The t_{max} will be analyzed non-parametrically. Estimates of the median difference and 90% CIs will be calculated.

The ratio of geometric least square means and CI between LY3202626 T1-12 fed versus fasted will be calculated for C_{max}, AUC_{0- ∞} , and AUC_{0-t_{last}}.

Incidence of treatment-emergent adverse events will be recorded.

2. Schedule of Activities

Study Schedule Protocol I7X-MC-LLCE

	Screening	Periods 1, 2, and 3										ET	Follow-up ^a	Comments
Procedure	≤28 days prior to Period 1, Day 1	Check-in Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8		~5 to 8 days after Period 3 Discharge	ET visit should occur as soon as possible, up to 8 days, after study discontinuation	
Informed Consent	X													
Subject Admission to CRU		X												
Subject Discharge from CRU				X										Subjects may be discharged from the CRU following completion of all 24-hour or 36-hour procedures on Day 2. If discharged after 24-hour procedures, subject will return to the CRU as an outpatient visit for the 36-hour PK sample collection.
Outpatient Visit				X	X	X	X	X	X	X				
Overnight Fast		X												Overnight fast of at least 10 h to begin in the evening prior to day of dosing in each study period.
High-fat Meal Administration			X											LY3202626 administered in a fed state (Food and Drug Administration [FDA] high-fat meal) for food effect period only
LY3202626 Administration			X											The washout period between dosing in 2 consecutive periods will be at least 10 days.
Medical History	X													
Height	X													
Weight	X													
Serology	X													
AE Assessment	X	X	X	X	X	X	X	X	X	X	X			
Vital Signs (supine and standing)	X		Predose, 3, 4, 6, 8 h	24 h	X	X		X		X	X			Additional vital signs may be measured during each study period, if warranted.

	Screening	Periods 1, 2, and 3										ET	Follow-up ^a	Comments
Procedure	≤28 days prior to Period 1, Day 1	Check-in Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8		~5 to 8 days after Period 3 Discharge	ET visit should occur as soon as possible, up to 8 days, after study discontinuation	
12-lead ECG	X		Predose, 3, 4, 6, h	24 h							X	X		TriPLICATE ECGs collected and stored. Screening ECG will be collected as single ECG and not stored.
Clinical Lab Tests	X		X	24 h							X	X		See Appendix 2 , Clinical Laboratory Tests, for details. Screening Clinical Lab Tests should be repeated and reviewed prior to dosing, if not performed within 10 days of dosing.
FSH	X													FSH will be performed on postmenopausal females only, with 6-12 months of amenorrhea.
Physical Exam/Medical Assessment	X		X								X	X		Physical exam performed at screening. After enrollment, medical assessment only performed to include medical review and targeted examination, as appropriate.
PK Sample			Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 h	24 and 36 h	48 h	72 h	96 h	120 h	144 h	168 h				Sampling times are relative to the time of study drug administration (0 h).
PD Sample			Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 h	24 and 36 h	48 h	72 h	96 h	120 h	144 h	168 h				For A _β 1-40 and A _β 1-42 assessments
Pharmacogenetic Sample			Predose											Single sample for pharmacogenetic analysis taken prior to/on Day 1 in Period 1 only.

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; h = hours; PD = pharmacodynamics; PK = pharmacokinetics.

^a Follow-up will be conducted as a telephone call and will include recording of adverse events and concomitant medication.

3. Introduction

3.1. Study Rationale

This study will explore the rate and extent of LY3202626 absorption when administered using a pilot tablet formulation using the CCI [REDACTED] as compared to the drug-in-capsule formulation using the CCI [REDACTED] that was used in previous studies. A 12-mg dose is the highest dose currently being evaluated in Phase 2 studies, and is projected to be the highest dose to be evaluated in Phase 3 studies. The effect of a high fat meal on the rate and extent of LY3202626 absorption will also be explored. The results of this study will be used when selecting doses for future clinical evaluations using a tablet formulation of LY3202626 and to understand whether the tablet formulation may be administered without regard to food. The change from baseline of amyloid beta (A β) isoforms (A β 1-40 and A β 1-42) will be evaluated at the 12-mg LY3202626 dose level for both tablet and capsule formulations.

