Protocol I9F-MC-SCAA(a)

Single-Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3323795 in Healthy Subjects

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Confidential Information

LY3323795

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 27 October 2016
Amendment (a) Electronically Signed and Approved by Lilly on approval date provided below.

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1. Protocol Synopsis

Title of Study:
Single-Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3323795 in Healthy Subjects

Rationale:
Lilly is developing LY3323795 for the treatment of Alzheimer's disease (AD). It is believed that inhibiting β-site amyloid precursor protein-cleaving enzyme-1 activity will prevent β-amyloid (Aβ) plaque formation and subsequent deposition, which is an early and necessary event in the pathogenesis of AD.

LY3323795 has not been administered to humans. This first-in-human dose study will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3323795 in healthy subjects. Safety and tolerability evaluations will be conducted over a range of single doses, and dose escalation will not proceed until safety data from previous doses have been reviewed. The data generated in this study will be used to help design and identify doses for subsequent clinical trials.

Objective(s)/Endpoints:

Objectives	**Endpoints**
Primary • To explore the safety and tolerability of single doses of LY3323795 in healthy subjects.	Incidence of treatment-emergent adverse events.
Secondary • To explore the plasma and cerebrospinal fluid (CSF) PK of single doses of LY3323795.	Maximum drug concentration (C_{max}) and the area under the concentration-versus-time curve (AUC) in plasma; and C_{max} and AUC in CSF for various time frames.
• To explore the plasma and CSF PD of single doses of LY3323795.	Minimum $A\beta_{1-40}$ or $A\beta_{1-42}$ concentration observed following administration of study drug, expressed as the percentage change in concentration from baseline.

Summary of Study Design:
Study I9F-MC-SCAA is a Phase 1 study of LY3323795 in healthy subjects that will be conducted in 3 parts. Part A (Doses 1 to 6) will be a subject- and investigator-blind, placebo-controlled, randomized, single-ascending dose, 3-period, 2-cohort (6:3 subjects, LY3323795:placebo per cohort), dose-escalation study to evaluate safety, tolerability, and plasma PK/PD of LY3323795. Part B will be a subject- and investigator-blind, placebo-controlled, randomized, single-dose, 3-cohort (5:2 subjects, LY3323795:placebo per cohort), single-period, lumbar catheter study to evaluate the central and plasma PK/PD of LY3323795. Doses in Part B will not be administered until equal or greater doses have been administered in Part A and shown to be well tolerated. Part C will be an open-label, 2-period, fixed-sequence, single-cohort design with 8 subjects to evaluate a potential CYP3A4 interaction when LY3323795 is coadministered with itraconazole.

Treatment Arms and Duration:
For Part A (Cohorts 1 and 2), subjects will receive oral doses of either LY3323795 or placebo; the anticipated doses are 0.3 mg, 1 mg, 3 mg, 10 mg, 30 mg, and 100 mg.

For Part B (Cohorts 3, 4, and 5), subjects will receive a single oral dose of placebo or LY3323795 less than or equal to doses previously administered and found to be well tolerated in Part A.

For Part C (Cohort 6), Period 1, subjects will be administered an oral dose of LY3323795 at a dose level that was well tolerated in Part A. For Period 2, subjects will be coadministered an oral dose of LY3323795 (same dose as Period 1) in the presence of itraconazole (on Day 16). Itraconazole 200 mg will be administered twice on Day 10 and once daily on Days 11 to 21.

Number of Subjects:
For Cohorts 1 and 2 in Part A, up to approximately 24 subjects may be enrolled so that approximately 18 subjects (9 subjects per cohort [6:3, LY3323975:placebo]) complete the study.

For Cohorts 3 to 5 in Part B, up to approximately 30 subjects may be enrolled so that approximately 21 subjects (7 subjects per cohort [5:2, LY3323975:placebo]) complete the study.

For Cohort 6 in Part C, up to 12 subjects may be enrolled so that approximately 8 subjects complete the study.

Statistical Analysis:

The sample size for Part A is customary for Phase 1 studies evaluating safety, PK, and/or PD parameters, and is not based on statistical mean estimation. Parts B and C are not formally powered to detect a prespecified anticipated effect; however, precision intervals have been calculated to show what may be observed for changes in cerebrospinal fluid (CSF) Aβ and effect of itraconazole on LY3323795 given the sample sizes.

No formal interim analyses are planned for this study. Interim access to data (IAD) is scheduled to occur throughout the study. The purpose of these IAD reviews is to examine the safety and or PK/PD data and guide dose selections.

All investigational product and protocol procedure adverse events will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. Safety laboratory parameters, vital signs, and electrocardiogram parameters will be listed and summarized using standard descriptive statistics for values at each time point as well as changes from baseline.

PK parameter estimates for LY3323795 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max} and AUC of LY3323795. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

For Parts A and B, plasma concentrations of $A\beta_{1-40}$ and $A\beta_{1-42}$ will be summarized for each dose group based on the nadir concentration (C_{nadir}) and the time to reach C_{nadir} (t_{nadir}).

In Part B, CSF concentrations of $A\beta_{1-40}$, $A\beta_{1-42}$, and CCI [redacted] will be summarized for each dose group based on the C_{nadir}, t_{nadir}, and the 24-hour average values, expressed as a percentage change from baseline. Statistical analysis of CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations obtained over the fixed-scheduled sampling period will be analyzed using a repeated-measures analysis with the primary statistical estimation of the overall mean percentage change from baseline and 90% confidence interval among the LY3323795 doses and placebo at each post dose time point.

For Part C, the area under the curve from time 0 extrapolated to infinity and C_{max} for LY3323795 administered alone and in the presence of itraconazole will be compared with an analysis of variance model.

2. Schedule of Activities

Study Schedule Protocol I9F-MC-SCAA: Part A, Periods 1 through 3

	Screen	Periods 1 to 3								FDC[a]	ED	Notes
Study Day	**-28 to -2**	**-1**	**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**			
Admit to CRU		X										
Discharge from CRU					X							
Physical examination	X	X								X	X	
Ethanol and urine drug screens	X											An additional ethanol and urine drug screen may be done at the discretion of the investigator at readmission to the CRU.
Ophthalmic examination	X				X					X	X	See Section 9.4.4.2 for details.
12-Lead ECG (hours)	X		0, 1, 2, 4, 6, 8, 12	24	48				X	X	X	ECGs coinciding with PK sample time points are to be conducted as close as possible to PK sampling. See Section 9.4.3 for other details.
Vital signs (hours)	X		0, 1, 2, 4, 6, 8, 12	24	X	X	X	X	X	X	X	See Section 9.4.2 for details.
Clinical laboratory values (hours)	X	X			48				X	X	X	Screening tests will occur at local laboratories and other analyses will be at central laboratory. Blood will be collected on Day -1 for both local and central labs. Investigator will review local lab results before dosing in each period.
LY3323795 study drug			X									Subjects are required to fast before and after drug administration. See Section 6.3.1 for details.
LY3323795 plasma PK samples (hours)			0, 0.5, 1, 2, 3, 4, 6, 8, 12	24	48	72	96	120	144			A maximum of 5 additional plasma samples per subject may be drawn during the study at the discretion of the investigator or sponsor. These additional samples may be drawn to measure LY3323795 or Aβ concentrations.
PD plasma samples (hours)			0, 0.5, 1, 2, 3, 4, 6, 8, 12	24	48	72	96	120	144			A maximum of 5 additional plasma samples per subject may be drawn during the study at the discretion of the investigator or sponsor.

	Screen	Periods 1 to 3							FDC[a]	ED	Notes
Study Day	**-28 to -2**	**-1**	**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**			
Storage plasma samples (hours)			0, 0.5, 1, 2, 3, 4, 6, 8, 12	24	48	72	96	120	144			This is not an additional draw; sample will be taken from PD blood sample and stored separately. Stored samples will be used for other assays yet to be determined.
Weight/height	X	X								X	X	Height measured at screening only.
Urine collection (hours)			0-24	24-48								Urine to be collected continuously during the 2 separate collection periods (0-24 and 24-48 hours).
Neurological survey (hours)	X	X		24	48			X		X	X	Neurological surveys on PK sampling days are to be conducted as close as possible to PK sampling. If abnormalities are noted, refer to Section 9.4.4.1.
Sample for genetic testing			X									Period 1 only.

Abbreviations: Aβ = β-amyloid; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FDC = final discharge; PD = pharmacodynamics; PK = pharmacokinetics.

[a] Study final discharge procedures should be completed 14-21 days after the last dose.

[b] Time 0 is predose.

Study Schedule Protocol I9F-MC-SCAA: Part B

Study Day	Screen -28 to -1	-1	1[a]	2	3	4	5	6	7	FDC[b]	ED	Notes
Admit to CRU		X										
Discharge from CRU					X							Discharge to be approximately 24 hours after CSF catheter is removed, at investigator's discretion.
Physical examination	X	X								X	X	
Ethanol and urine drug screens	X											An additional ethanol and urine drug screen may be done at the discretion of the investigator.
Ophthalmic examination	X					X			X	X	X	See Section 9.4.4.2 for details.
12-Lead ECG (hours)	X		0		48 ±2				X	X	X	These will be single ECGs. ECGs coinciding with PK sample time points are to be conducted as close as possible to PK sampling. Time of Day 3 ECG can vary depending on when the CSF catheter is removed. Other ECGs may be obtained – see Section 9.4.3.
Vital signs (hours)	X		0, 1, 2, 4, 6	24	X	X	X	X	X	X	X	Timing of vital sign collections may be adjusted. See Section 9.4.2 for details.
Clinical laboratory values (hours)	X	X			48				X	X	X	Blood will be collected on Day -1 for both local and central labs. Investigator will review local lab results before dosing.
LY3323795 study drug			X									Subjects are required to fast before and after drug administration. See Section 6.3.1 for details.

Study Day	Screen -28 to -1	-1	1[a]	2	3	4	5	6	7	FDC[b]	ED	Notes
LY3323795 plasma PK samples (hours)			0, 0.5, 1, 2, 3, 4, 6, 8, 12	24, 36	48	72	96	120	144			A maximum of 5 additional plasma samples per subject may be drawn during the study at the discretion of the investigator or sponsor. These additional samples may be drawn to measure LY3323795 or Aβ concentrations.
Plasma PD samples (hours)			0, 0.5, 1, 2, 3, 4, 6, 8, 12	24, 36	48	72	96	120	144			Additional samples possible as per LY3323795 plasma PK sample note above.
Storage PD plasma samples (hours)			0, 0.5, 1, 2, 3, 4, 6, 8, 12	24, 36	48	72	96	120	144			Additional samples possible as per LY3323795 plasma PK sample note above.
X-ray	X											Subjects who agree to have lumbar punctures may have a lumbar x-ray conducted at screening, at site's discretion. If an x-ray was done within 12 months of screening, this may be used.
Weight/height	X	X								X	X	Height measured at screening only.
CSF, continuous (hours)			-4, -2, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20	24, 28, 32, 36								CSF samples will be collected during the stabilization period. See Section 5.1.2 for details of how CSF samples at different time points will be processed.
Neurological survey (hours)	X	X		24	48					X	X	Neurological surveys on PK sampling days are to be conducted as close as possible to PK sampling. For Day 3, time can vary depending on

												when the CSF catheter is removed. If abnormalities are noted, refer to Section 9.4.4.1.
Sample for genetic testing			X									

Abbreviations: Aβ = β-amyloid; CRU = clinical research unit; CSF = cerebrospinal fluid; ECG = electrocardiogram; ED = early discontinuation; FDC = final discharge; PD = pharmacodynamics; PK = pharmacokinetics.

[a] Time 0 is predose.

[b] Study final discharge procedures should be completed 14-21 days after the last dose.

Study Schedule Protocol I9F-MC-SCAA: Part C

	Screen		Period 1		7-Day Wash-out	Period 2											FDC[a]	ED	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3-9**	**10**	**11 to 14**	**15**	**16[b]**	**17**	**18**	**19**	**20**	**21**	**22**	**23**			
Admit to CRU		X			X			X											Subjects will be admitted on Days -1, 9, and 15.
Discharge from CRU					X		X				X								Subjects will be discharged on Days 3, 11, and 18.
Physical examination	X	X															X	X	
Ethanol and urine drug screens	X																		An additional ethanol and urine drug screen may be done at the discretion of the investigator at readmission to the CRU.
Ophthalmic examination	X				48						X						X	X	See Section 9.4.4.2 for details of eye tests to be conducted.
12-Lead ECG (hours)	X		0, 1, 2, 4, 6, 8, 12	24	48				0, 1, 2, 4, 6, 8, 12	24	48				X		X	X	See Section 9.4.3 for details. At predose (time 0), 3 sets of triplicate ECGs will be obtained approximately 10 minutes apart. ECGs coinciding with PK sample time points are to be conducted as close as possible to PK sampling. See Section 9.4.3 for more details.

