Protocol J1Z-MC-HUAA (b)

Single- and Multiple-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study with LY3154885 in Healthy Subjects

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Confidential Information

LY3154885

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1. Protocol Synopsis

Title of Study:
Single- and Multiple-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study with LY3154885 in Healthy Subjects

Rationale:
LY3154885 is a positive allosteric modulator (also called "potentiator") of the dopamine D1 receptor (D1 PAM) being developed for the potential treatment of Alzheimer's dementia and Lewy body dementia, including dementia with Lewy bodies and Parkinson's disease dementia.

LY3154885 has not been administered to humans. This first-in-human study will investigate the safety, tolerability, and pharmacokinetics (PK) of single and multiple doses of LY3154885 in healthy subjects. The study will also investigate the impact of cytochrome P450 (CYP) 3A4 inhibition on the safety, tolerability, and PK of LY3154885, and the PK of LY3154885 after a single dose via a tablet or capsule formulation. The data generated in this study will be used to help design subsequent clinical studies.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
To explore the safety and tolerability of single and multiple doses of LY3154885 in healthy subjects	Incidence of treatment-emergent adverse events (TEAEs)
Secondary	
• To determine the pharmacokinetics (PK) of LY3154885 following administration of single and multiple oral doses of LY3154885	Maximum observed drug concentration (C_{max}), time to C_{max} (t_{max}), and area under the concentration versus time curve (AUC) of LY3154885
• To determine the PK of LY3154885 when administered with itraconazole (Part B only)	C_{max} and AUC for LY3154885 alone and in the presence of itraconazole
• To assess safety and tolerability of LY3154885 when administered with itraconazole (Part B only)	TEAEs
• To compare the PK of LY3154885 when administered with a capsule or tablet formulation (Part D only)	C_{max}, $t_{max,}$ and AUC of LY3154885 for capsule and tablet formulations
• To evaluate the effect of a high-fat diet on the PK of LY3154885 (Part D only)	C_{max}, $t_{max,}$ and AUC of LY3154885 with and without a high-fat diet

Summary of Study Design:

Study J1Z-MC-HUAA is a Phase 1, single-center study in healthy subjects to be conducted in 4 parts:

- Part A will be a subject- and investigator-blind, placebo-controlled, randomized, single-ascending dose, 3-period crossover study to evaluate safety, tolerability, and PK of LY3154885 in 2 alternating cohorts.
- Part B will be a subject- and investigator-blind to LY3154885/placebo, single period, drug-drug interaction study with itraconazole.
- Part C will be a subject- and investigator-blind, placebo-controlled, randomized, 14-day multiple-ascending dose, parallel-group, 3-cohort, single-period study to evaluate safety, tolerability, and PK of LY3154885.
- Optional Part D will be an open-label, 3-period, 3-sequence PK study of LY3154885 administered using a capsule or tablet formulation. Part D will also include a pilot food effect evaluation.

Treatment Arms and Planned Duration for an Individual Subject:

Part A: Subjects will attend a screening visit up to 28 days prior to dosing in Period 1. Admission to the clinical research unit (CRU) will be in the afternoon of Day -2 of the first period and on Day -1 for Periods 2 and 3. After an overnight fast, subjects will receive either LY3154885 or placebo as a single oral dose on Day 1 and will remain inpatient for at least 48 hours after dosing (until Day 3), after which they may be discharged at the discretion of the investigator. The washout time between doses for a given subject will be at least 7 days. A poststudy follow-up visit will be conducted at least 7 days after the final dose.

Part B: Subjects will attend a screening visit up to 28 days before dosing. Subjects will be admitted to the CRU in the afternoon of Day -2 and will receive a single oral dose of LY3154885 or placebo on Day 1 after an overnight fast. There will be a 7-day washout period followed by 10 days of dosing with 200 mg itraconazole (twice daily on Day 8 [dose separated by 12 hours], then once daily on Days 9 through 17). Subjects will receive LY3154885 or placebo on Day 14, approximately 1 hour after the dose of itraconazole.

Part C: Subjects will receive either LY3154885 or placebo as a single oral once-daily dose from Days 1 through 14. Study drug will be administered as a single oral dose in the morning under fasted conditions. Subjects will attend a screening visit up to 28 days prior to dosing and will be admitted to the CRU in the afternoon of Day -2. After the initial dose (Day 1), subjects will be required to remain in-house for at least 48 hours after dosing (Day 3) and at the discretion of the investigator. Subjects will attend the CRU on Days 4, 5, 6, 9, and 10 on an outpatient basis for daily dosing and will be permitted to leave the CRU at the discretion of the investigator. A poststudy follow-up visit will be conducted approximately 7 days after discharge.

Optional Part D: Subjects will attend a screening visit up to 28 days prior to dosing in Period 1; admission to the CRU will be in the afternoon of Day -2 (Periods 1 and 2) and on Day -1 (Period 3). In Period 1, subjects will undergo an overnight fast before receiving a single oral dose of LY3154885 (capsule formulation) on Day 1. Subjects will remain inpatient for at least 48 hours after dosing, after which they may be discharged at the discretion of the investigator. Subjects will be re-admitted to the CRU on Day 6, and will undergo an overnight fast before receiving a subsequent single oral dose of LY3154885 on Day 8 with the same formulation. Subjects will be discharged on Day 10, at least 48 hours after dosing.

Period 2 will be conducted as described for Period 1; however, LY3154885 will be administered as a tablet formulation. Period 3 will be conducted as described for Period 1; however, subjects will receive a single oral dose of LY3154885 (tablet formulation) after administration of a high-fat diet.

Number of Subjects:

For Part A, up to 30 subjects may be enrolled into Cohorts 1 and 2 in order to ensure that approximately 12 subjects per cohort (8 LY3154885; 4 placebo) complete this part of the study.

For Part B, up to 15 subjects may be enrolled in order to ensure that approximately 12 subjects (9 LY3154885; 3 placebo) complete this part of the study.

For Part C, up to 45 subjects may be enrolled in order to ensure that approximately 36 subjects complete this part of the study (with approximately 12 subjects [9 LY3154885; 3 placebo] completing each dose level).

For optional Part D, up to 12 subjects may be enrolled in order to ensure that approximately 9 subjects complete this part of the study.

Statistical Analysis:

Safety: Safety parameters that will be assessed include adverse events, clinical laboratory parameters, vital signs, and electrocardiogram parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

Pharmacokinetics: Pharmacokinetic parameters including maximum observed drug concentration (C_{max}), time to C_{max} (t_{max}), and area under the concentration versus time curve (AUC) following single and multiple doses of LY3154885 will be calculated using standard noncompartmental methods of analysis.

2. Schedule of Activities

Study Schedule Protocol J1Z-MC-HUAA (Part A: Single-Ascending Dose – 3 Study Periods)

	Screening	Periods 1, 2, and 3					ED	Follow-up	Comments
Procedure	-28 to -3 days prior to dosing in Period 1	Day -2	Day -1	Day 1	Day 2	Day 3		At least 7 days after final dose	
Informed consent	X								
Admission to CRU		X (Period 1)	X (Periods 2&3)						
Discharge from CRU						X			
Medical history	X								
AE/medication review			X	X	X	X	X	X	
Height/weight	X						X	X	Height at screening only.
Neurological exam (hours)	X			Predose, 4, 8	24	48	X	X	
LY3154885/Placebo administration (hours)				0					
Vital signs (BP, PR [supine], temperature) (hours)	X		X	Predose, 2, 4, 8, 12	24, 36	48	X	X	Time points may be added for each study period, if clinically indicated. On Day 1, temperature will be measured at predose only.
ABPM			X	X	X				The ABPM on Day -1 is a 24-hour collection in Period 1 only (baseline measurement). See Section 9.4.4.
Clinical laboratory tests	X	X		Predose		X	X	X	See Appendix 2, Clinical Laboratory Tests, for details. PI must review the result of Day-2 results prior to Day 1 dose in Period 1 only.
Pregnancy test	X	X					X	X	Serum test at screening and admission of Period 1 only; urine test at all other time points.
PE/MA	X			Predose			X	X	Full PE/MA at screening and prior to final discharge from the study. Symptom-directed PE/MA at all other time points and as deemed necessary by the investigator.

continued

Study Schedule Protocol J1Z-MC-HUAA (Part A: Single-Ascending Dose – 3 Study Periods) (concluded)

	Screening	Periods 1, 2, and 3					ED	Follow-up	Comments
Procedure	-28 to -3 days prior to Period 1	Day -2	Day -1	Day 1	Day 2	Day 3		At least 7 days after final dose	
Single safety 12-lead ECG (hours)	X			Predose, 2, 4	24	48	X	X	
PK sampling (hours)				Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48			Sampling times are relative to the time of study treatment administration (0 hour).
Stored non-PGx plasma sample (hours)				Predose, 8	24				Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).
PGx sample			X						Single sample for pharmacogenetic analysis taken prior to/on Day 1 of Period 1.
Urine collection (hours)				0-12, 12-24	24-36				Urine collection time starts from actual dosing time on Day 1 and finishes within ±30 minutes of the 36-hour time point.
Serum creatinine				Predose					To be collected at predose and sent to central laboratory.