3.2. Background

Alzheimer's disease (AD), a serious global health problem, is a neurodegenerative disease affecting older people that results in the decline of cognitive and behavioral functions. Currently, therapies for AD only reduce symptoms without affecting the underlying neurodegenerative pathology or clinical decline. Thus, there is a significant need to develop disease-modifying treatments that will slow or halt the progression of this debilitating brain disorder. Although the definitive cause of the disease is not yet clearly understood, much evidence support the hypothesis that A β peptide aggregates to form amyloid plaques and acts as an initial trigger of the disease (Shankar et al. 2008). These plaques are toxic to neurons and are believed to lead to synapse loss and eventual neuronal cell death. Hence, inhibition of A β formation is a logical strategy towards developing a therapy for AD.

Inhibition of β -secretase (now called β -site amyloid precursor protein [APP]-cleaving enzyme [BACE1]) and 2 other secretase enzymes leads to a reduction in the formation of A β isoforms. LY3202626, a synthetic small molecule, is a potent, active site BACE1 inhibitor which displays robust and persistent effects in a variety of cellular and animal models, as described in the Investigator's Brochure (IB).

LY3202626 has been demonstrated to produce robust, sustained reductions of A β isoforms in both the periphery and in cerebrospinal fluid (CSF) in clinical trials. Following doses of 1-, 6-, and 26-mg LY3202626 once daily (QD) for 14 days, concentrations of A β 1-40 in CSF were reduced from baseline by -50.1%, -75.7%, and -93.7% (respectively) in a cohort of healthy subjects. At those doses, the CCI [REDACTED] [REDACTED] [REDACTED]

Details of the results from these ongoing clinical trials are included in the IB.

The pharmacokinetics (PK) of LY3202626 were determined following single doses over a range from 0.1 to 45 mg, and at steady state from 1 to 26 mg QD administered as free base in capsule. Following oral dosing, LY3202626 reached maximum observed drug concentration (C_{max}) at approximately 4 hours, and then followed a multiexponential elimination profile with a half-life

associated with the terminal rate constant in noncompartmental analysis²⁰

The effect of concomitant administration of itraconazole (a strong cytochrome P450 [CYP] 3A inhibitor) on the PK of LY3202626 following single doses of 0.4 mg has been evaluated. In this evaluation, CCI

The LY3202626 capsule formulation has been administered with and without food. When administered with food, CCI

CCI

3.3. Benefit/Risk Assessment

LY3202626 has been administered to 85 healthy subjects over a range from 0.1 to 45 mg, and at steady state from 1 to 26 mg QD. LY3202626 has been administered to 2 patients with mild cognitive impairment due to AD or mild to moderate AD at a 6 mg dose level.

To date, no serious adverse events (SAEs) have been reported in subjects participating in clinical trials of LY3202626. Overall, 54.5% of all subjects who received LY3202626 or placebo reported one or more treatment-emergent adverse events (TEAEs). Reported by more than one study participant were the following TEAEs (Medical Dictionary for Regulatory Activities [MedDRA] preferred terms): discoloured faeces (18.2%), post-lumbar puncture syndrome (15.2%), headache (10.1%), dizziness (7.1%), diarrhoea (6.1%), nausea (4.0%), decreased appetite (3.0%), arthralgia, chest pain, dysgeusia, fatigue, and somnolence (all 2.0%). No subjects have discontinued either of the 2 ongoing clinical trials due to adverse events (AEs).

Orthostatic hypotension was reported by 1 study participant who received a single 10-mg LY3202626 dose in the single-ascending dose portion of the study, and postural orthostatic tachycardia syndrome was reported by 1 study participant who received a 26-mg LY3202626 dose in a multiple-ascending dose cohort. There was no dose response in the orthostatic hypotension (since the AEs occurred below the maximum dose 45 mg in the single-ascending dose portion of the study). While the clinical significance of these AEs is unclear, orthostatic vital signs will be collected in this study to further assess any potential cardiovascular effect of LY3202626.

There were no clinically significant changes in electrocardiograms (ECGs) or safety laboratories.

CCI

In order to acquire additional clinical QTc data for BACE IV, ECG assessments will be obtained in triplicate near C_{max} and at 24 hours postdose.

CCI

The 12-mg dose selected for this study is not expected to demonstrate significant safety or tolerability concerns based on the available data.

As this study is enrolling healthy subjects, no clinical benefit is anticipated from study participation.