	Screen		Period 1		7-Day Wash-out	Period 2										FDC[a]	ED	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3-9**	**10**	**11 to 14**	**15**	**16[b]**	**17**	**18**	**19**	**20**	**21**	**22**	**23**		
Vitals (hours)	X		0, 1, 2, 4, 6, 8, 12	24	X	X	X	X	0, 1, 2, 4, 6, 8, 12	24	X	X	X	X	X	X	X	X	See Section 9.4.2 for details.
Clinical laboratory values (hours)	X	X			48, Day 9				0		48				X		X	X	Screening tests will take place at local laboratories and other analyses will be at central laboratory. Blood will be collected on Day -1 for both local and central labs. Investigator will review local lab results before dosing in Period 1.
LY3323795 study drug			X						X										Subjects are required to fast before and after drug administration. See Section 6.3.1 for details.
Itraconazole study drug						BID	QD	X	X	X	X	X	X	X					Subjects will be dosed as inpatients on Days 10 and 15-17, and as outpatients on Days 11-14 and 18-21. Itraconazole will be dosed twice on Day 10, 12 hours apart. Additional daily doses may be added depending on the PK results of LY3323795. See Section 5.1.3 for further details.

	Screen		Period 1		7-Day Wash-out	Period 2										FDC[a]	ED	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3-9**	**10**	**11 to 14**	**15**	**16[b]**	**17**	**18**	**19**	**20**	**21**	**22**	**23**			
LY3323795 plasma PK samples (hours)			0, 0.5, 1, 2, 3, 4, 6, 8, 12	24	48, 72, 96, 120, 144				0, 0.5, 1, 2, 3, 4, 6, 8, 12	24	48	72	96	120	144	168			A maximum of 5 additional plasma samples per subject may be drawn during the study at the discretion of the investigator or sponsor. These additional samples may be drawn to measure LY3323795 or Aβ concentrations.
Itraconazole plasma PK samples (hours)									0, 1, 2, 3, 4, 6, 8, 12	24									Times are relative to the itraconazole dose administered on Day 16. See Section 9.5 for details.
Weight/height	X							X									X	X	Height measured at screening only.
Neurological survey (hours)	X	X		24	48, 144			X		24	48				144		X	X	Neurological surveys on PK sampling days are to be conducted as close as possible to PK sampling. If abnormalities are noted, refer to Section 9.4.4.1.
Sample for genetic testing		X																	

Abbreviations: Aβ = β-amyloid; BID = twice a day; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FDC = final discharge; PK = pharmacokinetics; QD = once a day.

[a] Study final discharge procedures should be completed 14-21 days after the last dose.

[b] Time 0 is predose.

3. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, loss of independent function, and ultimately death. While symptomatic treatments are available, their effects are temporary and do not affect the progression of disease pathology. Disease-modifying agents that target the underlying disease pathology are currently unavailable and represent a significant unmet medical need for patients, their families, and caregivers. The primary pathological hallmarks of AD identified at autopsy include neuritic β-amyloid (Aβ) plaques and neurofibrillary tangles composed of tau aggregates (Hyman et al. 2012). Mounting evidence indicates that, while both Aβ plaques and tau tangles may be drivers of neuronal degeneration and disease progression, Aβ is likely an early initiator of the AD neurodegenerative cascade. As such, progression of AD may be slowed down by inhibiting the generation of Aβ in the brain.

Aβ is part of the amyloid precursor protein (APP), which is a transmembrane protein widely expressed on the cell surface, particularly in neurons. APP is cleaved through 2 pathways involving 3 secretase enzymes: α-secretase, γ-secretase, and β-site APP-cleaving enzyme [BACE]1 (previously referred to as β-secretase). CCI [redacted] In the second pathway, BACE1 cleaves the APP molecule, generating membrane-associated C99 and releasing a larger secreted fragment called CCI . γ-Secretase then cleaves C99 in a heterogeneous manner 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-secretase and BACE1 inhibition represent effective means of precluding the formation of Aβ, BACE1 inhibition may provide improved safety and tolerability (Doody et al. 2013).

BACE1 shares approximately 64% amino acid similarity with BACE2. Unlike BACE1, which is primarily expressed in neurons, BACE2 appears to be primarily expressed in the periphery, with highest expression in the colon, kidney, pancreas, prostate, stomach, and trachea, but minimal expression in the brain (Bennett et al. 2000). While both enzymes appear to cleave APP, the cleavage site appears to be slightly different between the 2 enzymes, with BACE2 cleaving APP closer to the site associated with α-secretase. Based on the relative expression of these 2 enzymes, along with the differential cleavage sites for APP, BACE1 appears to be the primary enzyme responsible for the production of Aβ. This is further supported by studies in mice with a homozygous BACE1 knockout, where production of Aβ and C99 is effectively abolished (Vasser 2004). The physiological role of BACE2 is less well studied than that of BACE1. Multiple BACE2 substrates have been reported, including pigment cell-specific melanocyte protein 17, which plays a crucial role in eumelanin synthesis and melanogenesis (Rochin et al. 2013), and transmembrane protein 27 (TMEM27), which regulates pancreatic beta cell mass and modulates glucose homeostasis (Esterházy et al. 2011). Selectively targeting BACE1 with LY3323795 may mitigate any potential risks associated with BACE2 inhibition.

3.1. Study Rationale

Eli Lilly and Company (Lilly) is currently developing LY3323795, a synthetic small molecule that selectively inhibits BACE1 enzyme over BACE2, for the treatment of AD.

The aim of this first-in-human study is to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single doses of LY3323795 in healthy subjects, and to identify doses for subsequent studies. The reduction of cerebrospinal fluid (CSF) Aβ concentrations following LY3323795 administration is thought to be the most important biomarker for this study. Accordingly, serial CSF collection will be employed in Part B of this study to assess changes in CSF Aβ concentrations across 3 dose levels. It is intended that these data can be used to aid in selecting doses for future studies.

CCI

3.2. Background

Results from preclinical *in vivo* studies have suggested that BACE2 inhibition causes cutaneous hypopigmentation. The hypothesis is that a BACE1-selective inhibitor should mitigate this hypopigmentation risk and other unknown risks of chronic BACE2 inhibition, while slowing down the progression of AD through a reduction in Aβ plaque formation.

In preclinical *in vitro* and *in vivo* studies, LY3323795 was shown to potently inhibit BACE1 activity with a 35-fold selectivity for BACE1 over BACE2, and did not produce hypopigmentation in a 6-week study in beagle dogs at a dose of 0.1 mg/kg. In nonclinical pharmacological studies in a transgenic mouse model of amyloid deposition, oral administration of 0.1 mg/kg and 1 mg/kg of LY3323795 resulted in a 38% and 67% decrease, respectively, in brain cortical Aβ after 3 hours. A robust reduction in Aβ CSF levels out to 72 hours was also observed in beagle dogs following oral administration of 0.2 mg/kg of LY3323795.

The toxicity of LY3323795 was characterized in good laboratory practice (GLP), repeat-dose studies of up to 1-month duration in rats and dogs and in single-dose safety pharmacology studies assessing cardiovascular, respiratory, and central nervous system (CNS) effects. Primary findings in these studies are summarized below, and additional details are included in the Investigator's Brochure (IB) for LY3323795 (Section 5.2.1, Nonclinical Safety Pharmacology and Toxicology).

- Overt toxicity in the 1-month toxicity studies occurred at the highest doses administered to dogs (200 mg/kg).
    - In dogs, excessive body weight loss was observed at 200 mg/kg, leading to a dosing holiday and dose reduction to 120 mg/kg. CNS activity was noted in 1 male dog at 200 mg/kg.

- At the 120-mg/kg dose level in dogs, increased liver weight was noted, while 2- to 4-fold increases in alanine aminotransferase (ALT) concentrations (as compared to baseline values) were noted at 30 mg/kg and 120 mg/kg. These changes were considered nonadverse.
- Dose-dependent QT corrected for heart rate (QTc) prolongation occurred following repeated administration in dogs of doses at and above 5 mg/kg; peak changes at 5 mg/kg and 120 mg/kg were +7 msec and +31 msec, respectively. No qualitative electrocardiogram (ECG) abnormalities were observed. Decreases in heart rate also occurred following repeated administration in dogs of doses at and above 5 mg/kg; peak changes at 5 mg/kg and 120 mg/kg were -15 bpm and -39 bpm, respectively.
- In a single-dose cardiovascular safety study in dogs, QTc prolongation was noted at doses of 5 mg/kg (≤+4 msec) and 30 mg/kg (≤+9 msec). At all dose levels, minor decreases in heart rate were observed; at the 30-mg/kg dose level, a 6-bpm reduction in heart rate was observed (maximally). Also at the 30-mg/kg dose, minimally decreased systolic pressure (-7 mmHg), mean arterial pressure (-5 mmHg), and dP/dt_{max} (-240 mmHg/sec) occurred during the first 6 hours postdose.
- In rats, minimal increases in autofluorescent granules in the retinal pigmented epithelium were noted at the 150-mg/kg dose level and were considered nonadverse.
- The no-observed-adverse-effect level (NOAEL) of LY3323795 was 120 mg/kg in dogs and 150 mg/kg in rats.

Itraconazole, an antifungal agent, will be administered in Part C of this study as it is known to be a potent inhibitor of CYP3A, and is commonly used in drug interaction evaluations. Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following oral administration. As a consequence of nonlinear PK, itraconazole accumulates in plasma during multiple dosing. Bioavailability is increased when itraconazole is administered with food. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. The primary metabolite of itraconazole is hydroxy-itraconazole. Additional information including possible side effects of itraconazole can be found in the product insert.

3.3. Benefit/Risk Assessment

Nonclinical safety information for LY3323795 adequately supports the transition from preclinical status to a clinical, single-dose study. On the basis of the nonclinical data, LY3323795 is not considered to be a high-risk compound. This protocol reflects the fact that LY3323795 has not been administered to humans previously, and to mitigate this risk, the study has been designed to be conducted in accordance with principles outlined in the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (EMEA 2007). Any identified risks are considered to be monitorable and

manageable at the anticipated dose range of 0.3 mg to 100 mg for LY3323795 in healthy subjects.

It is intended that sentinel dosing will be conducted at all dose levels in Part A to minimize risk to subjects (see Section 5.1.1 for details), in accordance with the clinical research unit's (CRU) procedures. Additionally, the PK of LY3323795 will be assessed at pre-specified time points during the study, to ensure that median exposures do not exceed the lowest NOAEL exposure in toxicology studies conducted under GLP (in male rats). In this study, there is no expected therapeutic benefit for the subjects.

The risks of CSF drainage via indwelling catheter are similar to those of lumbar puncture (LP) and are well known (Jhee and Zarotsky 2003). The most common side effect reported is headache. However, a vast majority of these headaches are mild to moderate in severity and respond to such first-line therapies as analgesia and hydration. Individuals with persistent headaches may respond to a single blood patch without sequelae. The rare persistence of headaches is thought to result from continued leakage of CSF from the area surrounding the needle insertion point. If a persistent severe headache occurs, a "blood patch" should be performed. This is done by injecting a small amount of the subject's blood into the region of the supposed leak to try to seal it. The blood patch procedure is effective in 95% of the cases for stopping the headache.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of LY3323795 is to be found in the IB. Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB.