Note: Site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: ECG, vital signs, PK samples, clinical laboratory tests, urine samples, biomarkers, and storage samples.

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; PE = physical examination; PGx = pharmacogenetic; PI = principal investigator; PK = pharmacokinetic; PR = pulse rate.

Study Schedule Protocol J1Z-MC-HUAA (Part B: Drug-Drug Interaction with CYP3A4 Inhibition – Single Period)

	Screening	Days													
Procedure	-28 to -3	-2	-1	1	2	3	4-6	7	8	9	10-11	12	13	14	15
Informed consent	X														
Admission to CRU		X						X				X			
Discharge from CRU						X				X					
PE/MA	X														
Directed MA	X			Predose					Predose					Predose	
AE/medication review		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/height	X		X												
Pregnancy test	X	X													
Neurological exam (hours)[a]	X			Predose, 4, (8)	24	48								Predose, 4, (8)	24
Clinical laboratory tests	X	X		Predose					Predose					Predose	
ABPM			X	X	X								X	X	X
LY3154885/Placebo administration				X										X	
Administration of itraconazole									X	X	Outpatient dosing		X	X	X
Vital signs (BP, PR [supine], temperature) (hours)[a]			X	Predose 2, 4, 8, 12	24	48			Predose, 2, 4, 12	24				Predose 2, 4, 8, 12	24, 36
12-lead ECG			X	Predose					Predose					Predose	
PGx sample				X											
LY3154885 PK sampling (hours)[a]				Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48								Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36
Itraconazole and metabolite(s) PK sampling (hours)									-1, 0, 1, 2, 5, 8, 12						

continued

Study Schedule Protocol J1Z-MC-HUAA (Part B: Drug-Drug Interaction with CYP3A4 Inhibition – Single Period) (concluded)

	Days			ED	Follow-up	Comments
Procedure	16	17	18		Approx 7 days after discharge	
Discharge from CRU			X			
PE/MA			X	X	X	Full PE/MA at screening and prior to final discharge from the study. Symptom-directed PE/MA at all other time points and as deemed necessary by the investigator.
Directed MA				X	X	
AE/medication review	X	X	X	X	X	
Weight/height				X	X	Height at screening only.
Pregnancy test				X	X	Serum test at screening and admission; urine test at all other time points. Women with confirmed nonchildbearing potential status can be exempted from further pregnancy tests during the study after screening.
Neurological exam (hours)[a]	48					The 8-hour time point is optional.
Clinical laboratory tests			X	X	X	See Appendix 2, Clinical Laboratory Tests, for details. PI must review the Day -2 laboratory result before dosing on Day 1
ABPM	X					The ABPM on Day -1 is a 24-hour collection for baseline measurement. On dosing days, the ABPM recording will be initiated approximately 2 hours prior to dosing for measurement of predose baseline.
Administration of itraconazole	X	X				Itraconazole 200 mg will be administered twice daily on Day 8 (dose separated by 12 hours) and once daily on Days 9 through 17. Itraconazole should be administered at approximately the same time every morning. For the outpatient dosing days, subjects will record the actual time of dose administration on a diary card. On Day 14, itraconazole should be administered 1 hour before LY3154885 administration (see Section 5.1.2).
Vital signs (BP, PR [supine], temperature) (hours)[a]	48, 60	72	96	X	X	Time points may be added for each study period, if clinically indicated. On Day 1, temperature will be measured at predose only.
12-lead ECG			X	X	X	Single safety ECGs.
PGx Sample						Single sample for pharmacogenetic analysis.
LY3154885 PK sampling (hours)[a]	48, 60	72	96			Sampling times are relative to the time of LY3154885 administration (0 hour).

Note: Site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: ECG, vital signs, PK samples, and clinical laboratory tests.

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; CRU = clinical research unit; CYP = cytochrome P450; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; PE = physical examination; PI = principal investigator; PK = pharmacokinetic; PR = pulse rate.

[a] Predose time points refer to dosing before itraconazole and LY3154885. All postdose time points are relative to the LY3154885 dose.

Study Schedule Protocol J1Z-MC-HUAA (Part C: Multiple-Ascending Dose – Single Period)

	Screening	Days									ED	Follow-up	Comments
Procedure	-28 to -3	-2	-1	1	2	3-6	7	8-13	14	15		Approx 7 days after discharge	
Informed consent	X												
Admission to CRU		X				D6		D10					Afternoon admission.
Discharge from CRU						D3		D8		X			
Medical history	X												
AE/medication review			X	X	X	X	X	X	X	X	X	X	
Height/weight	X		X							X			Height at screening only.
Neurological exam (hours)	X			Predose, 4, (8)	24	48	Predose, 4, (8)	24, 48		X	X		The 8-hour time point is optional.
LY3154885/ Placebo administration				X	X	X	X	X	X				On Days 4, 5, 6, 9, and 10, subjects will receive their dose of LY3154885/placebo at the CRU and then may be discharged at the discretion of the investigator.
Vital signs (BP, PR [supine], temperature) (hours)	X		X	Predose, 2, 4, 8, 12	Predose, 2, 4, 8, 12	Predose, 2	Predose, 2, 4, 8, 12	Predose, 2	Predose, 2, 4, 8, 12	X	X	X	Time points on outpatient dosing days (Days 4, 5, 6, 9, and 10) may be adjusted based on emerging data from Part A and/or if clinically indicated. On Days 1 to 14, temperature will be measured at predose only.

continued

Study Schedule Protocol J1Z-MC-HUAA (Part C: Multiple-Ascending Dose – Single Period) (continued)

	Screening	Days									ED	Follow-up	Comments
Procedure	-28 to -3	-2	-1	1	2	3-6	7	8-13	14	15		Approx 7 days after discharge	
ABPM			X	X	X		X	D11& 12	X				The ABPM on Day -1 is a 24-hour collection for baseline measurement. On dosing days, the ABPM recording will be initiated approximately 2 hours prior to dosing for measurement of predose baseline.
Clinical laboratory tests	X	X		Predose			Predose			X	X	X	See Appendix 2, Clinical Laboratory Tests, for details. PI must review Day -2 result prior to dose on Day 1.
Pregnancy test	X	X					Predose			X	X	X	Serum test at screening and admission; urine test at all other time points per investigator discretion. Women with confirmed nonchildbearing potential status can be exempted from further pregnancy tests during the study after screening.
PE/MA	X			Predose						X	X	X	Full PE/MA at screening and prior to final discharge from the study. Symptom-directed PE/MA at all other time points and as deemed necessary by the investigator.

continued

Study Schedule Protocol J1Z-MC-HUAA (Part C: Multiple-Ascending Dose – Single Period) (concluded)

	Screening	Days									ED	Follow-up	Comments
Procedure	-28 to -3	-2	-1	1	2	3-6	7	8-13	14	15		Approx 7 days after discharge	
12-lead ECG (hours)	X			Predose (-45 min, -30 min, -15 min)	Predose		Predose		Predose, (-45 min, -30 min, -15 min), 2, 3, 4, 6, 8, 12	24	X	X	Single safety ECGs at screening and ED/follow-up; triplicate ECGs at all other times. ECGs coinciding with PK sample time points are to be conducted as close as possible prior to PK sampling.
PGx sample				X									Single sample for pharmacogenetic analysis taken prior to/on Day 1.
Stored non-PGx plasma sample (hours)				Predose, 8			Predose		Predose, 8				
PK sampling (hours)				Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	Predose		Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	Predose (D8 only)	Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24			Sampling times are relative to the time of LY3154885 administration (0 hour).
POMS-2®			X			D6 only		D13 only					
Exploratory cognition assessments (HVLT, DSST)			X			D6 only		D13 only					
PWC-20				Predose						X	X	X	
C-SSRS and Lilly Self-Harm Supplement Form	X	X				D3 & D6 only		D8 & D10 only		X	X	X	Administer at screening, each admission, and each discharge from the CRU.