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

4. Objectives and Endpoints

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

Table LLCE.1. Objectives and Endpoints

Objectives	Endpoints
<u>Primary</u>	The ratio of geometric least square means and corresponding 90% confidence interval (CI) between T1-12 and R will be calculated for: C_{max} , area under the concentration versus time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), and AUC from time zero to time t , where t is the last time point with a measurable concentration ($AUC_{0-t_{last}}$).
<u>Secondary</u>	<p>The ratio of geometric least square means and CI between LY3202626 T1-12 fed versus fasted will be calculated for: C_{max}, $AUC_{0-\infty}$, and $AUC_{0-t_{last}}$.</p> <p>Incidence of TEAEs.</p>
<u>Exploratory</u>	Plasma concentrations of $A\beta_{1-40}$ and $A\beta_{1-42}$ will be summarized for each treatment based on the nadir concentration (C_{nadir}), and the time to reach C_{nadir} (t_{nadir}). The percent change from baseline in $A\beta_{1-40}$ and $A\beta_{1-42}$ will be summarized for each treatment.

5. Study Design

5.1. Overall Design

This is a single-center, open-label, single-dose, randomized, 6-sequence, 3-period, crossover study in healthy subjects.

Screening will occur up to 28 days prior to the first dose of LY3202626.

Subjects will be admitted to the clinical research unit (CRU) on Day -1 of each period. In each period, subjects will be fasted overnight for at least 10 hours, and a single dose of 12 mg LY3202626, as either tablet (T1-12) in a fed state or fasted state or capsule (R) in a fasted state according to the randomization schedule, will be administered on the morning of Day 1. Blood sampling for assessment of LY3202626 PK and for pharmacodynamic (PD) assessments of A β 1-40 and A β 1-42 will be performed up to 168 hours postdose (Day 8). Subjects may be discharged from the CRU following completion of all 24-hour or 36-hour procedures on Day 2. If discharged after 24-hour procedures, subject will return to the CRU as an outpatient visit for the 36-hour PK sample collection. Subjects will return to the CRU daily for outpatient visits for PK sample collections Days 3 through 8. The washout period between dosing in 2 consecutive periods will be at least 10 days. A follow-up telephone call will be performed approximately 5 to 8 days after Period 3, Day 8.

Tolerability will be explored by clinical laboratory tests, vital sign measurements, 12-lead ECGs, and recording of AEs.

The 3 dose administrations received by each subject will be:

- A = Reference (R): 12-mg LY3202626 capsule; administered in a fasted state
- B = Test (T1-12): 12-mg LY3202626 tablet; administered in a fasted state
- C = Test (T1-12): 12-mg LY3202626 tablet; administered in a fed state (Food and Drug Administration [FDA] high-fat meal)

Subjects will be randomized to 1 of 6 dose administration sequences ([Table LLCE.2](#)).

Table LLCE.2. Dose Administration Sequences

Sequence	Period 1	Period 2	Period 3
ABC	R fasted	T1-12 fasted	T1-12 fed
BCA	T1-12 fasted	T1-12 fed	R fasted
CAB	T1-12 fed	R fasted	T1-12 fasted
CBA	T1-12 fed	T1-12 fasted	R fasted
ACB	R fasted	T1-12 fed	T1-12 fasted
BAC	T1-12 fasted	R fasted	T1-12 fed

Abbreviations: R = reference (capsule formulation); T1-12 = test (tablet formulation).

Figure LLCE.1 illustrates the study design.