4. Objectives and Endpoints

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

Table SCAA.1. Objectives and Endpoints

Objectives	Endpoints
Primary • To explore the safety and tolerability of single doses of LY3323795 in healthy subjects.	Incidence of treatment-emergent adverse events.
Secondary • To explore the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of single doses of LY3323795.	Maximum drug concentration (C_{max}) and the area under the concentration-versus-time curve (AUC) in plasma; and C_{max} and AUC in CSF for various time frames.
• To explore the plasma and CSF pharmacodynamics (PD) of single doses of LY3323795.	The measures for PD analysis will be the minimum $A\beta_{1-40}$ or $A\beta_{1-42}$ concentration observed following administration of study drug, expressed as the percentage change in concentration from baseline.
CCI	

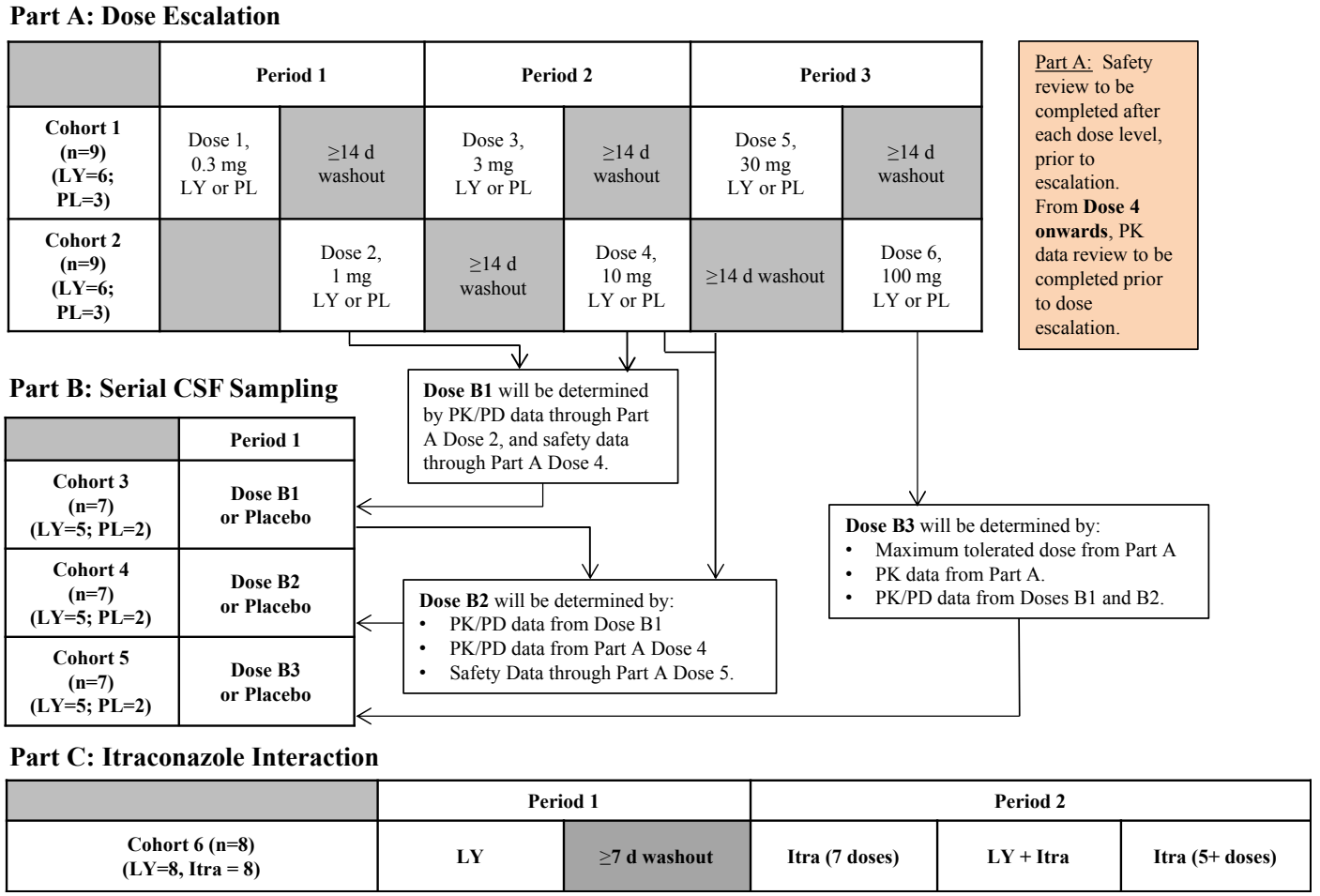
5. Study Design

5.1. Overall Design

Study I9F-MC-SCAA (SCAA) is a Phase 1 study in healthy subjects that will be conducted in 3 parts, as follows:

- Part A will be a subject- and investigator-blind, placebo-controlled, randomized, single-ascending dose, 3-period, dose-escalation study to evaluate safety, tolerability, and plasma PK/PD of LY3323795.
- Part B will be a subject- and investigator-blind, placebo-controlled, randomized, single-dose, single-period, lumbar catheter study with up to 3 cohorts/dose levels, to evaluate the central and plasma PK/PD of LY3323795.
- Part C will be an open-label, 2-period, fixed-sequence, single-cohort study to evaluate a potential CYP3A4 interaction when LY3323795 is coadministered with itraconazole.

Figure SCAA.1 illustrates the study design.



Abbreviations: CSF = cerebrospinal fluid; d = day; Itra = itraconazole; LY = LY3323795; PD = pharmacodynamics; PK = pharmacokinetics; PL = placebo; TBD = to be determined.

Figure SCAA.1. Illustration of study design for Protocol I9F-MC-SCAA.

5.1.1. Part A: Dose-Escalation Study

Part A is a dose-escalation study that will be conducted in 2 alternating cohorts (Cohorts 1 and 2), each consisting of approximately 9 subjects (6:3 subjects, LY3323795:placebo at each dose level) who will participate in 3 study periods (total of 6 dose levels in the 2 cohorts). The number of subjects intended to be enrolled is detailed in Section 5.2. The first 4 dose levels of LY3323795 are anticipated to be 0.3 mg, 1 mg, 3 mg, and 10 mg. Doses 5 and 6 are anticipated to be 30 and 100 mg, but will be confirmed following PK data reviews. See Section 5.1.1.1 for details of dose-escalation decisions.

Sentinel dosing will be used in this study. For all dose levels, LY3323795 and placebo will be administered first to a sentinel group of 2 subjects (1:1, LY3323795:placebo). These subjects will be followed for 24 hours postdose; if the dose is well tolerated, dosing of the remaining 7 subjects in the cohort may begin.

The proposed dose levels may be adjusted based on emerging safety and PK data (see Section 7.4.1).

Subjects will be admitted to the CRU on Day -1 (see Part A Schedule of Activities, Section 2) and will remain as inpatients for at least 48 hours after dosing on Day 1, after which they may be discharged at the discretion of the investigator. Subjects will then return for outpatient visits for up to 144 hours postdose (Day 7). The washout time between doses for a given subject will be at least 14 days.

PK and PD (plasma Aβ) data, as well as safety assessments, including clinical laboratory tests, ECGs, AEs, vital signs, ophthalmic examinations, and neurological surveys, will be collected at various time points pre- and postdosing with LY3323795/placebo, as described in Part A Schedule of Activities (Section 2). However, exact time points for PK/PD and safety assessments may be modified based on interim PK/PD results (see Section 5.1.1.1).

5.1.1.1. Dose Escalation and Interim Access to Data in Part A

The decision to dose escalate will be based on safety reviews conducted after each dose (and PK reviews from Dose 4 [planned to be 10 mg] onwards). Dose escalation will not occur until after a review of at least 3 days' safety data from the preceding dose level has been carried out, and the dose shown to be safe. Accordingly, safety data, including AEs, vital signs, neurological surveys, ophthalmic tests, ECGs, and clinical laboratory tests, will be assessed by both the investigator and the sponsor prior to each dose escalation. Any available PK data may be reviewed but PK data are not required for the initial dose-escalation decisions. However, from Dose 4 onwards, LY3323795 PK data will be reviewed before escalation to the next subsequent dose level to verify that the projected median exposure does not exceed one tenth the NOAEL exposure established in rats (i.e. median area under the concentration-versus-time curve (AUC) will not exceed 3,450 ng•hour/mL and median C_{max} will not exceed 214 ng/mL) (see Section 7.4.1). PK samples up to 96 hours postdose will be required to conduct the PK data reviews. The 96-hour PK sampling period may be adjusted based on emerging PK data. Plasma Aβ data may also be reviewed to assess the PD profile. Time points for PK and PD sampling and required safety assessments may be modified based on emerging PK and safety results.

In addition to the reviews of PK data required after Dose 4 for the purposes of dose escalation, interim access to PK and PD (including plasma Aβ) data will occur after the anticipated 1-mg dose (Dose 2) and 10-mg dose (Dose 4) of Part A. Data from this interim access to data (IAD) reviews, as well as results of the PK IADs following Doses 4, 5, and 6, will be used at different points to select doses in Part B (see Figure SCAA.1).

5.1.2. Part B: CSF Sampling Study

Part B is a single-dose, 3-cohort (5:2 subjects, LY3323795:placebo per cohort), single-period, lumbar catheter study to evaluate central PK/PD of LY3323795. See Section 5.2 for planned enrollment numbers. Part B may be conducted in parallel to Part A of the study, as long as the conditions have been met for each dose decision in Part B (see Section 5.1.2.1).

Subjects will be admitted to the CRU on Day -1 and will remain as inpatients until at least 24 hours after the CSF catheter is removed, after which they may be discharged at the discretion of the investigator. CSF will be collected from an indwelling catheter using a closed system. The catheter will be inserted approximately 4 hours prior to study drug administration. CSF samples will be taken during this "stabilization" period approximately every 2 hours, as feasible. If some samples during the stabilization period are not collected for any reason, this will not be considered a protocol violation.

CSF PK and PD data will be collected by frequent sampling for 4 hours predose and up to 36 hours postdose (as described in the Part B Schedule of Activities, Section 2). The minus 4-hour CSF sample will be collected for safety (red blood cell count, glucose, and protein, to be tested at the local laboratory) and PD biomarkers (which will be tested centrally). The minus 2-hour sample will be collected for PD biomarkers only; the 0-hour and subsequent postdose samples will be collected for LY3323795 concentration and PD biomarkers. An additional safety CSF sample will be collected at the removal of the catheter. CSF PD samples will be split and stored CCI

Plasma PK and PD (plasma Aβ) data will be collected up to 144 hours postdose (as described in the Part B Schedule of Activities, Section 2).

Safety assessments including clinical laboratory tests, ECGs, AEs, vital signs, ophthalmic examinations, and neurological surveys will be collected (as described in the Part B Schedule of Activities, Section 2).

Two IAD reviews are planned in Part B: the first after the completion of dosing for Cohort 3 and the second after dosing for Cohort 4. All CSF PK/PD data will be included in these reviews, as well as plasma PK data through Day 4. See Section 5.1.2.1 for details.

5.1.2.1. Dose Selection and Pharmacokinetic Analysis in Part B

Any dose selected for administration in Part B will be less than or equal to doses previously administered and found to be well tolerated in Part A. Emerging PK data (and PD data, as available) from the first 2 doses in Part A, and safety data through Dose 4 of Part A, will determine Dose B1 for Cohort 3.

Cohort 3

Cohort 3 is intended to gauge the degree to which LY3323795 crosses the blood-brain barrier. A 3-mg dose is intended to be administered in Cohort 3, if supported by Part A data. Modeling of nonclinical data suggests that this dose would result in CSF LY3323795 concentrations exceeding the lower limit of quantification (approximately 0.1 ng/mL) for at least 12 hours. This dose may be modified if Part A data suggest that the plasma exposure of LY3323795 is meaningfully different from the nonclinical predictions.

Cohorts 4 and 5

The dose for Cohort 4 will be selected based on data from Cohort 3, specifically the plasma and CSF PK/PD data, alongside data from Part A. The dose for Cohort 5 will also depend on these data from Cohort 3 and Part A, in addition to data from Cohort 4 (see Figure SCAA.1). Doses estimated to produce substantial reductions in CSF Aβ concentrations will be selected, with the goal that at least 1 of these doses will produce reductions in CSF Aβ of >50% (relative to baseline) for at least 4 hours. In no case will the doses selected exceed the maximum tolerated dose (MTD) found in Part A.

5.1.3. Part C: Itraconazole Interaction Study

Part C is an open-label, fixed-sequence, single-cohort study in 8 healthy subjects to evaluate potential CYP3A4 interaction when LY3323795 is coadministered with itraconazole. Part C is divided into 2 periods.

In Period 1, subjects will be administered a dose of LY3323795 (intended to be 3 mg); the dose will be at or below a level previously administered safely in Part A. There will be a washout period of at least 7 days following this dose, with PK assessed up to 144 hours postdose.