Note: Site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: ECG, vital signs, PK samples, clinical laboratory tests, biomarkers, and storage samples.

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; DSST = Digital Symbol Substitution Test; ECG = electrocardiogram; ED = early discontinuation; HVLT = Hopkins Verbal Learning Test; MA = medical assessment; PE = physical examination; PGx = pharmacogenetic; PI = principal investigator; PK = pharmacokinetic; POMS-2 = Profile of Mood States Second Edition; PR = pulse rate; PWC-20 = Penn Physician Withdrawal Checklist.

Study Schedule Protocol J1Z-MC-HUAA (Part D: Formulations/Food Effect – 3 Study Periods)

		Periods 1, 2, and 3																
	Screening	**Days**														**ED**	**Follow-up**	**Comments**
Procedure	-28 to -3	-2	-1	1	2	3	4-6	7	8	9	10	11-13	14	15	16		Approx 7 days after discharge	
Informed consent	X																	
Admission to CRU		X	X				X D6					X D13						Admission on Day -2 is for Periods 1 and 2. Admission on Day -1 is for Period 3.
Discharge from CRU						X					X				X			
Medical history	X																	
AE/medication review	X		X	X	X	X	X	X	X	X	X					X	X	
Height/weight	X		X					X								X	X	Height at screening only
Neurological exam	X			Predose, 4, (8)	24	48		X	Predose, 4, (8)	24	48		Predose, 4, (8)	24	48			The 8-hour time point is optional.
LY3154885 Administration				X					X				X					Period 1 (capsule) and 2 (tablet) will be under fasting conditions; Period 3 (tablet) will be under fed conditions (see Section 6.3.1).
Vital signs (BP, PR [supine], temperature) (hours)	X		X	Predose, 2, 4, 8, 12	24	48			Predose, 2, 4, 8, 12	24	48		Predose, 2, 4, 8, 12	24	48	X	X	Time points may be added for each study period, if clinically indicated. On Days 1, 8, and 14, temperature will be measured at predose only.

continued

Study Schedule Protocol J1Z-MC-HUAA (Part D: Formulations/Food Effect – 3 Study Periods) (continued)

		Periods 1, 2, and 3															
	Screening	**Days**													**ED**	**Follow-up**	**Comments**
Procedure	-28 to -3	-2	-1	1	2	3	4-6	7	8	9	10	11-13	14	15	16		Approx 7 days after discharge	
ABPM			X	X	X			X	X	X			X	X				For Periods 1 and 2 only. The ABPM on Day -1 is a 24-hour collection for baseline measurement. On dosing days, the ABPM recording will be initiated approximately 2 hours prior to dosing for measurement of baseline.
Clinical laboratory tests	X			Pre-dose					Pre-dose		X		Pre-dose		X	X	X	See Appendix 2, Clinical Laboratory Tests, for details.
Pregnancy test	X	X							Predose				Predose			X	X	Serum test at screening and admission of Period 1 only; urine test at all other times. Women with confirmed nonchildbearing potential status can be exempted from further pregnancy tests during the study after screening.

continued

Study Schedule Protocol J1Z-MC-HUAA (Part D: Formulations/Food Effect – 3 Study Periods) (concluded)

		Periods 1, 2, and 3																
	Screening	**Days**														**ED**	**Follow-up**	**Comments**
Procedure	-28 to -3	-2	-1	1	2	3	4-6	7	8	9	10	11-13	14	15	16		Approx 7 days after discharge	
PE/MA	X															X	X	Full PE/MA at screening and prior to final discharge from the study. Symptom-directed PE/MA at all other time points and as deemed necessary by the investigator.
12-lead ECG	X			Predose					Predose				Predose			X	X	Single safety ECGs. ECGs coinciding with PK sample time points are to be conducted as close as possible prior to PK sampling.
PK sampling (hours)				Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48			Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48		Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48			
PGx sample				Predose														Period 1 only

Note: Site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: ECG, vital signs, PK samples, clinical laboratory tests, biomarkers, and storage samples.

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; CRU = clinical research unit; D = day; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; PE = physical examination; PGx = pharmacogenetic; PK = pharmacokinetic; PR = pulse rate.

3. Introduction

Eli Lilly and Company (Lilly) is developing the small molecule, LY3154885, for the potential treatment of Alzheimer's dementia and Lewy body dementia (LBD), including dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).

Lewy body dementia is an umbrella term for a continuum of progressive neurodegenerative cognitive disorders that include DLB and PDD. Parkinson's disease dementia and DLB are pathologically indistinguishable with substantial overlap in clinical phenotype. Prominent clinical features of both include progressive cognitive impairment, recurrent visual hallucinations, fluctuations in attention and wakefulness, and parkinsonism (Lippa et al. 2007; Thomas et al. 2018). Diagnostic features of PDD and DLB are also similar, the key distinction being timing of dementia onset relative to parkinsonism, if present (McKeith et al. 2005; Emre et al. 2007). Per consensus criteria, PDD is diagnosed when onset of parkinsonism precedes dementia, whereas for DLB the onset of dementia should begin no later than 1 year after, and often preceding, parkinsonism that is variably present (McKeith et al. 2005). It is the arbitrarily defined sequencing of symptom onset that historically differentiated the 2 conditions.

Lewy body dementias are pathologically characterized by intraneuronal inclusions of Lewy bodies throughout subcortical and cortical brain regions, a major component of which is misfolded aggregated α-synuclein (Beyer et al. 2009). Lewy body formation and propagation is accompanied by progressive neurodegenerative processes, particularly affecting the dopaminergic and cholinergic neurons (Harding and Halliday 2001; Klein et al. 2010; Colloby et al. 2012). These neuropathological findings in both PDD and DLB are largely indistinguishable and characterized by subcortical, cortical, and limbic Lewy bodies and alpha-synuclein pathology.

The cognitive impairments overlap with progressive executive dysfunction, visual-spatial abnormalities, and relatively preserved memory early in the course of disease (Lippa et al. 2007). Cognitive impairments have the same genetic risk mutations with alpha-synuclein duplications and glucocerebrosidase mutations being associated with the development of either PDD or DLB. Prodromal features (ie, rapid eye movement sleep behavior disorder and hyposmia) are risk factors for both conditions. The conditions have similar nonmotor features with prominent visual hallucinations, fluctuations in arousal, autonomic dysfunction, depression/anxiety, and sleep disturbances and share neuroimaging characteristics with overlapping patterns of atrophy, glucose utilization, and neurotransmitter changes (cortical cholinergic deficits [Colloby et al. 2016] and striatal/cortical dopaminergic deficits [Klein et al. 2010]). Treatment approaches are similar, with avoidance of neuroleptics. Acetylcholine esterase inhibitors are used for the treatment of cognitive impairments in both conditions. Although PDD and DLB have traditionally been considered 2 distinct clinical entities, the constellation of supportive pathological, clinical, genetic, imaging, and neurochemical data suggest that they fall within a spectrum of the same disease (Berg et al. 2014; Gomperts 2016; Friedman 2018; Jellinger 2018; Jellinger and Korczyn 2018). The 2 diseases share similar and overlapping pathologies in monoaminergic and acetylcholinergic neurotransmitter deficits that a positive allosteric

modulator (also called "potentiator") of the dopamine D1 receptor (D1 PAM) may help ameliorate. Critical clinical components of LBDs are also found in Alzheimer's disease. For example, dopamine insufficiency has been observed in patients with Alzheimer's disease (Mitchell et al. 2011); thus, a meaningful number of patients with Alzheimer's disease exhibit parkinsonian symptoms. Alzheimer's disease is an age-related neurodegenerative disease that results in the slow decline of cognitive and behavioral functions with the characteristic symptom of memory loss in patients (Takizawa et al. 2015). Currently available treatments for Alzheimer's disease have modest benefits for treating cognitive impairment and limited or no benefit for other symptoms such as vigilance, depressive symptoms, daytime alertness, and apathy. By potentiating the response to the remaining brain dopamine (or administered levodopa), a D1 PAM should improve cognitive performance by enhancing frontal dopaminergic neurotransmission, and it is therefore proposed for the treatment of dementia in LBDs (PDD and DLB). In addition to facilitating dopamine neurotransmission, a D1 PAM may be effective in improving cognitive dysfunctions in Alzheimer's disease through activation of cortical neurons, markers of synaptic plasticity, and enhanced release of the acetylcholine neurotransmitter. Other effects such as reduced daytime sleepiness, improved mood, and goal-directed behaviors leading to reduced apathy (via activation of cortical and striatal D1 receptors) would also be beneficial in the LBD and Alzheimer's disease population.