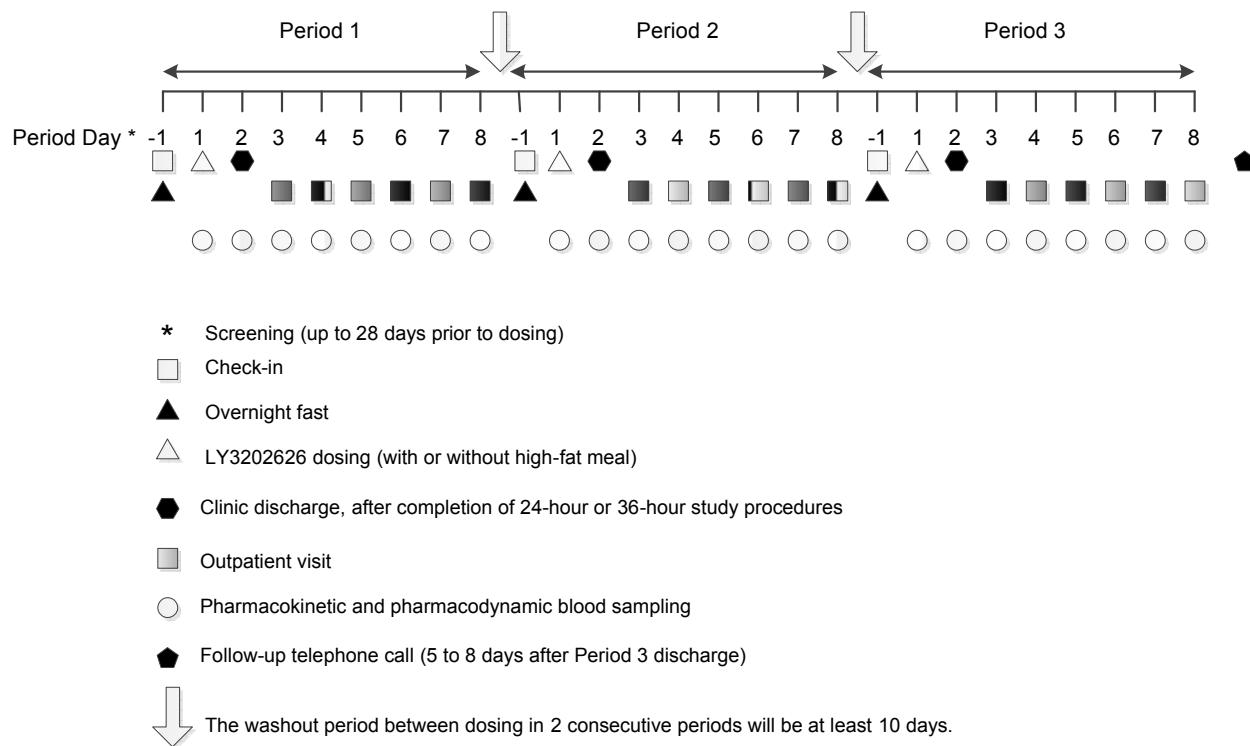


Figure LLCE.1. Illustration of Study Design for Protocol I7X-MC-LLCE.

5.2. Number of Participants

Initially, up to approximately 24 healthy subjects may be enrolled so that approximately 20 subjects complete the study. Study completion is defined as completing all 3 study periods. If multiple subjects who are randomized withdraw before study end, up to 6 additional subjects may be enrolled to ensure completion of 20 subjects. In the event that these 6 additional subjects are enrolled, a maximum of 30 subjects may be enrolled in the trial.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This study uses a randomized, open-label, crossover design such that each subject acts as their own control, thus reducing variability. The open-label design with no placebo control is considered appropriate because determining the relative bioavailability of the reference capsule and test tablet formulation of LY3202626 is the primary objective of the study.

A capsule formulation of LY3202626 has been used in the clinical studies with LY3202626 to date. However, a tablet formulation of LY3202626 is being developed for later phase studies. Therefore a relative bioavailability study enables the assessment of the relative PK between the

reference capsule and test tablet formulations of LY3202626. LY3202626 has been administered as high as 26 mg for 14 days in Phase I studies. However, the highest dose in the current Phase 2 study is 12 mg; therefore the relative bioavailability of a 12 mg dose of the capsule and tablet formulation will be assessed in this study.

Reductions of A β 1-40 from baseline were seen following doses of 1-, 6-, and 26-mg LY3202626 QD for 14 days in a cohort of healthy subjects. The change from baseline of A β isoforms (A β 1-40 and A β 1-42) after a single 12-mg dose of LY3202626 as a tablet formulation (test formulation [T1-12]) and capsule formulation (reference formulation [R]) will be evaluated in plasma in this study.

Based on the reported LY3202626 half-life associated with the terminal rate constant ($t_{1/2}$) determined using noncompartmental analysis (approximately CCI [REDACTED] the interval of at least 10 days between dosing in each period is adequate to ensure that there is no carryover of exposure from one dose to the next.

5.5. Justification for Dose

Nonclinical data as well as safety, PK and PD data to date from the ongoing Phase 1 study in healthy subjects and patients with mild cognitive impairment (Study LLCA, see Section 3 above) support a single dose study in healthy subjects. It is anticipated that a single dose of 12 mg LY3202626 will be well tolerated by healthy subjects (see Section 3.3).

The 12-mg dose selected is the highest dose currently being evaluated in Phase 2 studies, and is projected to be the highest dose to be evaluated in Phase 3 studies. Administration of this dose of LY3202626 predicts a CCI [REDACTED] in CSF A β , the primary dose selection biomarker for LY3202626. The FDA guidance (FDA Guidance, 2002) recommends the highest strength of a drug product intended to be marketed should be tested in food-effect studies. The 12-mg dose will enable the objectives of this trial to be addressed and fully characterize the single oral dose PK of the compound.

6. Study Population

Eligibility of subjects for study enrollment will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG.