In Period 2, subjects will be dosed with itraconazole for 6 consecutive days prior to coadministration with LY3323795. On Day 10, subjects will receive itraconazole 200 mg twice, approximately 12 hours apart. On Day 11, subjects will receive a morning dose of itraconazole 200 mg prior to discharge. On Days 12 to 14, subjects will attend the CRU on an outpatient basis and will receive doses of itraconazole 200 mg once daily in the morning. On Day 15, subjects will be re-admitted to the CRU and will receive a single dose of itraconazole 200 mg. On Day 16, subjects will be administered 200-mg itraconazole 1 hour prior to receiving LY3323795 (using the same LY3323795 dose administered in Period 1). The timing may be adjusted based on available PK results from Part A. All subjects in the cohort will receive LY3323795; there will be no placebo. From Day 17 onwards, it is intended that subjects will receive daily doses of 200-mg itraconazole alone for 5 days; based on emerging PK data, this period of daily itraconazole dosing may be extended to ensure that CYP3A inhibition is maintained throughout the elimination of LY3323795. Based on the projected half-life of LY3323795 (23 hours), 168 hours of sampling allows more than 3 half-lives of coverage in the event that clearance doubles; this would be sufficient to characterize a doubling in clearance.

Samples will be collected to assess itraconazole PK on the day of dosing with LY3323795 (see Part C Schedule of Activities [Section 2]). Exact time points for PK/PD and safety assessments may be modified based on emerging PK/PD results.

5.2. Number of Participants

For Cohorts 1 and 2 in Part A, up to approximately 24 subjects may be enrolled so that approximately 18 subjects (9 subjects per cohort [6:3, LY3323795:placebo per dose level]) complete the study.

For Cohorts 3 to 5 in Part B, up to approximately 30 subjects may be enrolled so that approximately 21 subjects (7 subjects per cohort [5:2, LY3323795:placebo]) complete the study.

For Cohort 6 in Part C, up to 12 subjects may be enrolled so that approximately 8 subjects complete the study.

Subjects in 1 part of the study will not be allowed to participate in any other part of the study.

Subjects will be replaced as needed, rather than over-enrolled. See Section 10 for details on the replacement of subjects.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This study will be conducted to determine the safety and tolerability of LY3323795 in healthy subjects.

The crossover design in Part A of this study will allow each subject to act as their own control and allow for an assessment of within- and between-subject variability in evaluating tolerability and PK of different doses of LY3323795. The placebo-controlled, dose-escalation strategy allows safety and PK/PD data to be obtained with a large degree of within-subject control data.

The collection times for PK samples and washout period between doses are based on the predicted PK and PD of LY3323795 from nonclinical studies. Based on the estimated half-life of approximately 23 hours, sample collection for up to 144 hours should be sufficient to fully assess the concentration-time profile, and a washout period of at least 14 days should be sufficient to ensure that there is no carryover between periods. Either or both may be revised based on reviews of preliminary PK data generated during the study.

It is intended that a range of 3 doses of LY3323795 be administered in Part B of the study based on the LY3323795 exposures and plasma PD response observed in Part A. The aim is to determine a dose level that produces a substantial reduction in CSF Aβ. The exact doses of LY3323795 administered in Part B will be determined after reviewing the emerging data from Part A, as well as available data from any previous doses carried out in Part B. However, doses in Part B will not exceed a dose that has been assessed in Part A as being safe and well tolerated.

To minimize confounding effects of the catheterization on Aβ concentrations, the indwelling catheter for CSF collection will be inserted approximately 4 hours prior to study drug administration to allow Aβ CSF measurements to stabilize. Previous CSF catheter studies have shown large variability in CSF Aβ in the first few hours of collection after catheterization (Ereshefsky et al. 2007).

In healthy subjects, CSF indwelling catheter studies conducted by Lilly have shown increases in CSF Aβ concentration over 24 to 40 hours of sampling (Lucey et al. 2015). In these CSF catheter studies, the initial 4-hour sampling interval following the catheter placement showed a 10% to 15% increase in Aβ concentration. Subjects receiving placebo following the catheter placement showed additional increases of 20% to 30% over a 36-hour CSF sampling period. Similar findings were shown by Bateman (2008). Therefore, placebo will also be included in Part B of this study. Previous studies have also shown that CSF Aβ concentrations slowly return to baseline following a treatment that disrupts Aβ synthesis; however, due to the large variability in CSF Aβ concentrations both within and between individuals, a long duration of sampling is required to fully characterize the PD time course.

An assessment of LY3323795 PK with concomitant itraconazole administration is planned in Part C. In vitro recombinant CYP isoform phenotyping studies indicate CYP3A4 is the only tested CYP isoform that metabolizes LY3323795. In vitro metabolism studies with human hepatocytes suggest that CYP-mediated metabolism accounts for approximately 70% of the overall metabolism in hepatocytes. Taken together, these data result in a predicted LY3323795 AUC increase of approximately 4-fold when LY3323795 is coadministered with the strong CYP3A inhibitor itraconazole. Accordingly, coadministration with itraconazole will help determine the clinical relevance of CYP3A inhibition on LY3323795 clearance. The dosing regimen for itraconazole was optimized using a physiologically based PK model with the goal of reaching steady-state concentrations as rapidly as possible (Ke et al. 2014). The use of the oral solution formulation of itraconazole is specified as it has higher bioavailability and less variability in absorption than solid dosage formulations.

5.5. Justification for Dose

This study will evaluate plasma and CSF PK/PD of LY3323795 in an attempt to define a pharmaceutically relevant dose range for future studies. The initial proposed dose is 0.3 mg, which is anticipated to provide a maximum drug concentration (C_{max}) of 0.625 ng/mL (90% confidence interval [CI]: 0.36, 1.11), and an area under the curve from time 0 extrapolated to infinity ($AUC_{[0-\infty]}$) of 24.5 ng•hour/mL (90% CI: 9.09, 65.9). This dose (by body surface area) is substantially lower than the dose levels identified as the NOAELs in 1-month GLP toxicology studies and is therefore appropriate for use (Table SCAA.2). The doses (based on body surface area) identified as the NOAELs in rats and dogs are 4,500- and 12,000-fold greater than the starting dose in humans. Margins calculated based on AUC exposure at the NOAELs relative to predicted human exposures at 0.3 mg are ≥1,408-fold (due to a gender difference in exposure) in rats and 2,214-fold higher in dogs.

In a cardiovascular safety pharmacology study in dogs, no changes in QTc prolongation occurred at a dose of 0.5 mg/kg; this dose (based on body surface area) is 63-fold higher than the proposed starting dose in Study SCAA of 0.3 mg.

Part A

The doses studied in Part A will be selected to ensure that the exposures tested are anticipated to produce significant CSF Aβ reductions at steady state. Based on nonclinical modeling, a plasma AUC of 1,800 ng•hour/mL (90% CI: 1240, 2600) is anticipated to produce a 90% time-averaged reduction in CSF Aβ at steady state. Based on allometric scaling of clearance, it is anticipated that a dose of 22 mg (90% CI: 7.5, 63) will achieve this exposure. Accordingly, it is intended that doses of at least 100 mg will be explored to ensure that the full range of pharmacologically relevant exposures is tested in Study SCAA.

The upper dose in SCAA is projected to be 100 mg. However, assessments of PK at pre-specified times are planned during the dose escalation, and the anticipated doses may be modified to ensure that median exposures do not exceed one tenth of the rat NOAEL determined in toxicology studies (i.e. median AUC will not exceed 3,450 ng•hour/mL and median C_{max} will not exceed 214 ng/mL).

Part B

Part B is an assessment of CSF PK/PD, with CSF collected over 36 hours following dose administration using a lumbar catheter. The initial dose in Part B is anticipated to be 3 mg, which is anticipated to produce measurable CSF LY3323795 concentrations. As described in Section 5.1.2.1, this dose may be increased if necessary, as long as the same dose level was well tolerated in Part A, to ensure that quantifiable LY3323795 concentrations are obtained. The maximum dose administered in Part B is intended to be the MTD in Part A, although a lower dose may be selected if indicated by emerging PK/PD data from either Part A or Part B.

Part C

Part C will assess the interaction of LY3323795 with itraconazole, a CYP3A inhibitor. The dose of LY3323795 administered in this part of the study will be the same as, or lower than, a dose that was safely administered in Part A. The dose will be no greater than one-tenth of the MTD administered in Part A. The planned itraconazole dose (200 mg) has been safely administered in previous drug interaction studies of this design.

Table SCAA.2. Margin of Safety for Oral Administration of LY3323795 Based on Administered Dose and Predicted Exposure

	Dose (mg/kg)	Dose (mg/m^2)	Dose Multiple[a]	AUC (µg•hour/mL) or C_{max} (ng/mL)	Exposure Multiple[a]
Human[b] (0.3 mg)		0.2	-	0.0245 or 0.627	-
Rat NOAEL[c]	150	900	4500	M=34.5 or 2140 F=91.5 or 4950	M=1408 F=3735
Dog NOAEL[d]	120	2400	12,000	51.8 or 3095	2114
QTc LOEL (5 mg/kg) Day 1 TK	NA	NA	NA	C_{max}=1018 C_{max} multiple=1623	-
Human[b] (100 mg)		52.9	-	8.18 or 210	-
Rat NOAEL[c]	150	900	17	M=34.5 or 2140 F=91.5 or 4950	M=4 F=11
Dog NOAEL[d]	120	2400	45	51.8 or 3095	6
QTc LOEL (5 mg/kg) Day 1 TK	NA	NA	NA	C_{max}=1018 C_{max} multiple=5	

Abbreviations: AUC = area under the plasma concentration-versus-time curve; C_{max} = maximum drug concentration; F = female; LOEL = lowest-observed-effect-level; M = male; NA = not applicable; NOAEL = no-observed-adverse-effect level; QTc = QT corrected for heart rate; TK = toxicokinetics.

a Dose multiple is the dose in animals/dose in humans based on mg/m^2. Exposure multiple is the calculated AUC in animals/projected AUC in humans (Projected human exposures located in Table 5.7 of the IB).

b Day 28 AUC from the repeat-dose toxicity study in either rats or dogs (as indicated), unless otherwise specified.

c NOAEL determined in a 1-month repeat-dose toxicity study in rats (Report 8339313).

d NOAEL determined in a 1-month repeat-dose toxicity study in dogs (Report 8339298).

6. Study Population

Eligibility of subjects for study enrollment will be based on the results of a screening medical history, physical examination, vital signs, clinical laboratory tests, ophthalmic examination, and ECGs. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

A generic screening informed consent may be used for screening procedures. Screening may occur up to 28 days prior to enrollment. 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, is 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] male subjects must agree to use an effective method of birth control during the study and for 3 months following the last dose of the investigational product. At least 1 effective method of contraception will be used (eg, condoms with spermicide, male sterilization, oral contraceptive pill, intrauterine device, etc.). The subject may choose to use a barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method. Thus, each barrier method must include use of a spermicide (ie, condom with spermicide, diaphragm with spermicide, female condom with spermicide). However, the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

[1b] female subjects are of nonchildbearing potential if they have undergone surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation) or are postmenopausal (defined as women aged at least 45 years with an intact uterus, who have not taken hormones or oral contraceptives for >1 year), and have either:

[i] spontaneous amenorrhea for 6 to 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications that induced the amenorrhea (eg, oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy);

[ii] a follicle-stimulating hormone level >40 mIU/mL

[2] are aged at least 20 years at the time of screening

[3] have a body mass index (BMI) between 18.0 kg/m^2 and 32.0 kg/m^2, inclusive

[4] have clinical laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations (with the exception of liver tests, which must be below the upper limit of normal [ULN]) 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 and research unit policies

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

6.2. Exclusion Criteria

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

[8] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, or biological or legal guardian, child, or sibling

[9] are Lilly employees or employees of Parexel

[10] 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

[11] 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

[12] have previously completed or withdrawn from this study or any other study investigating LY3323795, and have previously received the investigational product

[13] have known allergies to LY3323795, related compounds, or any components of the formulation, itraconazole (if the subject is assigned to Part C), or history of significant atopy

[14] have a QTc (using Bazett's formula) interval value of >450 msec (males) or >470 msec (females) or any abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[15] have clinically significant abnormal blood pressure as determined by the investigator

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

[17] have known or ongoing psychiatric disorders, or active neuropsychiatric disease deemed clinically significant in the opinion of the investigator