3.1. Study Rationale

LY3154885 has not been administered to humans. This first-in-human study will investigate the safety, tolerability, and pharmacokinetics (PK) of single and multiple doses of LY3154885 in healthy subjects. The study will also investigate the impact of cytochrome P450 (CYP) 3A4 inhibition on the safety, tolerability, and PK of LY3154885 after a single dose via a tablet or capsule formulation. The data generated in this study will be used to help design subsequent clinical studies.

3.2. Background

LY3154885 is a D1 PAM. By increasing the affinity of the D1 receptor for dopamine, a D1 PAM should amplify the response to endogenous dopamine, increasing D1 tone when and where dopamine is released. By increasing the affinity of the D1 receptor for dopamine, D1 PAMs amplify the response to endogenous dopamine, increasing D1 tone when and where dopamine is released (Svensson et al. 2017; Bruns et al. 2018).

This mode of activity is in contrast to direct acting D1 agonists, which activate all D1 receptors to which they have access for as long as they are present. Some D1 agonists also show rapid development of tolerance due to constant activation of the D1 receptor. In contrast, because the mechanism of action of a D1 PAM is dependent on endogenous dopamine tone and thus subject to normal feedback control, a D1 PAM should have a much lower propensity for overstimulation and desensitization.

LY3154885 has demonstrated a favorable safety profile in good laboratory practice (GLP)-compliant toxicology and safety pharmacology studies to support clinical trials, with cardiovascular (CV) and central nervous system (CNS) effects that are transient, monitorable,

and void of correlating adverse pathologic changes. CCI

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LY3154885 has demonstrated suitable absorption, distribution, metabolism, and excretion properties in in vitro experiments and in nonclinical in vivo studies to warrant clinical investigation. The compound is lipophilic and neutral, with acceptable solubility and high permeability. It is eliminated mainly via hepatic metabolism by CYP3A4 and UDP-glucuronosyltransferase (UGT). In humans, LY3154885 is projected to have low oral clearance and a half-life of approximately 12 hours. The drug-drug interaction risk with LY3154885 is considered low based on in vitro data and projected human dose and exposures. However, since there is some uncertainty about the extent that CYP3A4 metabolism contributes to the overall clearance of LY3154885, this will be evaluated as part of this study by coadministering LY3154885 with itraconazole, a strong CYP3A4 inhibitor. Itraconazole is predicted to result in a LY3154885 area under the concentration versus time curve (AUC) that is 2.6-times the AUC when LY3154885 is administered alone.

3.3. Benefit/Risk Assessment

The nonclinical safety information for LY3154885 adequately supports the transition from preclinical status to clinical development. On the basis of the nonclinical data, LY3154885 is not considered to be a high-risk compound. This protocol reflects the fact that LY3154885 has not been administered to humans previously, and to mitigate this risk, the study will 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. Any potential risk could be identified early through close monitoring and surveillance, such as electrocardiograms (ECGs) and assessment of vital signs.

There is no anticipated therapeutic benefit for the subjects.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of LY3154885 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

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

Table HUAA.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary To explore the safety and tolerability of single and multiple doses of LY3154885 in healthy subjects	Incidence of treatment-emergent adverse events (TEAEs)
Secondary • To determine the pharmacokinetics (PK) of LY3154885 following administration of single and multiple oral doses of LY3154885	Maximum observed drug concentration (C_{max}), time to C_{max} (t_{max}) and, area under the concentration versus time curve (AUC) of LY3154885
• To determine the PK of LY3154885 when administered with itraconazole (Part B only)	C_{max} and AUC for LY3154885 alone and in the presence of itraconazole
• To assess safety and tolerability of LY3154885 when administered with itraconazole (Part B only)	TEAEs
• To compare the PK of LY3154885 when administered with a capsule or tablet formulation (Part D only)	C_{max}, $t_{max,}$ and AUC of LY3154885 for capsule and tablet formulations
• To evaluate the effect of a high-fat diet on the PK of LY3154885 (Part D only)	C_{max}, $t_{max,}$ and AUC of LY3154885 with and without a high-fat diet
Exploratory (Part C Only) • To explore any procognitive effects of LY3154885 in healthy subjects using the Hopkins Verbal Learning Test (HVLT) and Digital Symbol Substitution Test (DSST)	HVLT and DSST
• To explore the effect of LY3154885 on subjective mood using the Profile of Mood States Second Edition (POMS-2)	Effect on mood profile
• To evaluate any potential withdrawal symptoms following multiple once-daily dosing of LY3154885	Responses to Penn Physician Withdrawal Checklist (PWC-20)

5. Study Design

5.1. Overall Design

This is a Phase 1, single-center study in healthy subjects to be conducted in 4 parts:

- Part A will be a subject- and investigator-blind, placebo-controlled, randomized, single-ascending dose (SAD), 3-period crossover study to evaluate safety, tolerability, and PK of LY3154885 in 2 alternating cohorts.
- Part B will be a subject- and investigator-blind to LY3154885/placebo, single-period, drug-drug interaction study with itraconazole.
- Part C will be a subject- and investigator-blind, placebo-controlled, randomized, 14-day multiple-ascending dose (MAD), parallel-group, 3-cohort, single-period study to evaluate safety, tolerability, and PK of LY3154885.
- Optional Part D will be an open-label, 3-period 3-sequence PK study of LY3154885 administered using a capsule or tablet formulation. Part D will also include a pilot food effect evaluation.

Study governance considerations are described in detail in Appendix 3.

5.1.1. Part A (Single-Ascending Dose)

Part A will be conducted in 2 alternating cohorts (Cohorts 1 and 2), each consisting of approximately 12 subjects who will participate in up to 3 study periods. The planned doses of LY3154885 to be tested are 15, 45, 100, 200, 400, and 500 mg (see Section 5.5 for details).

Sentinel dosing will be used in Part A of the study. For all dose levels, LY3154885 and placebo will be administered first to 2 subjects (1:1 LY3154885:Placebo) in a blinded manner. These subjects will be followed up for 24 hours postdose; if the dose is well tolerated, dosing of the remaining 10 subjects in the cohort at the same dose level may begin.

Each subject in Cohorts 1 and 2 will be randomized to receive 2 single oral doses of LY3154885 and 1 oral dose of placebo as a capsule formulation over 3 study periods in a crossover fashion. For each study period, it is intended that 8 subjects will receive LY3154885 and 4 subjects will receive placebo.

In Period 1, subjects will be admitted to the clinical research unit (CRU) on the afternoon of Day -2 for set up of baseline ambulatory blood pressure monitoring (ABPM) (see Section 9.4.4) and on Day -1 for Periods 2 and 3. Subjects will undergo an overnight fast (Section 6.3.1) before dosing with LY3154885 or placebo as a single oral dose on Day 1 and will remain inpatient for at least 48 hours after dosing (until Day 3), after which they may be discharged at the discretion of the investigator. The washout time between doses for a given subject will be at least 7 days. A poststudy follow-up visit will be conducted at least 7 days after the final dose.

All available safety data, including AEs, vital signs (blood pressure [BP] and pulse rate [PR]), ECGs, and clinical laboratory tests, from all subjects dosed will be assessed prior to escalating to

the next dose level (see Section 10.3.5). Safety data must include data from at least 2 days from a minimum of 6 subjects who received LY3154885. The investigator and sponsor will review the data, with the investigator remaining blinded. If dose escalation is terminated prior to reaching Dose 6 because of tolerability issues, previous dose levels may be repeated or lower/intermediate dose levels may be tested.

Subjects will provide total urine collections for the 36 hours postdose in each period for exploratory metabolism and potential assessment of drug absorption and renal elimination; an additional blood sample will be collected to determine serum creatinine measurements.

Figure HUAA.5.1 illustrates the study design for Part A.

	Period 1		Period 2		Period 3	
Cohort 1 (n=12; 8LY:4PL)	Dose 1 LY or PL	≥7 day washout	Dose 3 LY or PL	≥7 day washout	Dose 5 LY or PL	≥7 day washout
Cohort 2 (n=12; 8LY:4PL)		Dose 2 LY or PL	≥7 day washout	Dose 4 LY or PL	≥7 day washout	Dose 6 LY or PL

Safety review completed after each dose level prior to escalation

Abbreviations: LY = LY3154885; n = number of subjects; PL = placebo.
Each subject will receive 2 doses of LY3154885 and 1 placebo dose.