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

Screening may occur up to 28 days prior to first dose. Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

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

- [1] are overtly healthy males or females, as determined by medical history and physical examination
 - [1a] female subjects:
 - must be of non-childbearing potential confirmed by medical history or menopause
 - 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 50 years of age or older not on hormone therapy, who have had 6 to 12 months of spontaneous amenorrhea with a follicle-stimulating hormone level greater than 40 mIU/mL; or
 - [ii] women at least 50 years of age with a diagnosis of menopause prior to starting hormone replacement therapy
- [2] are at least 21 years old at the time of screening
- [3] have a body mass index (BMI) of 18.5 to 32.0 kg/m², inclusive, at screening
- [4] have clinical laboratory test results within normal reference range for the investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator
- [5] have venous access sufficient to allow for blood sampling as per the protocol
- [6] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

- [7] are willing and able to eat the protocol-specified high-fat breakfast
- [8] are able and willing to give signed informed consent

6.2. Exclusion Criteria

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

- [9] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling
- [10] are Lilly or Covance employees
- [11] are currently enrolled in a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- [12] have participated, within the last 30 days, in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed
- [13] have previously completed or withdrawn from this study or any other study investigating LY3202626, and have previously received the investigational product
- [14] have known allergies to LY3202626, related compounds or any components of the formulation, or history of significant atopy
- [15] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study
- [16] have an abnormal blood pressure or pulse rate (supine or standing) that, in the opinion of the investigator, increases the risks associated with participating in the study
- [17] have a history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data
- [18] have a history of seizure(s) (except childhood febrile seizure)
- [19] have a history of head trauma with loss of consciousness within the last 5 years
- [20] have known or ongoing psychiatric disorders
- [21] regularly use known drugs of abuse
- [22] show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies

- [23] show evidence of hepatitis C and/or positive hepatitis C antibody
- [24] show evidence of hepatitis B and/or positive hepatitis B surface antigen
- [25] are women who are lactating, nursing, or have a positive pregnancy test
- [26] intend to use over-the-counter or prescription medication including herbal medications within 7 days prior to dosing
- [27] have donated blood of 450 mL or more within the last 3 months or provided any blood donation within the last month before screening
- [28] have an average weekly alcohol intake that exceeds 21 units per week for males under 65 years of age and 14 units per week for females and for males over 65 years of age, or are unwilling to stop alcohol consumption from 48 hours prior to each admission and while resident in the CRU (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)
- [29] have consumed grapefruits or grapefruit-containing products, Seville oranges or Seville orange-containing products, star fruit or star fruit-containing products within 7 days prior to dosing or intend to consume during the study
- [30] are currently or have been smokers or users of tobacco or nicotine replacement products within the 6 months prior to admission
- [31] are unwilling to refrain from consuming xanthine-containing food and drink from 48 hours prior to each admission until discharge from the CRU
- [32] are unwilling to comply with the dietary requirements/restrictions during the study or unwilling to consume only the meals provided during the inpatient visits
- [33] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Standardized meals will be provided during each subject's stay in the CRU.

Subjects will not consume grapefruits or grapefruit-containing products, Seville oranges or Seville orange-containing products, star fruit or star fruit-containing products for at least 7 days prior to the first dose of LY3202626 until the final PK sample is collected following the last dose of LY3202626.

Administration of LY3202626 in the fasted state

Administration of each LY3202626 dose will be preceded by at least a 10-hour fast. No fluid will be allowed from 1 hour prior to dosing until 1 hour after dosing except for the approximate 240 mL water required for dose administration. No food will be allowed until approximately 4 hours postdose.

Administration of LY3202626 in the fed state

Following an overnight fast of at least 10 hours, subjects will start the high-fat, high-calorie meal 30 minutes prior to administration of LY3202626; the meal should contain approximately 800 to 1000 calories in total, of which approximately 500 to 600 calories should be derived from fat and approximately 150 and 250 calories should be derived from protein and carbohydrate, respectively. An example meal is detailed in [Table LLCE.3](#). It is intended that the meal will be ingested in its entirety over an approximate 25-minute period, such that it is completed at least 5 minutes before dosing. No water will be allowed from 1 hour prior to dosing until 1 hour after dosing except for the approximate 240 mL water required for dose administration. No further food will be permitted until at least 5 hours postdose.

Table LLCE.3. High-Fat Meal Composition

2 eggs fried in butter
2 strips of bacon
2 slices of toast with butter
4 ounces of hash brown potatoes
8 ounces of whole milk

For the dosing period in the fed state, the date and start time of high fat meal consumption on Day 1 will be recorded.