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

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

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

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

[22] are women who are lactating

[23] have used or intend to use over-the-counter or prescription medication (including herbal medications) within 14 days prior to dosing or during the study, with the exception of vitamins and mineral supplements (not providing >100% of the recommended dietary allowance [RDA]), occasional paracetamol/acetaminophen up to 2-g dose in a 24-hour period, and/or hormone replacement therapy or thyroid replacement therapy. If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the sponsor

[24] have donated blood >500 mL within the last month

[25] have an average weekly alcohol intake that exceeds 3 units per day or 21 units per week (males up to age 65 years) and 14 units per week (females, and males older than 65 years), or are unwilling to stop alcohol consumption 48 hours prior to dosing until the completion of each study period (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)

[26] have an increased risk of seizures as evidenced by a history of head trauma with loss of consciousness within the last 5 years or ≥1 seizure (except childhood febrile seizure); have prior electroencephalogram with epileptiform activity; or surgery to the cerebral cortex

[27] have a history of clinically significant stroke that is deemed to be a risk to subject participation in the study, in the opinion of the investigator

[28] have a history of, or current, significant ophthalmic disease in the opinion of the investigator

[29] are unwilling or unable to refrain from eating any food or drinking any beverage containing grapefruit or grapefruit juice (or other restricted foods as listed in Section 6.3.1) for at least 2 weeks prior to first dose until completion of the study

[30] consume more than 10 cigarettes per day or unable/unwilling to abide by CRU smoking restrictions before and during admissions

[31] in the opinion of the investigator and/or sponsor, are unsuitable for inclusion in the study

In addition, for Part B only:

[32] show clinically significant abnormalities in lumbar spine previously known or determined by screening lumbar x-ray (if conducted) that are considered incompatible with LP by the investigator and/or the person conducting the LP (if not the investigator)

[33] have a history of clinically significant back pain, back pathology, and/or back injury (eg, degenerative disease, spinal deformity, or spinal surgery) that may predispose to complications or technical difficulty with LP

[34] have evidence or history of significant active bleeding or coagulation disorder or have taken nonsteroidal anti-inflammatory drugs or other drugs that affect coagulation or platelet function within 14 days prior to lumbar catheter insertion

[35] have an allergy to lidocaine (Xylocaine®) or its derivatives

[36] have medical or surgical conditions in which LP/lumbar catheterization is contraindicated

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

Fasting – For all parts of the study, subjects will be required to fast overnight (at least 8 hours) prior to each dosing day and for at least 4 hours after LY3323795 or placebo dosing, with the exception of water that will be freely available before and after dosing. However, no water is allowed 1 hour prior to ECG measurement.

For Part C, there will be no fasting required before or after dosing itraconazole alone. However, for coadministration of itraconazole with LY3323795, subjects will be required to fast overnight (at least 8 hours) prior to and for at least 4 hours after LY3323795 dosing.

Grapefruit – Subjects should refrain from eating any food or drinking any beverage containing grapefruit, pomelo, star fruit, Seville oranges, or juice from any of these fruits, from 2 weeks prior to dosing until completion of the study.

Hydration – Subjects should be adequately hydrated throughout the study. Therefore, subjects should be encouraged to drink several glasses of water each day.

6.3.2. Caffeine, Alcohol, and Tobacco

Caffeine – Consumption of caffeine- and xanthine-containing products is allowed, provided that the subject's consumption has been consistent for the last 30 days, and will remain consistent throughout the duration of the study.

Alcohol – Subjects will not be permitted to consume alcohol from 48 hours prior to CRU admissions until after the last PK sample is collected for each study period. During outpatient periods, male subjects should be advised to limit alcohol consumption to no more than 21 units per week and female subjects to no more than 14 units per week, and all subjects should be advised to limit alcohol consumption to no more than 3 units in a day.

Tobacco – Subjects will not be permitted to smoke from 24 hours before visiting the CRU until discharge from the CRU.

6.3.3. Activity/Other Requirements

Subjects should avoid strenuous physical activity 48 hours prior to CRU visit and until final discharge from the study.

Subjects should avoid exposure to the sun, and not use sun lamps or tanning beds throughout the duration of the study. High-factor sunscreen should be used if prolonged sun exposure is unavoidable.

Blood or plasma donations are not permitted while participating in the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) will not be allowed to rescreen.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of LY3323795 and placebo over a planned dose range of 0.3 mg to 100 mg in Parts A and B, and administration of LY3323795 alone and with itraconazole in Part C. Table SCAA.3 shows the treatment regimens.

After an overnight fast (see Section 6.3.1), capsules of LY3323795 or placebo will be administered orally with approximately 240 mL of room-temperature water in the morning of each dosing day.

For Part A, subjects should remain upright (standing or sitting) for at least 4 hours after dosing, with the exception of any requirements for protocol procedures (eg, supine for ECGs). For Part B, subjects will be encouraged to remain supine for the entire lumbar catheterization period.

In Part C, itraconazole will be administered as an oral solution with extra water if subjects prefer. No fast is required before or after dosing with itraconazole alone.

To ensure blinding is maintained in each cohort in Parts A and B, subjects assigned to LY3323795 and those assigned to placebo will receive the same number of capsules. In Part A, the number of capsules between periods may vary based on dose-escalation decisions, but within a period, all subjects will receive the same number of capsules.

Table SCAA.3. Treatments Administered

Treatment Name	LY3323795	Placebo	Itraconazole
Dosage Formulation	0.3-, 1-, and 10-mg capsules	Capsules to match	10 mg/mL solution
Planned Dosage Levels	0.3, 1, 3, 10, 30, and 100 mg	-	200 mg
Route of Administration	Oral	Oral	Oral

The investigator's designee is responsible for:

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

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. Subjects 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. All clinical trial materials provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the investigational products will be fully documented and verified by a second person. Detailed records of the amounts of the investigational product received, dispensed, and remaining at the end of the study will be maintained.

7.1.1. Packaging and Labeling

Clinical trial materials will be labeled according to the country's regulatory requirements. Each capsule of LY3323795 will be size 2, blue in color and will contain 0.3 mg, 1 mg, or 10 mg of active ingredient. Placebo capsules will match LY3323795 capsules in appearance. LY3323795 and matching placebo capsules will be supplied to the investigator by Lilly for dispensing by unblinded pharmacy staff.

CCI [redacted]

Clinical trial materials will be manufactured in accordance with good manufacturing practice. All drug supplies will be labeled according to applicable local regulatory requirements.

7.2. Method of Treatment Assignment

Randomization tables for allocation of LY3323795 and placebo will be prepared by the Lilly statistician.

7.2.1. Selection and Timing of Doses

Doses of LY3323795 will be administered at approximately the same time on each day. The actual time of all dose administrations will be recorded in the subject's case report form (CRF). For LY3323795 or placebo dosing, the dosing time is defined as the time when the first capsule is swallowed.

7.3. Blinding

This study will be subject- and investigator-blinded except in Part C (itraconazole interaction), which will be open-label. 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. The randomization tables will be provided to the study site pharmacists or pharmacy staff involved in dose preparation.

As dosing occurs in the study, the pharmacy staff will document dosing at the site using an accountability log. Individuals involved with study drug preparation will not be involved in any clinical aspects of the study, including study drug administration and AE assessments. The sponsor team will not be blinded and may see the randomization tables and/or treatment table before the end of the study but this will be kept to a minimum. While the study blind is in effect,

individuals with access to the randomization tables and/or treatment table will not share the identifying information with investigative site staff involved with direct subject care or safety assessments. An exception is if sharing such information is required for emergency unblinding.

AEs and clinical safety abnormalities will be interpreted with the subject- and investigator-blind intact, on the assumption that active study drug was administered. If the AE is a clinically significant event (CSE), the investigator should judge whether the CSE is related to study drug administration while remaining blinded. A CSE will be defined as a moderate-to-severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the subject.

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. Subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly clinical pharmacologist or clinical research physician (CRP) prior to unblinding a study subject's treatment assignment unless this could delay emergency treatment of the subject. If a study subject's treatment assignment is unblinded, Lilly must be notified immediately.

If a subject's study treatment assignment is unblinded, the subject must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist or CRP for the study participant to continue in the study.

Upon completion of the study, all emergency codes must be returned to Lilly or its designee.

A detailed blinding/unblinding plan will be issued to the study site.

7.4. Dose Modification

7.4.1. Dose Decision/Escalation

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

Safety data will be the primary criteria for the dose escalation. As described in Sections 5.1.1.1 and 5.1.2.1, certain dose-escalation decisions will also be based on PK (C_{max}, AUC, and clearance) data where available. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly clinical pharmacologist/CRP/study team.

Safety data, in particular AEs, SAEs, and adverse laboratory abnormalities, will be independently assessed by the investigator, and will be considered related to the investigational product unless there is clear evidence that the event is not related. See Section 10.3.1 for details.

After review of these data, an agreement on the appropriate dose escalation will be made by the investigator and sponsor for the next cohort. The magnitude of the dose escalation may be reduced following data review, but subsequent escalations cannot be increased by more than 3.3 times the original dose (a half-log increment).

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

1) a single subject experiences an SAE that is considered related to LY3323795 administration;
2) ≥2 subjects at the same dose level experience moderate or severe AEs that impair normal activities, and are considered related to LY3323795, but do not meet the CSE criteria;
3) ≥2 subjects at the same dose level experience similar CSEs considered related to LY3323795;
4) ≥2 subjects at the same dose level have an ophthalmic finding considered related to LY3323795;
5) ≥2 subjects, at any dose of LY3323795, have a QTc reading (mean of 3) that is >500 msec or an increase of >60 msec above the mean QTc control value for at least 2 consecutive time points. The mean QTc control value (mean of 3) is defined as the average of the Day 1, predose ECGs of the corresponding period.

Dosing may continue, if deemed appropriate by the investigator and sponsor, at doses lower than those that resulted in the dose escalation being stopped.

In the event of an SAE that is related to study drug, precautionary inpatient observation will be implemented, and dosing may be suspended. Dosing of a subject may resume only after the investigator and sponsor agree that it is appropriate to continue.

7.5. Preparation/Handling/Storage/Accountability

Only participants enrolled in the study may receive investigational product 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 accountable for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

Prohibited medications are summarized in the inclusion and exclusion criteria (Section 6). Use of vitamins/mineral supplements (not providing more than 100% of the RDA), thyroid hormone replacement, and/or estrogen hormone replacement is allowed. Occasional use of paracetamol/acetaminophen up to 2 g in a 24-period without prior consultation with a Lilly clinical pharmacologist will be allowed. Drugs that are known substrates, inducers, or inhibitors of CYP3A are specifically excluded. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

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

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Subjects who discontinue the investigational product 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, a discussion must occur between the Lilly clinical pharmacologist and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

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

9. Study Assessments and Procedures

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

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

Appendix 3 details the study governance, regulatory and ethical considerations.

Appendix 4 details the hepatic monitoring tests for treatment-emergent abnormalities.

Appendix 5 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 investigational product or the study, or that caused the subject to discontinue the investigational product 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 is signed, study site personnel will record, via CRF, 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 the disease, concomitant treatment, or pathologies.

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

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 investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 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 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.

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 Code of Federal Regulations 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 investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3323795 is considered any dose higher than the dose assigned through randomization. General supportive medical management will be provided at the investigator's discretion.

Refer to the IB for LY3323795 for information on the clinical consequences of an overdose.

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).

9.4.2. Vital Signs

Vital signs will comprise blood pressure, pulse rate, and body temperature.

For each subject, vital sign measurements should be performed according to the Schedule of Activities (Section 2). The timing of vital sign collections may be adjusted after a review of the PK data.

At screening, blood pressure and pulse rate will be obtained after subjects have been sitting for at least 5 minutes.

For vital signs after study entry, subjects will lie down for at least 5 minutes and undergo supine blood pressure and pulse rate measurements. For Parts A and C only, subjects will then sit for approximately 2 minutes and stand for approximately 3 minutes and undergo standing blood pressure and pulse rate measurements. If subjects are unable to stand, only supine vital signs will be recorded. If subjects are unable to stand or sit, omission of the standing or sitting vital signs will not be considered a protocol violation.

Subjects who are unable to sit or stand for approximately 3 minutes because of adverse symptoms should be placed immediately in a supine position with their legs elevated above the level of their chest. An unscheduled measurement of blood pressure and pulse rate should be obtained as soon as possible without causing delay in the resumption of recumbency.