Figure HUAA.5.1. Illustration of study design for Part A.

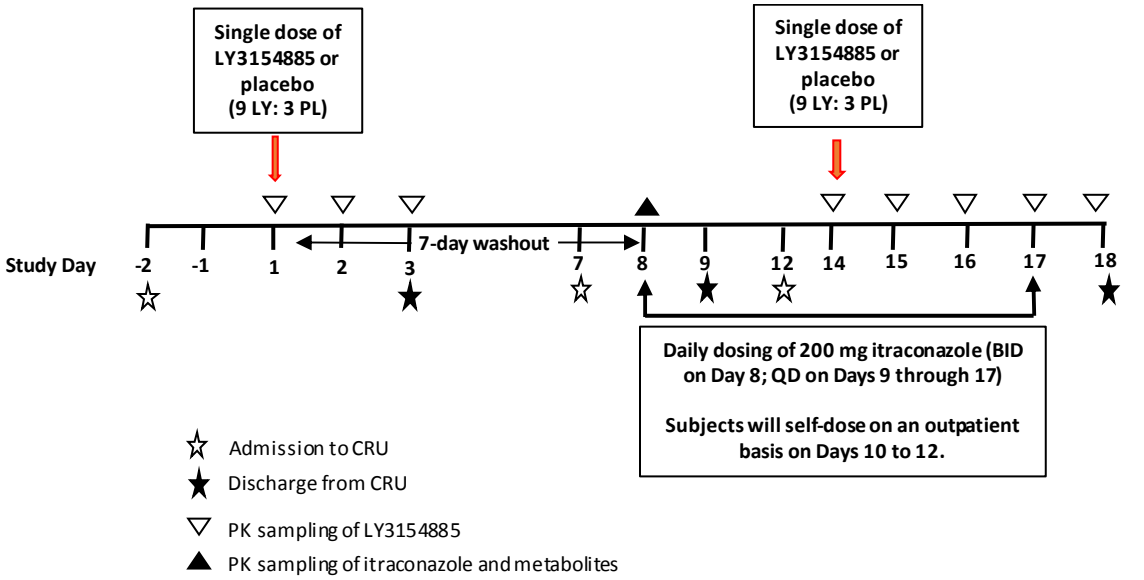
5.1.2. Part B (CYP3A4 Inhibition)

Part B will consist of approximately 12 subjects [9 LY3154885; 3 placebo] and will assess the effect of itraconazole, a CYP3A4 inhibitor, on the safety, tolerability, and PK of LY3154885. The LY3154885 dose to be studied in Part B will be determined based on safety, tolerability, and PK data from Part A and will be administered as a capsule formulation. See Section 5.5 for further LY3154885 dose justification.

As detailed in the Schedule of Activities (Section 2), subjects will be admitted to the CRU in the afternoon of Day -2 for set up of baseline ABPM (see Section 9.4.4) and will undergo an overnight fast (see Section 6.3.1) before receiving a single oral dose of LY3154885 or placebo on Day 1. Subjects may be discharged from the CRU on Day 3 and will be re-admitted on Day 7. There will be a 7-day washout period followed by 10 days of dosing with 200 mg itraconazole (twice daily on Day 8 [dose separated by 12 hours], then once daily on Days 9 through 17). See Section 6.3.1 for the fasting requirements for the itraconazole dosing. Subjects will be discharged from the CRU on Day 9 after receiving their dose of itraconazole and will be self-dosing on an outpatient basis from Days 10 through 12. Subjects will be asked to complete a diary card to document the actual date and time of dose administration.

Subjects will be re-admitted to the CRU in the evening of Day 12 and will undergo an overnight fast (see Section 6.3.1) before receiving a single oral dose of LY3154885 or placebo on Day 14, approximately 1 hour after the dose of itraconazole. Blood sampling for PK purposes (LY3154885 and itraconazole) will occur according to the Schedule of Activities in Section 2. Subjects will remain in the CRU until discharge on the morning of Day 18, approximately 24 hours after the final dose of itraconazole.

Figure HUAA.5.2 illustrates the study design for Part B.



Abbreviations: BID = twice daily; CRU = clinical research unit; LY = LY3154885; PK = pharmacokinetic; PL = placebo; QD = once daily.

Figure HUAA.5.2. Illustration of study design for Part B.

5.1.3. Part C (Multiple-Ascending Dose)

The decision to conduct Part C will be made after review of safety, tolerability, and PK data from Parts A (SAD) and B (CYP3A4 Inhibition).

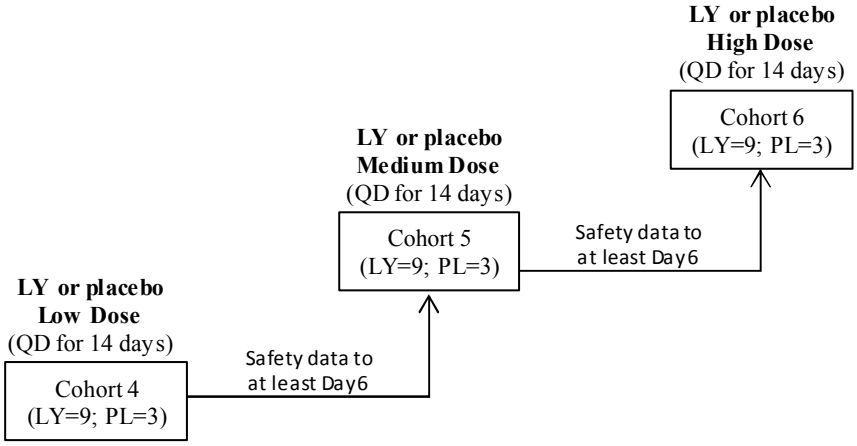
Part C will explore up to 3 dose levels in 3 separate cohorts (Cohorts 4 to 6) of healthy subjects. Each cohort will consist of approximately 12 subjects (9 LY3154885; 3 placebo) dosed daily for 14 days with a capsule formulation.

Subjects will participate in a single study period consisting of 14 days of once-daily dosing with LY3154885 or placebo; study drug will be administered as a single oral dose in the morning under fasted conditions (see Section 6.3.1). Subjects will be admitted to the CRU on the afternoon of Day -2 for set up of baseline ABPM (see Section 9.4.4) and will be required to remain in-house for at least 48 hours after dosing (Day 3), and at the discretion of the investigator. As detailed in the Schedule of Activities (Section 2), subjects will attend the CRU on Days 4, 5, 6, 9, and 10 on an outpatient basis for daily dosing and will be permitted to leave the CRU at the discretion of the investigator. Pharmacokinetic sampling will be conducted as detailed in Section 2. To assess CV effects and potential accommodation over time, ABPM will

be included on Day -1 (baseline) and on Days 1, 2, 7, 11 and 12, and 14. A poststudy follow-up visit will be conducted approximately 7 days after discharge.

The doses evaluated will be selected based on emerging data from Parts A and B and from the lower doses from Part C (see Section 5.5 for details). If the safety data do not support increasing the dose in subsequent cohorts, then a dose may be repeated or lower/intermediate doses may be explored. The PK data obtained during the study may be used to assist in dose-escalation decisions, but such data are not required for dose-escalation purposes. For the safety review prior to dose decisions between cohorts, all available safety data (AEs, vital signs, ECGs, and laboratory results) to Day 14 from at least 6 subjects taking LY3154885 must be reviewed by the sponsor and investigator. In addition, each cohort (including at least 6 subjects treated with LY3154885) will complete dosing to Day 14 prior to the next cohort being admitted to the CRU for dosing.

Figure HUAA.5.3 illustrates the study design for Part C.



Abbreviations: LY = LY3154885; PL = placebo; QD = once daily.

Figure HUAA.5.3. Illustration of study design for Part C.

5.1.4. Optional Part D (Pharmacokinetics of Capsule and Tablet Formulations and Food Effect)

The decision to conduct Part D will be made after review of safety, tolerability, and PK data from Parts A (SAD) and B (CYP3A4 Inhibition). Part D may be conducted in parallel with Part C.