6.3.2. Xanthine, Alcohol, and Tobacco

Subjects will be advised to refrain from consuming xanthine-containing food or drinks from 48 hours prior to admission and while resident in the CRU.

Subjects will not consume alcohol for 48 hours prior to admission and while resident in the CRU.

Smoking will not be permitted throughout the study.

6.3.3. Activity

Subjects should avoid strenuous physical activity for 72 hours before the first dose of LY3202626 until completion of the study.

6.4. Screen Failures

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

7. Treatment

7.1. Treatment Administered

One 12-mg capsule or one 12-mg tablet of LY3202626 will be administered orally with approximately 240 mL of room temperature water in the morning of each dosing day in a sitting position. Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

The investigator or designee is responsible for:

- explaining the correct use of the investigational products to the subject and site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of investigational product dispensing and collection,
- and returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

7.1.1. Packaging and Labeling

The drug product should be stored according to instructions on the label.

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

7.2. Method of Treatment Assignment

Subjects will be randomized to 1 of 6 dose administration sequences using a computer-generated allocation schedule (see [Table LLCE.2](#)).

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same time on each dosing day. The actual date, time, LY3202626 amount, formulation (capsule-reference or tablet-test) as well as administration condition (fasted or fed) of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

Dose reductions or adjustments will not be allowed during this study.

7.5. Preparation/Handling/Storage/Accountability

Only participants enrolled in the study may receive investigational product (IP) and only authorized site staff may supply or administer study treatment. All study treatments should be

stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

7.6. Treatment Compliance

The investigational product will be administered at the clinical site, and documentation of dose administration will occur at the site.

7.7. Concomitant Therapy

Additional drugs are to be avoided during the study unless required to treat an AE. If the need for concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist (CP) or clinical research physician (CRP), or designee. The use of topical medicine, provided there is no evidence of chronic dosing with risk of systemic exposure, is acceptable. Hormone replacement therapy and/or occasional acetaminophen administration will be allowed at the discretion of the investigator. Any additional medication used during the course of the study must be documented.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

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

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the Sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, the subject will be discontinued from the study and early discontinuation assessments will be performed as described in the Schedule of Activities (Section 2).

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

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

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

8.3. Subjects Lost to Follow-up

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

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing.

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

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

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

Investigators must document their review of each laboratory safety report.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

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

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

After the informed consent form (ICF) is signed, study site personnel will record, via eCRF, the occurrence and nature of each subject's preexisting conditions. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

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

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- events considered significant by the investigator based upon appropriate medical judgment

Study site personnel must alert Lilly, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Subjects should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3202626 is considered any dose higher than the dose assigned. There is no specific antidote for LY3202626. In the event of overdose, the subject should receive appropriate supportive care and any AEs should be documented.

9.4. Safety

9.4.1. Laboratory Tests

For each subject, laboratory tests detailed in [Appendix 2](#) should be conducted according to the Schedule of Activities (Section [2](#)) and following the manual of operations.

9.4.2. Vital Signs

For each subject, vital sign measurements should be conducted according to the Schedule of Activities (Section [2](#)). Additional unscheduled vital sign measurements may be conducted if clinically indicated.

Blood pressure and pulse rate will be measured with automated equipment. Use of the same arm for blood pressure determination throughout the study is recommended, whenever possible. The cuff should be the correct size for the subject's arm. The arm with the cuff should be supported at approximately the heart level whether supine or standing.

Blood pressure and pulse rate will be measured supine and standing. Supine blood pressure and pulse rate should be taken after at least 5 minutes of supine rest. The subject should then sit for 3 minutes before standing. Standing blood pressure and pulse rate should be taken 3 minutes after standing. If the subject feels unable to stand, only supine vital signs will be recorded. Symptoms occurring during a subject's change in position or that prevent standing should be recorded as AEs.

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

9.4.3. Body Weight

Body weight will be recorded as specified in the Schedule of Activities (Section [2](#)).

9.4.4. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities (Section [2](#)).

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the IP, should be reported to Lilly, or its designee, as an AE via eCRF.

For each subject during each dosing period, a 12-lead digital ECG will be collected in triplicate and stored. Screening ECG will be collected as a single ECG and not stored.

Electrocardiograms must be recorded before collecting any blood for safety or pharmacokinetic

tests. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Consecutive replicate ECGs will be obtained at approximately 1 minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

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

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subject for symptoms (for example, palpitations, near syncope, syncope) to determine whether the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

9.4.5. Safety Monitoring

The Lilly CP or CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist when appropriate, and periodically review:

- trends in safety data
- laboratory analytes
- AEs

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 collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for

the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

9.5.1. *Bioanalysis*

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of LY3202626 will be assayed using a validated liquid chromatography with tandem mass spectrometric detection method.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 2 years 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*

At the visits and times specified in the Schedule of Activities (Section 2) venous blood samples of approximately 2 mL will be collected for measurement of plasma A β concentrations.