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

9.4.3. Electrocardiograms

For each subject, 12-lead ECGs will be obtained according to the Schedule of Activities (Section 2). ECGs must be recorded before collecting any blood for safety or PK tests. Subjects must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high-quality records. All ECGs recorded should be stored at the investigational site. The timing of the ECG collections may be adjusted after a review of the PK data.

At screening and final discharge/early discontinuation, a single ECG will be obtained and does not need to be transmitted to the ECG vendor. The screening ECG will be interpreted by the investigator or qualified designee at the site to determine whether the subject meets entry criteria.

For the predose ECG measurement of each period in Parts A and C (but not Part B), 3 sets of triplicate ECGs will be obtained approximately 10 minutes apart. For Part B, predose ECG measurements will be single.

For Parts A and C, after study entry, ECGs will be obtained in triplicate at approximately 1-minute intervals at each ECG time point. At least 1 ECG in each triplicate set will be interpreted by the investigator or qualified designee at the site as soon as possible after the time of ECG collection, and ideally while the subject is still present, for immediate subject management.

For Part B, at each time point, a single ECG will be collected and subsequently interpreted by the investigator or qualified designee in the same way as above.

If at any time a clinically significant increase in the QTc interval is present or the ECG shows a clinically important change, then the investigator should assess if the subject can continue in the study. Any clinically significant findings that result in a diagnosis should be recorded on the CRF. Any clinically significant findings that do not result in a diagnosis should be commented on and appropriately documented. If a clinically significant change is seen, additional ECGs may be obtained at appropriate intervals until readings return to within normal levels. In addition, a 12-lead Holter recording may be initiated in an individual subject with a clinically significant ECG abnormality. In these cases, digital recordings of continuous ECG recordings will be transferred to a central ECG laboratory designated by Lilly. The ECG laboratory will perform quality control checks for the time points of interest (eg, acquisition quality for ability to measure/interpret demographics and study details). The ECG laboratory will then store the recording and a cardiologist at the central ECG laboratory may conduct a full over-read on extracted ECG time points of interest. No reports will be issued from the central ECG laboratory back to the sites for any ECGs. All data from the ECG over-reads and measured intervals will be placed in a Lilly database for analytical and study report purposes. Any new clinically relevant finding should be reported as an AE.

The ECGs will subsequently be electronically transmitted to the centralized ECG vendor designated by Lilly for storage. The automated ECG parameters will be used for data analysis

and report-writing purposes. ECGs may be overread by a medically qualified professional (eg, cardiologist) to assess clinically significant findings on the automated ECG readings, should these occur.

9.4.4. Other Tests

9.4.4.1. Neurological Survey

A directed neurological survey will be performed by a physician, nurse practitioner, or physician's assistant according to the Schedule of Activities (Section 2). If abnormalities are noted, additional examinations should be performed at daily intervals until the subject's test scores have returned to baseline levels. The examiner should be familiar with the subject's baseline survey and may examine the subject prior to dosing as needed. Mandated elements of the survey include inspection for tremor, extraocular movements, brachial and patellar deep tendon reflexes, finger-nose pointing, and Romberg sign.

Table SCAA.4 presents how the findings of the neurological survey will be scored. For subjects with mild (1+) tremor or nystagmus at baseline, increases in these findings should not be scored at a higher level unless the examiner judges them to be significantly exacerbated compared with baseline. Other elements of the physical examination may be included on an optional or symptom-directed basis.

Table SCAA.4. Scoring of Neurological Surveys

Score	0	1	2	3	4
Tremor, nonspecific location	Absent	Visible with limb extension and/or careful inspection	Visible without limb extension	Interferes with motor function	
Nystagmus, nonspecific location	Absent	1-3 beats on lateral gaze	>3 beats on lateral gaze	Present on forward gaze	
Reflex test, nonspecific location	Absent	Trace	Normal	Increased	Clonic
Finger-nose	Normal	Abnormal			
Romberg sign	Absent	Present			

9.4.4.2. Ophthalmic Examinations

Ophthalmic assessments will be performed or supervised by a board-certified ophthalmologist or optometrist as specified in the Schedule of Activities (see Section 2) and/or as clinically indicated.

Eye testing will include distance and near visual acuity (best-corrected or pinhole using the Snellen chart and Near Reading Card), Humphrey visual field testing (using the 10-2 protocol with a red-on-white target), and ophthalmoscopy.

Only subjects who pass all other inclusion/exclusion criteria at screening should be sent for these eye examinations. Results from subsequent eye tests during the study will be compared with the screening results to track any changes in subjects' vision.

9.4.5. Safety Monitoring

The Lilly clinical pharmacologist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist 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
- product complaints

9.4.5.1. Hepatic Safety Monitoring

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

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

9.5. Pharmacokinetics

In Parts A and B, at the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the plasma concentrations of LY3323795. A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. For subjects participating in the itraconazole interaction (Part C), on the day of LY3323795 and itraconazole coadministration (Day 16), venous blood samples will be collected for measurement of itraconazole and its metabolites at the times specified in the Schedule of Activities for Part C. LY3323795 PK samples will also be drawn on Day 1 and on the day of coadministration (Day 16). 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.

For Part B, CSF samples will be collected at the times specified in the applicable Schedule of Activities (Section 2) to determine the CSF LY3323795 and PD biomarker concentrations.

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

In Part A, urine samples will be collected for the characterization of renal clearance. Total urine output for 48 hours post investigational product administration will be collected, pooled, and

refrigerated. The final urine sample will be collected at a time that coincides with a PK sample. At the end of the collection period, the total urine volume will be recorded. Urine samples will be used to determine creatinine, quantification of LY3323795, and possible exploratory metabolite identification.

At the visits and times specified in the Schedule of Activities, venous blood samples will be collected to determine serum creatinine measurements.

See Appendix 5 for blood and CSF sampling details.

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 LY3323795 in plasma and in CSF will be assayed using validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) methods. Plasma concentrations of itraconazole will be assayed using LC/MS/MS methods. If appropriate, plasma concentrations of itraconazole metabolites may also be quantified. Analyses of samples collected from subjects who are given placebo are not planned.

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 (eg, metabolism, protein binding).

9.6. Pharmacodynamics

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

A maximum of 5 additional plasma samples per subject may be drawn during the study at the discretion of the investigator or sponsor. These additional samples may be drawn to measure LY3323795 or Aβ concentrations.

Plasma concentrations of $A\beta_{1-40}$ and $A\beta_{1-42}$ and CSF concentrations of $A\beta_{1-40}$, $A\beta_{1-42}$, CCI [redacted] will be determined using validated immunoassay methods.

CCI [redacted].

Plasma and CSF samples collected for PD measurements will have aliquots stored for future exploratory work. The sample(s) will be identified by the subject number (coded) and stored for up to a maximum of 15 years after the last subject visit for the study at a facility selected by the sponsor. Any sample remaining after this period will be destroyed. Research will be limited to investigation of the safety and disposition of LY3323795, PD biomarkers relevant to neurological disease, the mechanism of action of LY3323795, and/or identification of metabolites of LY3323795.

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 LY3323795. 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 ERBs/institutional review boards [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 LY3323795 or after LY3323795 is commercially available.

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

9.8. Biomarkers

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

Plasma and CSF samples for nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, variable response to LY3323795, pathways associated with AD and/or other neurological diseases, mechanism of action of LY3323795, and/or research method, or for validating diagnostic and research analytes, tools, or assay(s) related to AD and/or other neurological diseases.

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 ERBs/IRBs impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to

regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3323795 or after LY3323795 is commercially available.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The sample size of 9 in each cohort of Part A is customary for Phase 1 studies evaluating safety, PK, and/or PD parameters, and is not based on statistical mean estimation.

For Part B, given the CSF Aβ variability observed in prior studies that measured CSF Aβ, the sample size of 5 subjects per LY3323795 dose and 2 subjects per placebo in a parallel cohort, pooled placebo design is sufficient to detect a mean Aβ reduction of approximately 21% or more from baseline. Assuming a standard deviation of 22% for the CSF $A\beta_{1-40}$, a sample size of 5 subjects per dose would provide approximately 90% coverage probability that the half-width of the 80% CI for the mean of percentage change from baseline of CSF $A\beta_{1-40}$ would be within 21%. For example, if the estimate of the percentage change from baseline CSF $A\beta_{1-40}$ at nadir concentration (C_{nadir}) is 50%, then the confidence limit for the percentage change from baseline would be (29%, 71%).

For Part C, assuming a within-subject variability of 25% for the PK parameter (AUC or C_{max}) of LY3323795, a sample size of 8 subjects would provide approximately 90% coverage probability that the half-width of the 90% CI for the geometric mean ratio of LY3323795 with itraconazole, compared with LY3323795 alone, would be within 0.3 in log scale, or 1.35 in natural scale. For example, if the estimate of the ratio of LY3323795 with itraconazole over LY3323795 alone is 1.2, then the confidence limit would be (88%, 162%).

Subjects who drop out may be replaced at the discretion of the sponsor and investigator to achieve protocol-required completers. In Part A, a replacement subject's treatment assignment will follow that of the subject being replaced but may not require completion of all study periods. In Part B, a replacement subject's treatment assignment will follow that of the subject being replaced. In Part C, all subjects, and any replacements, will be on the same treatment assignment.

Subjects who are randomized but not administered treatment may be replaced to ensure that a sufficient number of subjects complete the study, in accordance with the enrollment numbers given in Section 5.2.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

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, race, weight, BMI, height, smoking habits, or other demographic characteristics will be recorded and may be used in the PK, PD, and safety analyses as quantitative or classification variables.

10.3. Statistical Analyses

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

PK/PD analyses will be performed on the full analysis set. This set includes all data from all randomized subjects receiving at least 1 dose of the investigational product according to the treatment the subjects actually received. Safety analyses will be performed for all enrolled subjects, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be performed 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.

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 treatment will be presented by severity and by association with investigational product 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 laboratory parameters, CNS monitoring, eye assessments, vital signs, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analyses will be performed if warranted upon review of the data. The statistical analysis plan will contain all details on the evaluation of safety measurements.

Analysis of QTc data from ECG monitoring in a Phase 1 trial is performed to judge the extent and/or risk of QT prolongation. A scatter plot will be generated to explore the relationship between QTc and drug exposure, and will assess the mean change in QTc using Fridericia's formula as a function of plasma drug concentration. The QTc analysis will not include ECGs collected in Part C (itraconazole interaction), due to the potential for non-LY3323795-induced changes in QTc.

Frequency tables of QTc changes from baseline and large QTc values may also be obtained in accordance with International Conference on Harmonisation guidance, and additional analyses may be conducted if required.

For each method of eye assessment, change from baseline (yes/no) and change from baseline clinically significant (yes/no) will be listed, and if there are sufficient changes they will be summarized by treatment group and compared with Fisher's exact test.

Additional analyses may be performed for the purpose of fulfilling the Clinical Trial Registry requirements.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3323795 will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max} and AUC of LY3323795. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

Renal clearance of LY3323795 will be calculated as the ratio of amount excreted/AUC. This will be compared to the unbound glomerular filtration rate, which is estimated using creatinine levels.

In Part C, PK parameter estimates for itraconazole samples collected on Day 16 will be calculated using standard noncompartmental methods of analysis. C_{max} and AUC will be reported. Itraconazole concentrations collected as part of this study may be analyzed along with data collected in other studies as part of a larger assessment of itraconazole PK. If such an analysis is performed, the results of the analysis will be reported separately from the final report for this study. Concentrations of itraconazole metabolites may be characterized on an exploratory basis.

10.3.2.2. Pharmacokinetic Statistical Inference

In Part C, the $AUC_{(0-\infty)}$ and C_{max} for LY3323795 administered alone and in the presence of itraconazole will be compared using an analysis of variance (ANOVA) model. The parameters will be log-transformed prior to analysis. The model includes a fixed effect for the treatment and a random effect for subject. The following model will be built: ln(PK parameter) = treatment + subject + random error where treatment is a fixed effect with 2 levels: LY3323795 alone (reference) and LY3323795 with itraconazole (test).

The least square means for each treatment and the 90% CI for the difference in means will be estimated from the ANOVA model and back-transformed from the log scale to provide estimates of the geometric means and 90% CIs for the ratio of the geometric means of LY3323795 + itraconazole versus LY3323795 alone.

The time to C_{max} (t_{max}) parameter will be analyzed using the Wilcoxon-signed rank test. Median differences and 90% CIs for the difference between LY3323795 + itraconazole (test) and LY3323795 alone (reference) will be calculated.