Part D is optional and will assess the PK of single oral doses of LY3154885 in approximately 9 healthy subjects when administered as a capsule (Period 1), as a tablet (Period 2), and as a tablet with a high-fat diet (Period 3). The dose for Part D will not exceed the highest dose tested in Part A (SAD) that was deemed safe and well tolerated.

In Periods 1 and 2, subjects will be admitted to the CRU the afternoon of Day -2 for set up of baseline ABPM (see Section 9.4.4); admission for Period 3 will be on Day -1. In Period 1, subjects will undergo an overnight fast (see Section 6.3.1) before receiving a single oral dose of

LY3154885 (capsule formulation) on Day 1. Subjects will remain inpatient for at least 48 hours after dosing, after which they may be discharged at the discretion of the investigator. Subjects will be re-admitted to the CRU on Day 6 and will undergo an overnight fast before receiving a subsequent single oral dose of LY3154885 on Day 8 with the same formulation. Subjects will be discharged on Day 10, at least 48 hours after dosing. Re-admission to the CRU will be on Day 13, and following an overnight fast, subjects will receive a single oral dose of LY3154885 on Day 14 with the same formulation. Final discharge from the CRU will occur on Day 16. Pharmacokinetic sampling will be conducted as detailed in the Schedule of Activities (Section 2).

Period 2 will be conducted as described for Period 1; however, LY3154885 will be administered as a tablet formulation.

Period 3 will be conducted as described for Period 1; however, subjects will receive a single oral dose of LY3154885 (tablet formulation) after administration of a high-fat diet (see Section 6.3.1).

The follow-up visit will occur approximately 7 days after final discharge.

Figure HUAA.5.4 illustrates the study design for Part D.

	Period 1		Period 2		Period 3	
LY3154885 n=9	LY3154885 capsule (Days 1, 8 and 14)	≥7 day washout	LY3154885 tablet (Days 1, 8 and 14)	≥7 day washout	LY3154885 tablet after high fat meal (Days 1, 8 and 14)	≥7 day washout

Intensive PK sampling on Days 1, 8, and 14

Abbreviation: n = number of subjects; PK = pharmacokinetic.

Figure HUAA.5.4. Illustration of study design for Part D.

5.2. Number of Participants

For Part A, up to 30 subjects may be enrolled into Cohorts 1 and 2 in order to ensure that approximately 12 subjects per cohort (8 LY3154885; 4 placebo) complete this part of the study.

For Part B, up to 15 subjects may be enrolled in order to ensure that approximately12 subjects (9 LY3154885; 3 placebo) complete this part of the study.

For Part C, up to 45 subjects may be enrolled in order to ensure that approximately 36 subjects complete this part of the study (with approximately 12 subjects [9 LY3154885; 3 placebo] completing each dose level).

For optional Part D, up to 12 subjects may be enrolled in order to ensure that approximately 9 subjects complete this part of the study.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This study will be conducted to evaluate the safety, tolerability, and PK of single and multiple doses of LY3154885 in healthy subjects.

In Parts A, B, and C, the subjects and site staff (except pharmacy staff) will be blinded to treatment allocation to allow an unbiased assessment of the safety and tolerability data, which will allow a more robust comparison between LY3154885 and placebo data.

In Part A, B, and D, a washout period of at least 7 days has been selected to minimize carryover effects between doses based on the predicted human PK of LY3154885 from nonclinical studies.

A tablet formulation is being developed for upcoming studies and the effect of food on the PK of LY3154885 is unknown; therefore, Part D will compare the PK profile of a tablet formulation versus capsule formulation and the effect of food on the PK of LY3154885 given with the tablet formulation.

5.5. Justification for Dose

In Part A, the planned clinical doses to be tested are 15, 45, 100, 200, 400, and 500 mg based on animal toxicology/toxicokinetics, preclinical pharmacology, and PK information. In Part B (CYP3A4 Interaction), the LY3154885 dose selection will be based on emerging data from Part A but is currently planned to be ≤200 mg. In Part C (MAD), dose selection will be based on emerging safety, tolerability, and PK data from Part A and Part B, but Part C is currently planned to start at 35 mg and not exceed the highest dose in Part A or the maximum exposure achieved in Part A or B that are found to be well tolerated. In Part D, the dose for the capsule and tablet is planned to be ≤400 mg but will ultimately be based on emerging safety, tolerability, and PK data from Part A.

The toxicity profile of LY3154885 has been characterized in rats and monkeys through a package of GLP compliant, repeat-dose toxicology, safety pharmacology, and genetic toxicology studies; non-GLP toxicity studies were conducted with LY3154885 as well and are discussed in the IB. These studies with LY3154885 demonstrate an acceptable safety profile for human testing with CV and CNS effects that are transient and monitorable.

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(Table HUAA.5.1).

The maximum dose for this study is expected to be 500 mg based on animal toxicology studies and human PK predictions for LY3154885, A 500-mg dose in humans is predicted to result in a mean plasma AUC of µg×hr/mL and C_{max} of µg/mL; these values are equivalent to 1/10th the AUC at the NOAEL in monkeys and 1/10th the C_{max} at the NOAEL in rats. The C_{max} and AUC-based multiples associated with from the non-GLP study in rats, which were not observed at similar exposures in the GLP study, are also presented in Table HUAA.5.1. To note, the predicted human C_{max} at 500 mg is below the C_{max} at the NOEL for in both rats and monkeys. Pharmacokinetic data will be reviewed during the study to support dose escalations (see Section 10.3.5 for details) and maintain predicted drug exposures below 1/10th the AUC at the NOAEL in monkeys and 1/10th the C_{max} at the NOAEL in rats. A dose higher than 500 mg may be studied if human PK data from previous cohorts suggests the predicted exposure will be below 1/10th the AUC at the NOAEL in monkeys and 1/10th the C_{max} at the NOAEL in rats.

In Part B (CYP3A4 Interaction), the LY3154885 dose selection will be based on emerging data from Part A but is currently planned to be ≤200 mg. It is predicted that the maximum exposure increase in LY3154885 when administered with itraconazole, a strong CYP3A4 inhibitor, is

approximately 2.6-fold. Therefore, the LY3154885 dose selected will be below the highest dose deemed well tolerated that has a plasma exposure to allow for up to a 2.6-fold increase in exposure that may result from coadministration with itraconazole, and the predicted LY3154885 plasma exposure at this dose when coadministered with itraconazole will be below 1/10th the AUC at the NOAEL in monkeys and 1/10th the C_{max} at the NOAEL in rats. The dose regimen for itraconazole will be 200 mg twice daily on Day 8 (dose separated by 12 hours) and once daily on Days 9 through 17.

In Part C (MAD), the doses will be based on emerging safety, tolerability, and PK data from Part A (SAD) and Part B. Emerging safety and tolerability data from Part C will also be considered for dose escalation. The highest dose tested in Part C will not exceed the highest dose in Part A (currently planned to be 500 mg) that was well tolerated or the maximum exposure achieved in Part A or B found to be well tolerated.

In Part D, the planned dose for the capsule and tablet will be ≤400 mg but will ultimately be based on emerging safety, tolerability, and PK data from Part A.

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6. Study Population

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

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, are not permitted.

6.1. Inclusion Criteria

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

[1] are overtly healthy males or females, as determined by medical history and physical examination

[1a] male subjects:

Men, regardless of their fertility status, with partners who are nonpregnant women of childbearing potential, must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms with spermicide as well as 1 additional highly effective (<1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide) for 3 months following dosing.

Men with pregnant partners should use condoms with spermicide during intercourse for the duration of the study or for 3 months following dosing, whichever is longer.

Men who are in exclusively same-sex relationships (as their preferred and usual lifestyle) or with female partners of nonchildbearing potential are not required to use contraception.

Men should refrain from sperm donation for the duration of the study or for 3 months following the last dose of study drug, whichever is longer.