Plasma concentrations of A β ₁₋₄₀ and A β ₁₋₄₂ will be determined using validated immunoassay methods. The samples will be identified by the subject number (coded) and stored for up to a maximum of 1 year after the last subject visit for the study at a facility selected by the sponsor.

9.7. *Genetics*

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

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3202626 and to investigate genetic variants thought to play a role in neurodegenerative disease. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or Ethical Review Boards (ERBs/IRBs) impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3202626 or after LY3202626 is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, multiplex assays, and candidate gene studies.

Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

This section is not applicable for this study.

9.9. Health Economics

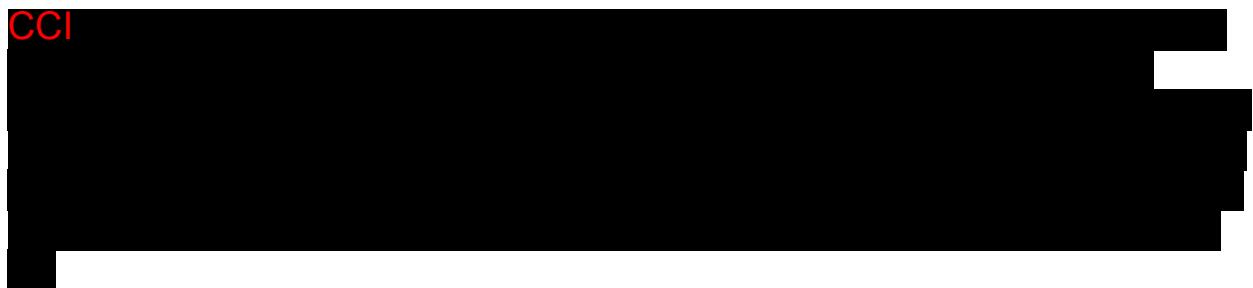
This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to approximately 24 healthy subjects may be enrolled to ensure that at least 20 subjects complete the study. This sample size is based on a calculation of precision of the estimated ratio of area under the concentration versus time curve (AUCs).

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At the discretion of the investigator and sponsor, if multiple subjects who are randomized withdraw before study end, an additional 6 subjects (up to a total enrollment of 30 subjects) may be enrolled to ensure completion of 20 subjects. The replacement subject will be assigned the same dose administration sequence as the withdrawn subject's dose administration sequence (receiving each dose administration allocated).

10.2. Populations for Analyses

10.2.1. *Study Participant Disposition*

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

10.2.2. *Study Participant Characteristics*

The subject's age, sex, weight, height, BMI, race, and other demographic characteristics will be recorded and summarized using descriptive statistics.

10.3. Statistical Analyses

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

Pharmacokinetic analyses will be conducted on the full analysis set. This set includes all data from all subjects receiving at least 1 dose of LY3202626, according to the dose administration the subjects actually received. Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

No adjustments for multiple comparisons will be made.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

The incidence of symptoms for each dose administration will be presented by severity and by association with LY3202626 as perceived by the investigator. Symptoms reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of investigational product-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety lab parameters and vital signs. The parameters and changes from baseline (check-in), where appropriate, will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3202626 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max} , AUC from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to time t , where t is the last time point with a measurable concentration ($AUC_{0-t_{last}}$), and time of maximum observed drug concentration (t_{max}) of LY3202626. Other noncompartmental parameters, such as $t_{1/2}$, apparent total body clearance of drug calculated after extra-vascular administration (CL/F), and apparent volume of distribution during the terminal phase after extra-vascular administration (V_z/F) will be reported if evaluable based on available data.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameter estimates will be evaluated to delineate relative bioavailability and food effects.

The following comparisons will be interests of statistical analysis of PK parameters:

- relative bioavailability: LY3202626 T1-12 fasted (test) versus LY3202626 R fasted (reference)
- food effect: LY3202626 T1-12 fed (test) versus LY3202626 T1-12 fasted (reference).

Log-transformed C_{max} and AUC estimates will be evaluated in a linear mixed-effects model with fixed effects for dose administration and period and a random effect for subject. The ratio of geometric least squares means and corresponding 90% CI will be presented for LY3202626

T1-12 versus LY3202626 R for analysis of relative bioavailability, and LY3202626 T1-12 administered with a high-fat meal versus LY3202626 T1-12 administered fasted for the analysis of the food effect. One model will be used for the assessment of relative bioavailability and the effect of food.