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

In Parts A and B, plasma concentrations of $A\beta_{1-40}$ and $A\beta_{1-42}$ will be summarized for each dose group based on the C_{nadir} and the time to reach C_{nadir} (t_{nadir}).

In Part B, CSF concentrations of $A\beta_{1-40}$, $A\beta_{1-42}$, and CCI will be summarized for each dose group based on the C_{nadir}, t_{nadir}, and the 24-hour average values, expressed as a percentage change from baseline. CCI [redacted] Other parameters may be calculated, as appropriate.

10.3.3.2. Pharmacodynamic Statistical Inference

For Part B of this protocol, statistical analysis of CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations obtained over the fixed-scheduled sampling period will be analyzed using a repeated-measures analysis with the primary statistical inference of pairwise comparison of the overall mean difference among the LY3323795 doses and placebo using a 90% CI. The statistical model may include the baseline CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations obtained during predose CSF collection period and fixed effects of dose groups (placebo and doses of LY3323795), scheduled CSF sampling time, and the interaction between dose groups and sampling times. A compound symmetric covariance structure may be used. From the statistical model, the primary statistical estimates will be the mean percentage reduction from baseline in CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations at each time point with LY3323795 over the 36-hour sampling interval. The above model will fit both the log-transformed and percentage change from baseline in CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations.

CCI [redacted]

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

It is intended that a compartmental modeling approach will be used to describe the plasma and CSF PK and CSF PD of LY3323795. Compartmental modeling will be performed using nonlinear mixed-effects modeling. Although it is not intended that the model will assess the impact of patient-specific factors (such as age, body weight, or race/subrace) on LY3323795 PK, these may be included if appropriate. Modeling may be performed sequentially by first modeling plasma PK and then fixing the values from that model when developing a model to describe CSF PK. It is intended that an indirect response model will be used to characterize the PD effect of LY3323795 on CSF $A\beta_{1-40}$ formation, with PK parameters fixed to those values determined in previous steps. Other PD endpoints (eg, $A\beta_{1-42}$) may be modeled, if warranted.

Other modeling approaches or graphical analyses may be used, as deemed appropriate. The results of this modeling may not necessarily be included in the final study report.

10.3.5. Interim Analyses

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

Safety and/or PK IAD reviews are scheduled to occur throughout the study. The purpose of these IAD reviews is to examine the safety data and guide dose selections.

In Part A, the investigator and the Lilly clinical pharmacologist/CRP/study team will make the determination regarding dose escalation based on their review of the safety and tolerability data, along with PK data, as applicable (Section 5.1.1).

In Part B, dose selection will be based on PK/PD data as described in Section 5.1.2.

The investigator will remain blinded and the Lilly clinical pharmacologist/CRP/study team will be unblinded during these IAD reviews.

The specifics about the timing of the IAD reviews and the procedures for selecting doses are described in the study design section of the protocol (Section 5).

Additional IAD reviews may be conducted at any time throughout the study as required to ensure subjects' safety or to help guide dosing. An assessment committee will not be formed.

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Appendix 1. Abbreviations and Definitions

Term	Definition
Aβ	β-amyloid
AD	Alzheimer's disease
AE	adverse event: Any untoward medical occurrence in a subject 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.
ALT	alanine aminotransferase
ANOVA	analysis of variance
APP	amyloid precursor protein
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
AUC	area under the concentration-versus-time curve
$AUC_{(0-\infty)}$	area under the curve from time 0 extrapolated to infinity
BACE	β-site APP-cleaving enzyme
blinding	A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
CI	confidence interval
C_{max}	maximum drug concentration
C_{nadir}	nadir concentration
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.

compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
CSE	clinically significant event
CSF	cerebrospinal fluid
CYP	cytochrome P450
ECG	electrocardiogram
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	ethical review board
GLP	good laboratory practice
HIV	human immunodeficiency virus
IAD	interim access to data
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.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

Investigational New Drug	An application to the FDA to allow testing of a new drug in humans.
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 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.
IRB	institutional review board
LC/MS/MS	liquid chromatography with tandem mass spectrometry
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
LP	lumbar puncture
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
non-investigational product	A product that is not being tested or used as a reference in the clinical trial, but is provided to subjects and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
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.
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
QTc	QT corrected for heart rate
RDA	recommended dietary allowance
SAE	serious adverse event
CCI [redacted]	
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.
SUSAR	suspected unexpected serious adverse reaction
t_{max}	time to C_{max}
CCI [redacted]	

t_{nadir}	time to reach C_{nadir}
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
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Hematology[a]
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Cell morphology
  - [Absolute counts of]:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Platelets

Urinalysis[a]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite

Coagulation (Part B only):
- Prothrombin time
- International normalized ratio
- Partial thromboplastin time

Clinical chemistry[a]
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Phosphorus
- Magnesium
- Glucose [random]
- Blood urea nitrogen
- Uric acid
- Total cholesterol
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Creatinine
- Gamma-glutamyl transferase

Ethanol testing[b,c]
Urine drug screen[b,c]
Hepatitis B surface antigen[b]
Hepatitis C antibody[b]
HIV[b]
Pregnancy test[d] (if applicable)
FSH[b]

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

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

[b] Performed at screening to confirm postmenopausal status.

[c] Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit.

[d] At investigator's discretion.

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 informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject 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 ethical review board (ERB) was properly constituted and convened as required by International Conference on Harmonization (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). The ERB(s) will review the protocol as required.

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

- the current Investigator's Brochure (IB) and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) applicable ICH good clinical practice (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, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

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

Appendix 4. 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 subjects in consultation with 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
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody**[a]
AST	
GGT	**Anti-smooth muscle antibody (or anti-actin antibody)**[a]
CPK	

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

[a] Assayed by Covance Central Laboratory Services (CCLS).

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

Appendix 5. Blood and CSF 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 I9F-MC-SCAA Blood Sampling Summary (Part A – 3 Periods)

Purpose	Maximum Blood Volume Per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	25	1	25
Clinical laboratory tests (central)[a]	5	12	60
Clinical laboratory tests (local lab)	12.5	3	37.5
LY3323795 plasma PK[b]	2	45 (+5)	90 (10)
PD plasma samples[b]	2	45 (+5)	90 (10)
CCI	2	45	90
Blood discard for cannula patency	1	33	33
Pharmacogenetics	10	1	10
Total			435.5 (455.5)
Total for clinical purposes [rounded up to nearest 10 mL]			440 (460)

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics.

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

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

Protocol I9F-MC-SCAA Blood Sampling Summary (Part B – 1 Period)

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	25	1	25
Clinical laboratory tests (central)[a]	5	4	20
Clinical laboratory tests (local lab)	12.5	1	12.5
LY3323795 plasma PK[b]	2	17 (+5)	34 (10)
PD plasma samples[b]	2	17 (+5)	34 (10)
Storage plasma samples	2	17	34
Blood discard for cannula patency	1	12	12
Pharmacogenetics	10	1	10
Total			181.5 (201.5)
Total for clinical purposes [rounded up to nearest 10 mL]			190 (210)

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics.

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

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

Protocol I9F-MC-SCAA CSF Sampling Summary (Part B – 1 Period)

Purpose	Maximum CSF Volume Per Sample (mL)	Maximum Number of CSF Samples	Maximum Total Volume (mL)
CSF PK	1	20	20
CSF PD and storage	3	22	66
RBC count (safety sample)	2	2	4
CSF flush	2	22	44
Total			134
Total for clinical purposes [rounded up to nearest 10 mL]			140

Abbreviations: CSF = cerebrospinal fluid; PD = pharmacodynamics; PK = pharmacokinetics; RBC = red blood cell.

CCI

CCI	1	22	22
Pharmacogenetics	10	1	10
Total			196
Total for clinical purposes [rounded up to nearest 10 mL]			200

CCI

Appendix 6. Protocol Amendment I9F-MC-SCAA(a) Summary
Single-Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3323795 in Healthy Subjects

Overview

Protocol I9F-MC-SCAA [Single-Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3323795 in Healthy Subjects] has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Based on feedback received from the US Food and Drug Administration (FDA), the optional Dose 7 (Period 4) from Part A has been removed and the protocol has been updated to state that exposure must not exceed one tenth the NOAEL exposure established in male rats (i.e. median AUC will not exceed 3,450 ng•hour/mL and median C_{max} will not exceed 214 ng/mL). In addition, for Part A, PK data reviews will be conducted before dose escalation from Dose 4 onwards, not Dose 5 onwards.

The following changes have been made based on feedback received from the site and errors noted in the original protocol:

- For Parts A and B, ethanol and urine drug screens have been moved from Day -1 to screening, consistent with the original intent. For Part C, ethanol and urine drug screens were removed from the 7-Day Wash-out period. The investigator will discern the need for additional ethanol and urine drug screens based on each subject's presentation on readmission to the CRU.
- For Part B, the Day 3 ophthalmic examination has been moved to Day 4 to allow for at least a 24-hour recovery period following catheter removal.
- A CSF safety sample has been added to Part B to reflect the site's lumbar catheter standard operating procedure.
- For Part C, additional vital sign measurements have been added to the schedule of activities to comply with the CRU standard operating procedures.
- For Part C, a clinical laboratory assessment has been inserted on Day 9 prior to study drug dosing in Period 2. This is consistent with the original intent.
- For Part C, weight measurements have been added to FDC and ED for consistency with Parts A and B of the study.

- For Part B, Dose B1 will be determined by safety data through Part A Dose 4 instead of Dose 3 in order to collate additional data in the dose decision.
- The capsule size has been corrected from Size 0 to Size 2, consistent with information in the IND.
- The ECG recording information has been updated to reflect that ECGs will be recorded in triplicate for Part C and single in Part B, consistent with the original intent.
- Several typographical updates and clarifications have been made to ensure consistency and accuracy.

Revised Protocol Sections

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

1. Protocol Synopsis

Summary of Study Design:

Study I9F-MC-SCAA is a Phase 1 study of LY3323795 in healthy subjects that will be conducted in 3 parts. Part A (Doses 1 to 6) will be a subject- and investigator-blind, placebo-controlled, randomized, single-ascending dose, 3-period, 2-cohort (6:3 subjects, LY3323795:placebo per cohort), dose-escalation study to evaluate safety, tolerability, and plasma PK/PD of LY3323795. ~~An optional Period 4 may be implemented to evaluate Dose 7 depending on available PK data.~~ Part B will be a subject- and investigator-blind, placebo-controlled, randomized, single-dose, 3-cohort (5:2 subjects, LY3323795:placebo per cohort), single-period, lumbar catheter study to evaluate the central and plasma PK/PD of LY3323795. Doses in Part B will not be administered until equal or greater doses have been administered in Part A and shown to be well tolerated. Part C will be an open-label, 2-period, fixed-sequence, single-cohort design with 8 subjects to evaluate a potential CYP3A4 interaction when LY3323795 is coadministered with itraconazole.

Treatment Arms and Duration:

For Part A (Cohorts 1 and 2), subjects will receive oral doses of either LY3323795 or placebo; the anticipated doses are 0.3 mg, 1 mg, 3 mg, 10 mg, 30 mg, and 100 mg. ~~An additional dose may be administered in Cohort 1, Period 4 if required.~~

2. Schedule of Activities

Study Schedule Protocol I9F-MC-SCAA: Part A, Periods 1 through 34

	Screen	Periods 1 to 34								FDC[a]	ED	Notes
Study Day	**-28 to -2**	**-1**	**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**			
Ethanol and urine drug screens	X	~~X~~										An additional ethanol and urine drug screen may be done at the discretion of the investigator at readmission to the CRU.

Study Schedule Protocol I9F-MC-SCAA: Part B

Study Day	**Screen -28 to -1**	**-1**	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**FDC[b]**	**ED**	**Notes**
Ethanol and urine drug screens	X	~~X~~										An additional ethanol and urine drug screen may be done at the discretion of the investigator.
Ophthalmic examination	X				~~X~~	X			X	X	X	See Section 9.4.4.2 for details.