[1b] female subjects of nonchildbearing potential, including those who are:

A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, confirmed tubal ligation, or tubal occlusion) or congenital anomaly such as Müllerian agenesis; or

B. postmenopausal, defined as 1 of the following:

i. a woman at least 50 years of age with an intact uterus, not on hormone replacement therapy, who has had either:

   a. cessation of menses for at least 1 year; or

   b. at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone level ≥40 mIU/mL at screening

ii. a woman at least 55 years of age, not on hormone replacement therapy, who has had at least 6 months of spontaneous amenorrhea; or

iii. a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

[2] are between 21 and 65 years of age, inclusive, at the time of screening

[3] have a body mass index (BMI) of 18.0 to 35.0 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 that are judged to be not clinically significant by the investigator

[5] have venous access sufficient to allow for blood sampling per the protocol

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

[7] are able and willing to give signed 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, biological or legal guardian, child, or sibling

[9] are Lilly employees

[10] are currently enrolled in a clinical study 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 study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed

[12] have previously completed or withdrawn from this study or any other study investigating LY3154885, and have previously received LY3154885

[13] have known allergies to LY3154885, related compounds or any components of the formulation, itraconazole, or history of significant atopy

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

[15] have a marked baseline prolongation of corrected QT (QTc) interval (for example, repeated demonstration of a QTcB interval >450 msec for males or >470 msec for females);

A history of additional risk factors for Torsades de Pointes (for example, heart failure, hypokalemia, family history of Long QT Syndrome);

The use of concomitant medications that prolong the QT/QTc interval

[16] have an abnormal BP (taken after the subject has been in a supine position for at least 5 minutes) for the population, as determined by a systolic BP >140 mm Hg or a diastolic BP >90 mm Hg at screening or a preexisting history of hypertension. Up to 2 additional measurements may be taken after an appropriate resting interval at screening to confirm eligibility

[17] have a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine (such as Cushing syndrome, hyperthyroidism, hyperaldosteronism), hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational medicinal product (IMP); or of interfering with the interpretation of data

[18] have a history of or current significant psychiatric disorders

[19] have a history of head injury (eg, skull fracture, cerebral contusion, trauma resulting in prolonged unconsciousness), intracranial neoplasm or hemorrhage, prior seizure (other than remote history of childhood febrile seizure), or other condition that would place the subject at increased risk of seizure

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

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

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

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

[24] are women who are lactating

[25] have used or intend to use over-the-counter/herbal supplements (eg, St. John's wort) or prescription medication within 14 days or 5 half-lives, whichever is longer, before initial dosing or during the study (vitamin/mineral supplements and occasional paracetamol/acetaminophen up to 3-g dose in a 24-hour period are allowed). If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the investigator and sponsor. Medications that inhibit or induce CYP3A4 are specifically excluded within 14 days prior to dosing and during the study

[26] have donated blood of more than 450 mL or have participated in a clinical study that required similar blood volume drawn within the past 3 calendar months

[27] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (males >65 years and females) or are unwilling to stop alcohol consumption for 24 hours prior to CRU admissions 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)

[28] have tobacco consumption of more than 10 cigarettes per day (or the equivalent) or are unable or unwilling to refrain from nicotine use while resident at the CRU

[29] consume Seville oranges or Seville orange–containing products, grapefruit or grapefruit-containing products, star fruits or star fruit-containing products, pomegranates, and/or pomelos within 14 days prior to dosing or during the study

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

In addition, for Part B only:

[31] have impaired hearing or a history of hearing problems

In addition, for Part C only:

[32] Presence of significant uncontrolled neuropsychiatric disorder; have recent history (within 30 days prior to the screening visit and any time between screening and admission) of a suicide attempt; or develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the "Suicidal Ideation" portion of the Columbia Suicide-Severity Rating Scale [C-SSRS]) or develops suicide-related behaviors as recorded on the C-SSRS at screening or admission; or are clinically judged by the investigator to be at risk for suicide

6.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria [8] and [9] prevent conflict of interest in study participants. Exclusion Criteria [10] through [29] and [32] exclude medical conditions, medication intolerance, and concomitant medication use that may constitute a risk for the subject and/or may confound the

assessment of study endpoints. Exclusion Criterion [31] excludes subjects with hearing problems in Part B because itraconazole has been associated with transient or permanent hearing loss.

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

Part A: Subjects will be required to fast overnight (at least 8 hours) prior to dosing on Day 1 and for at least 4 hours after dosing with LY3154885/placebo, with the exception of water, which will be freely available after dosing.

Part B: Subjects will be required to fast overnight (at least 8 hours) prior to each dosing day (including itraconazole dosing) and for at least 4 hours after dosing with LY3154885, and coadministration of LY3154885 and itraconazole, with the exception of water that will be freely available after dosing. Subjects will also need to fast for approximately 2 hours prior to the evening dose of itraconazole on Day 8 and at least 1 hour after dosing, with the exception of water, which will be freely available after dosing.

Part C: Subjects will be required to fast overnight (at least 8 hours) on all dosing days and for at least 4 hours after dosing on Days 1, 7, and 14 (intensive PK days), with the exception of water, which will be freely available after dosing. On nonintensive PK days, subjects may receive a light breakfast approximately 1 hour after dosing.

Part D: In Periods 1 and 2, subjects will be required to fast overnight (at least 8 hours) prior to dosing on Days 1, 8, and 14 and for at least 4 hours after dosing with LY3154885, with the exception of water, which will be freely available after dosing. All other meals will be provided according to CRU procedures. In Period 3, following an overnight fast of at least 8 hours, subjects will start the high-fat diet (see below) 30 minutes prior to administration of the study drug on Days 1, 8, and 14. Subjects will consume this entire meal in 30 minutes or less; however, the study drug will be administered 30 minutes after the start of the meal. The study drug should be administered with approximately 240 mL of room temperature water. No further food will be allowed for at least 4 hours postdose. Fluids will be restricted from 1 hour prior to and until 1 hour after dosing, except for fluid provided with the meal and water required for dose administration.

The standardized high-fat, high-calorie meal (fat comprises approximately 50% of total caloric content of the meal) should consist of approximately 1000 calories. No additional food or substitute is allowed. A typical test meal is 2 eggs fried or scrambled in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. This test meal derives approximately 150, 250, and 500 to 600 calories from protein, carbohydrates, and fat, respectively.

6.3.2. Caffeine, Alcohol, and Tobacco

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.

Subjects will not be permitted to consume alcohol from 48 hours prior to CRU admissions and while resident at the CRU. During the study, while not resident at the CRU, the maximum daily alcohol intake should not exceed 2 units (see Exclusion Criterion [27], Section 6.2, for unit definition).

Smoking, tobacco consumption, or use of any nicotine-replacement therapy is not permitted while resident at the CRU. While not resident in the CRU, smoking should not exceed 10 cigarettes per day or equivalent in nicotine use or nicotine substitutes.

6.3.3. Activity

Subjects should avoid strenuous exercise and/or activity for at least 48 hours prior to CRU admission and while resident at the CRU.

Subjects should remain upright for at least 2 hours after dosing, with the exception of any requirements for protocol procedures (eg, supine for ECGs).

6.3.4. Blood and Plasma Donations

Subjects are not permitted to make blood or plasma donations while participating in the study.

6.4. Screen Failures

As this study will be conducted in healthy subjects only, individuals who do not meet the criteria for participation (ie, screen failure) may not be re-screened, although specific tests such as clinical laboratory tests and vital signs/ECGs may be repeated at the discretion of the investigator to confirm study eligibility.

Subjects who were eligible for inclusion in previous cohorts but were not randomized for nonmedical reasons may be reassessed for eligibility/inclusion in a subsequent cohort.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of LY3154885 or matching placebo administered orally. Table HUAA.7.1 shows the treatment regimens.

Capsules (or tablets for optional Part D) of LY3154885 and/or placebo will be administered orally with approximately 240 mL of room temperature water in the morning of each dosing day with subjects in a sitting position. Subjects will not be allowed to lie supine for approximately 2 hours after dosing, unless clinically indicated or for study procedures.

Table HUAA.7.1. Treatments Administered

Treatment Name	LY3154885	LY3154885	Placebo	Itraconazole
Dosage Formulation	Capsule	Tablet	Capsule	Solution
Unit Dose Strength(s)/ Dosage Level(s)	Extemporaneous preparation 15 to 500 mg	Extemporaneous preparation Dose to be determined	Matching placebo	10 mg/mL
Route of Administration	Oral	Oral	Oral	Oral

The investigator or designee is responsible for:

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

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

7.1.1. Packaging and Labeling

The LY3154885 capsules or tablets will be prepared extemporaneously. The proposed range of strengths to be prepared is listed in Table HUAA.7.1.

In Parts A, B and C, for any specific cohort/dosing period, the total number of capsules administered will be the same for all subjects, regardless of whether assigned to placebo or LY3154885. However, the number of capsules may vary between dosing periods and cohorts to maintain the blind.

Instructions for extemporaneous preparation of the study drug will be provided by the sponsor. This will be performed by trained personnel (eg, pharmacist) within a facility at the CRU who are qualified to perform these types of operations.