The t_{max} will be analyzed non-parametrically. Median of differences and approximate 90% CI for the median of differences will be calculated. P-values will also be calculated using a Wilcoxon signed rank test.

Additional analyses may be performed if deemed necessary.

10.3.3. *Pharmacodynamic Analysis*

10.3.3.1. *Pharmacodynamic Parameter Estimation*

Plasma concentrations of $A\beta_{1-40}$ and $A\beta_{1-42}$ will be summarized for each treatment based on the nadir concentration (C_{nadir}), the time to reach C_{nadir} (t_{nadir}), and the 24-hour average values expressed as percentage change from baseline.

10.3.3.2. *Pharmacodynamic Statistical Inference*

No formal statistical testing will be conducted.

10.3.4. *Interim Analyses*

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

11. References

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.

FDA. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. 2002.

Appendix 1. Abbreviations and Definitions

Term	Definition
Aβ	amyloid beta
AD	Alzheimer's disease
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
APP	amyloid precursor protein
AUC	area under the concentration versus time curve
AUC_{0-t_{last}}	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC_{0-∞}	area under the concentration versus time curve from time zero to infinity
BACE1	β-site amyloid precursor protein-cleaving enzyme
BMI	body mass index
CI	confidence interval
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	maximum observed drug concentration
C_{nadir}	nadir concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist

CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CSF	cerebral spinal fluid
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
end of trial (study)	End of trial is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last subject.
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
MEDRA	Medical Dictionary for Regulatory Activities
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
QD	once daily
R	reference formulation (12 mg capsule)
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial.
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
SUSARs	suspected unexpected serious adverse reactions
t_{1/2}	half-life associated with the terminal rate constant (λ) in noncompartmental analysis
T1-12	test formulation (12 mg tablet)
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time of maximum observed drug concentration
t_{nadir}	time to reach nadir concentration
V_{z/F}	apparent volume of distribution during the terminal phase after extra-vascular administration

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Hematology ^a	Clinical Chemistry ^a
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Glucose, random
Mean cell hemoglobin concentration	Blood urea
Leukocytes (WBC)	Total protein
Absolute counts of:	Creatinine
Neutrophils	Liver tests:
Lymphocytes	Albumin
Monocytes	Total bilirubin
Eosinophils	Alkaline phosphatase (ALP)
Basophils	Aspartate aminotransferase (AST)
Platelets	Alanine aminotransferase (ALT)
	Gamma-glutamyl transferase (GGT)
Urinalysis ^a	
Specific gravity	
pH	
Protein	Hepatitis B surface antigen ^d
Glucose	Hepatitis C antibody ^d
Ketone	HIV ^d
Bilirubin	FSH ^b
Urobilinogen	
Blood	
Nitrite	
Leukocyte	
Microscopy ^c	

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

Note: Results of these assays will be validated by the local laboratory at the time of testing.

Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

a Results will be validated by the local lab at the time of testing.

b Performed at screening only, in post-menopausal women with 6-12 months of amenorrhea.

c If clinically indicated, per investigator's discretion.

d Performed at screening only. This test will be performed unless results of the same test have been obtained from the subject within the last 6 months.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

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

Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

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

- the current IB
- ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with:

- 1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- 2) applicable ICH GCP Guidelines
- 3) applicable laws and regulations

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

Protocol Signatures

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

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

Final Report Signature

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

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

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

Study and Site Closure***Discontinuation of Study Sites***

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

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I7X-MC-LLCE Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests ^a	15	1	15
Clinical laboratory tests ^a	9	9	81
Pharmacokinetics ^b	3	59	177
Pharmacodynamics	2	57	114
Pharmacogenetics	10	1	10
Total			397
Total for clinical purposes [rounded up to nearest 10 mL]			400

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

b Includes an additional 2 samples which may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

Leo Document ID = 114c4e79-b2cf-4dc1-83b6-75b5265dbfc9

Approver: PPD

Approval Date & Time: 08-Sep-2016 20:33:51 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 10-Sep-2016 07:18:09 GMT

Signature meaning: Approved

Leo Document ID = 8dc6cd7c-6e78-4134-9dc8-cc4750e454e4

Approver: Oliver Schmidt (AM\C243405)

Approval Date & Time: 08-May-2018 18:17:39 GMT

Signature meaning: Approved