Study Schedule Protocol I9F-MC-SCAA: Part C

	Screen		Period 1		7-Day Wash-out	Period 2										FDC[a]	ED	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3-9**	**10**	**11 to 14**	**15**	**16[b]**	**17**	**18**	**19**	**20**	**21**	**22**	**23**			
Ethanol and urine drug screens	X				~~X~~														An additional ethanol and urine drug screen may be done at the discretion of the investigator at readmission to the CRU.
Vitals (hours)	X		0, 1, 2, 4, 6, 8, 12	24	X	X	X	X	0, 1, 2, 4, 6, 8, 12	24	X	X	X	X	X	X	X	X	See Section 9.4.2 for details.
Clinical laboratory values (hours)	X	X			48, Day 9				0		48				X		X	X	Screening tests will take place at local laboratories and other analyses will be at central laboratory. Blood will be collected on Day -1 for both local and central labs. Investigator will review local lab results before dosing in Period 1.
Weight/height	X							X									X	X	Height measured at screening only.

5.1. Overall Study Design

- Part A will be a subject- and investigator-blind, placebo-controlled, randomized, single-ascending dose, 3-period ~~(with an optional fourth period for Cohort 1)~~, dose-escalation study to evaluate safety, tolerability, and plasma PK/PD of LY3323795.

Figure SCAA.1

Part A: Dose Escalation

	Period 1		Period 2		Period 3		Optional Period 4
Cohort 1 (n=9) (LY=6; PL=3)	Dose 1, 0.3 mg LY or PL	≥14 d washout	Dose 3, 3 mg LY or PL	≥14 d washout	Dose 5, 30 mg LY or PL	≥14 d washout	Dose 7, TBD LY or PL
Cohort 2 (n=9) (LY=6; PL=3)		Dose 2, 1 mg LY or PL	≥14 d washout	Dose 4, 10 mg LY or PL	≥14 d washout	Dose 6, 100 mg LY or PL	

Part A: Safety review to be completed after each dose level, prior to escalation. From **Dose 5 onwards**, PK data review to be completed prior to dose escalation.

Part B: Serial CSF Sampling

	Period 1
Cohort 3 (n=7) (LY=5; PL=2)	**Dose B1 or Placebo**
Cohort 4 (n=7) (LY=5; PL=2)	**Dose B2 or Placebo**
Cohort 5 (n=7) (LY=5; PL=2)	**Dose B3 or Placebo**

Dose B1 will be determined by PK/PD data through Part A Dose 2, and safety data through Part A Dose 3.

Dose 7, if administered, to be determined by Dose 6 PK.

Dose B2 will be determined by:
- PK/PD data from Dose B1
- PK/PD data from Part A Dose 4
- Safety Data through Part A Dose 5.

Dose B3 will be determined by:
- Maximum tolerated dose from Part A (either Dose 6 or optional Dose 7)
- PK data from Part A Dose 6.
- PK/PD data from Doses B1 and B2.

Part C: Itraconazole Interaction

	Period 1		Period 2		
Cohort 6 (n=8) (LY=8, Itra = 8)	**LY**	**≥7 d washout**	**Itra (7 doses)**	**LY + Itra**	**Itra (5+ doses)**

Part A: Dose Escalation

	Period 1		Period 2		Period 3	
Cohort 1 (n=9) (LY=6; PL=3)	Dose 1, 0.3 mg LY or PL	≥14 d washout	Dose 3, 3 mg LY or PL	≥14 d washout	Dose 5, 30 mg LY or PL	≥14 d washout
Cohort 2 (n=9) (LY=6; PL=3)		Dose 2, 1 mg LY or PL	≥14 d washout	Dose 4, 10 mg LY or PL	≥14 d washout	Dose 6, 100 mg LY or PL

Part A: Safety review to be completed after each dose level, prior to escalation. From **Dose 4 onwards**, PK data review to be completed prior to dose escalation.

Part B: Serial CSF Sampling

	Period 1
Cohort 3 (n=7) (LY=5; PL=2)	**Dose B1 or Placebo**
Cohort 4 (n=7) (LY=5; PL=2)	**Dose B2 or Placebo**
Cohort 5 (n=7) (LY=5; PL=2)	**Dose B3 or Placebo**

Dose B1 will be determined by PK/PD data through Part A Dose 2, and safety data through Part A Dose 4.

Dose B2 will be determined by:
- PK/PD data from Dose B1
- PK/PD data from Part A Dose 4
- Safety Data through Part A Dose 5.

Dose B3 will be determined by:
- Maximum tolerated dose from Part A
- PK data from Part A.
- PK/PD data from Doses B1 and B2.

Part C: Itraconazole Interaction

	Period 1		Period 2		
Cohort 6 (n=8) (LY=8, Itra = 8)	**LY**	**≥7 d washout**	**Itra (7 doses)**	**LY + Itra**	**Itra (5+ doses)**

5.1.1. Part A: Dose-Escalation Study

Part A is a dose-escalation study that will be conducted in 2 alternating cohorts (Cohorts 1 and 2), each consisting of approximately 9 subjects (6:3 subjects, LY3323795:placebo at each dose level) who will participate in 3 study periods (total of 6 dose levels in the 2 cohorts)~~, with an optional fourth period for Cohort 1, if indicated by review of emerging data, comprising Dose 7~~. The number of subjects intended to be enrolled is detailed in Section 5.2. The first ~~5~~4 dose levels of LY3323795 are anticipated to be 0.3 mg, 1 mg, 3 mg, and 10 mg~~, and 30 mg~~. Doses 5 and 6 are~~is~~ anticipated to be 30 and 100 mg, but will be confirmed following ~~pending~~ PK data reviews ~~from Dose 5~~. See Section 5.1.1.1 for details of dose-escalation decisions. ~~The optional Dose 7 may be implemented based on review of emerging data as described in Section 5.5.~~

5.1.1.1.Dose Escalation and Interim Access to Data in Part A

The decision to dose escalate will be based on safety reviews conducted after each dose (and PK reviews from Dose ~~5~~4 [planned to be 10 mg] onwards). Dose escalation will not occur until after a review of at least 3 days' safety data from the preceding dose level has been carried out, and the dose shown to be safe. Accordingly, safety data, including AEs, vital signs, neurological surveys, ophthalmic tests, ECGs, and clinical laboratory tests, will be assessed by both the investigator and the sponsor prior to each dose escalation. Any available PK data may be reviewed but PK data are not required for the initial dose-escalation decisions. However, from Dose ~~5~~4 onwards, LY3323795 PK data will be reviewed before escalation to the next subsequent dose level to verify that the projected median exposure does not exceed one tenth the NOAEL exposure established in rats (~~34,500ng.hour/mL~~i.e. median area under the concentration-versus-time curve (AUC) will not exceed 3,450 ng•hour/mL and median C_{max} will not exceed 214 ng/mL) (see Section 7.4.1). PK samples up to 96 hours postdose will be required to conduct the PK data reviews. The 96-hour PK sampling period may be adjusted based on emerging PK data. Plasma Aβ data may also be reviewed to assess the PD profile. Time points for PK and PD sampling and required safety assessments may be modified based on emerging PK and safety results.

In addition to the reviews of PK data required after Dose ~~5~~4 for the purposes of dose escalation, interim access to PK and PD (including plasma Aβ) data will occur after the anticipated 1-mg dose (Dose 2) and 10-mg dose (Dose 4) of Part A. Data from this interim access to data (IAD) reviews, as well as results of the PK IADs following Doses 4, 5, and 6, ~~and potentially 7,~~ will be used at different points to select doses in Part B (see Figure SCAA.1).

5.1.2. Part B: CSF Sampling Study

Subjects will be admitted to the CRU on Day -1 and will remain as inpatients until at least 24 hours after the CSF catheter is removed, after which they may be discharged at the discretion of the investigator. CSF will be collected from an indwelling catheter using a closed system. The catheter will be inserted approximately 4 hours prior to study drug administration. CSF

samples will be taken during this "stabilization" period approximately every 2 hours, as feasible. If some samples during the stabilization period are not collected for any reason, this will not be considered a protocol violation.

CSF PK and PD data will be collected by frequent sampling for 4 hours predose and up to 36 hours postdose (as described in the Part B Schedule of Activities, Section 2). The minus 4-hour CSF sample will be collected for safety (red blood cell count, glucose, and protein, to be tested at the local laboratory) and PD biomarkers (which will be tested centrally). The minus 2-hour sample will be collected for PD biomarkers only; the 0-hour and subsequent postdose samples will be collected for LY3323795 concentration and PD biomarkers. An additional safety CSF sample will be collected at the removal of the catheter. CCI [redacted]

5.1.2.1 Dose Selection and Pharmacokinetic Analysis in Part B

Any dose selected for administration in Part B will be less than or equal to doses previously administered and found to be well tolerated in Part A. Emerging PK data (and PD data, as available) from the first 2 doses in Part A, and safety data through Dose ~~3~~4 of Part A, will determine Dose B1 for Cohort 3.

5.5. Justification for Dose

The upper dose in SCAA is projected to be 100 mg. However, assessments of PK at pre-specified times are planned during the dose escalation, and the anticipated doses may be modified to ensure that median exposures do not exceed one tenth of the rat NOAEL determined in toxicology studies (i.e. median AUC will not exceed 3,450 ng•hour/mL and median C_{max} will not exceed 214 ng/mL).

~~An optional Dose 7 may be administered in Cohort 1, Period 4 if safety data from previous doses are shown to be well tolerated and the maximum proposed exposure (ie, NOAEL established in rats AUC= 34,500 ng•hour/mL in males, the gender with the lowest exposure) has not been reached in the single dose escalation. If the maximum exposure is reached at any dose level, the additional planned dose period may be used to explore lower dose levels if warranted. Alternatively, Dose 7 may test a dose within the previously tested dose range, in order to better understand the safety, PK, or PD profile of LY3323795.~~

6.3.1. Meals and Dietary Restrictions

Fasting – For all parts of the study, subjects will be required to fast overnight (at least 8 hours) prior to each dosing day and for at least 4 hours after LY3323795 or placebo dosing, with the exception of water that will be freely available before and after dosing. However, no water is allowed 1 hour prior to ~~pre- and post-~~ECG measurement.

7.1.1. Packaging and Labelling

Clinical trial materials will be labeled according to the country's regulatory requirements. Each capsule of LY3323795 will be size ~~zero~~2, blue in color and will contain 0.3 mg, 1 mg, or 10 mg of active ingredient. Placebo capsules will match LY3323795 capsules in appearance. LY3323795 and matching placebo capsules will be supplied to the investigator by Lilly for dispensing by unblinded pharmacy staff.

9.4.3. Electrocardiograms

For Parts A and ~~B~~C, after study entry, ECGs will be obtained in triplicate at approximately 1-minute intervals at each ECG time point. At least 1 ECG in each triplicate set will be interpreted by the investigator or qualified designee at the site as soon as possible after the time of ECG collection, and ideally while the subject is still present, for immediate subject management.

For Part ~~C~~ B ~~(itraconazole interaction)~~, at each time point, a single ECG will be collected and subsequently interpreted by the investigator or qualified designee in the same way as above.

Appendix 5. Blood and CSF Sampling Summary

Protocol I9F-MC-SCAA Blood Sampling Summary (Part A – ~~4~~ 3 Periods)

Purpose	Maximum Blood Volume Per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	25	1	25
Clinical laboratory tests (central)[a]	5	~~16~~12	~~80~~60
Clinical laboratory tests (local lab)	12.5	~~4~~3	~~50~~37.5
LY3323795 plasma PK[b]	2	~~60~~ 45(+5)	~~120~~ 90 (10)
PD plasma samples[b]	2	~~60~~ 45(+5)	~~120~~ 90 (10)
Storage plasma samples	2	~~60~~ 45	~~120~~ 90
Blood discard for cannula patency	1	~~4~~4~~3~~3	~~4~~4~~3~~3
Pharmacogenetics	10	1	10
Total			~~569 (589)~~435.5 (455.5)
Total for clinical purposes [rounded up to nearest 10 mL]			~~570 (590)~~440 (460)

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics.

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

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

Protocol I9F-MC-SCAA CSF Sampling Summary (Part B – 1 Period)

Purpose	Maximum CSF Volume Per Sample (mL)	Maximum Number of CSF Samples	Maximum Total Volume (mL)
CSF PK	1	20	20
CSF PD and storage	3	22	66
RBC count (safety sample)	2	~~1~~2	~~2~~4
CSF flush	2	22	44
Total			134~~2~~
Total for clinical purposes [rounded up to nearest 10 mL]			140

Abbreviations: CSF = cerebrospinal fluid; PD = pharmacodynamics; PK = pharmacokinetics; RBC = red blood cell

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