For LY3154885 capsules, the LY3154885 pure compound with no inactive ingredients will be filled into capsules.

For LY3154885 tablets, the LY3154885 pure compound will be combined with other common excipients and compressed into tablets for use in Part D.

Matching placebo for the LY3154885 capsules will be sourced centrally. Itraconazole will be sourced locally by the site.

The investigational product will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

In Parts A, B, and C, the randomization table will be prepared by the statistician (or appropriate delegate) for the study and provided to the CRU pharmacists or pharmacy staff involved in dose preparation. The allocation and dispensing of the study drug will be fully documented and verified by a second person. Detailed records of the amounts of the study drug received, prepared, dispensed, and remaining at the end of the study will be maintained by the CRU pharmacist.

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the subject's case report form (CRF). In Part B, for the outpatient dosing days for itraconazole, subjects will record the actual time of dose administration on a diary card.

Dosing with itraconazole should occur approximately 1 hour before dosing with LY3154885 (or placebo) when the 2 drugs are coadministered.

7.3. Blinding

Parts A, B, and C will be investigator- and subject-blind; Part D will be open-label. The sponsors and site monitors are not blinded.

To preserve the blind, only a minimum number of personnel at the CRU (namely, CRU pharmacy staff) will see the randomization table before the study is complete. Individuals involved with study drug preparation will not be involved in any of the clinical aspects of the study, including study drug administration and AE assessments. Blinding will be maintained throughout the conduct of the study until after all data are cleaned to an acceptable level of quality and the CRF is entry locked.

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

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

7.4. Dose Modification

Dose levels, sampling schedule, timing of procedures (eg, PK and ECG assessments), and length of CRU stay may be adjusted in view of emerging safety or PK data during the study. Dose increments may be changed, a dose level may be repeated, or a lower dose may be administered. If a dose reduction is required, the dose level for the following cohort (ie, the cohort following the one that received a lower than planned dose) cannot exceed ½ log. The timing of blood samplings may be adjusted, but the number of samples will not exceed what has been planned, plus the additional samples. The duration of the CRU stay or the duration of safety follow-up may be increased (eg, if the half-life of LY3154885 is longer than anticipated) but not decreased. These changes must be appropriately documented and communicated by the sponsor to the investigator. Because these adjustments to timings or dose levels are allowable changes permitted by the protocol, they would not require a protocol amendment.

7.4.1. Dose Decision/Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the maximum tolerated dose (MTD) is determined or the highest planned dose is 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. In addition, if available at the time of the dose-escalation decision, PK results will be used as supporting data. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly study team. See Sections 5.1.1 and 5.1.3 for further details.

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

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 related to LY3154885 administration
2) 2 subjects experience a clinically significant event of persistent tremors that is deemed to be related to LY3154885 administration
3) 2 subjects experience clinically significant increases in scheduled vital signs that are deemed to be related to LY3154885 administration
4) 2 or more subjects at 1 dose level experience other moderate or severe treatment-related AEs that impair normal activities and are deemed to be related to LY3154885 administration

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm that appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all investigational product received and that any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive IMP or study materials, and only authorized site staff may supply or administer IMP. All IMP should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

Subjects on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. These permitted medications have been described in Exclusion Criterion [25].

In general, concomitant medication should be avoided; however, paracetamol/acetaminophen (1g, maximum 3g/24 hours) may be administered at the discretion of the investigator for treatment of headaches, etc. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the subject in the study may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist. Drugs that are known inducers or inhibitors of CYP3A4 are specifically excluded. Any medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

This section is not applicable for this study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

A subject will be discontinued from receiving further doses of IMP if the investigator assesses that continuation on IMP may pose a risk to the well-being of the subject in question. Subjects may also be discontinued from the IMP if a clinically significant event (CSE) occurs in the opinion of the investigator. Following the investigator's determination that CSE criteria have been met and the investigator's judgment of relatedness to the IMP is documented, a decision will be made between the investigator and Lilly or its designee regarding subject discontinuation.

Discontinuation of the IMP for abnormal liver tests **should be considered** by the investigator when a subject meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× upper limit of normal (ULN)
- ALT or AST >3× ULN and total bilirubin level (TBL) >2× ULN or international normalized ratio >1.5 or
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Alkaline phosphatase (ALP) >3× ULN
- ALP >2.5× ULN and TBL >2× ULN
- ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Subjects discontinuing from the treatment prematurely for any reason should complete AE and other follow-up procedures per Section 2 of this protocol.

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 study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the subject should be discontinued from the study
    - if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- Subject Decision
    - the subject requests to be withdrawn from the study
- If any of the potentially clinically significant vital sign criteria (Table HUAA.8.1) are met at 3 **consecutive scheduled** time points using in-clinic vital sign monitoring on Day 1 and following study drug dosing, the subject should be discontinued from the study drug. The relative value of the potentially clinically significant vital sign criteria is calculated by comparing the mean of the 3 supine BP and PR measurements at Time 0 on that day.

Table HUAA.8.1. Potentially Clinically Significant Vital Sign Criteria

	Low[a]	High[a]
Systolic BP (mm Hg)	≤90 AND ≥20 decrease	≥180 AND ≥20 increase
Diastolic BP (mm Hg)	≤50 AND ≥15 decrease	≥105 AND ≥15 increase
Pulse Rate (bpm)	≤50 AND ≥15 decrease	≥120 AND ≥15 increase

Abbreviations: BP = blood pressure, bpm = beats per minute, mm Hg = millimeters of mercury

[a] Both conditions on absolute AND relative values are required for the measures to meet the criteria for potentially clinically significant (for example BP ≥180 AND ≥20 increase are both required for systolic blood pressure to meet the criteria for potentially clinically significant)

    - For vital sign measurements that meet the criteria for potentially clinically significant vital signs (Table HUAA.8.1), action will be left to the discretion of the investigator and may include discontinuation of study drug or subject. Prior to subject being discontinued from the study, the investigator should consult with the Lilly clinical pharmacologist (CP) or designee.
- Subjects will be discontinued from the study if the mean QT interval corrected for heart rate using Fridericia's formula (QTcF) on the ECG is >500 milliseconds or there is an absolute change of >60 milliseconds when compared with baseline

8.3. Subjects Lost to Follow-up

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

9. Study Assessments and Procedures

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

The specifications in this protocol for the timing of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual procedure time has to be correctly recorded in the CRF, including samples that are collected outside of the allowable time window. Failure or being late (ie, outside stipulated time allowances) to perform procedures or obtain samples due to legitimate clinical issues (eg, equipment technical problems, venous access difficulty, or subject defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations but the CRU will still be required to notify the sponsor in writing via a file note.

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

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

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

9.1. Efficacy Assessments

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.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the 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.

The investigator will record all relevant AE and SAE information in the CRF. After the informed consent form is signed, study site personnel will record, via CRF, the occurrence and

nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

A "reasonable possibility" means that there is a potential cause and effect relationship between the investigational product 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 IMP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above

Study site personnel must alert the Lilly CP/clinical research physician (CRP), or designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, 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 IMP) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to investigational product or procedure. 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 they have 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 LY3154885 is considered any dose higher than the dose assigned through randomization. General supportive medical management will be provided at the investigator's discretion.

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).

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

9.4.2. Vital Signs

For each subject, vital sign measurements should be conducted according to the Schedule of Activities (Section 2). Vital signs will comprise BP, PR, and body temperature.

For supine measurements of BP and PR, subjects should be in the supine position for at least 5 minutes before the procedure.

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.

For orthostatic measurements of BP and PR, subjects should be supine for at least 5 minutes and stand for at least 2 minutes for supine and standing measurements, respectively. If the subject feels unable to stand, supine vital signs only will be recorded.

9.4.3. Electrocardiograms

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

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

At screening, early discontinuation, and follow-up, 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. In Parts A, B and D, single ECGs will be collected at all time points.

In Part C, at all time points other than screening, early discontinuation, and follow-up, ECGs will be collected in triplicate.

Electrocardiograms should preferably be recorded before collecting any blood samples. Subjects must be supine for approximately 5 minutes before ECG collection and remain supine but awake during ECG collection. Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECG replicates than expected at a particular time point will be permitted to ensure high-quality records.

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

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

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

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

9.4.4. Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring will be performed in all parts of the study. The ABPM device will be fitted to the subject's nondominant arm and will record ambulatory BP and PR every 30 minutes during awake hours (0700 hours to 2200 hours) and every 60 minutes throughout the night (2200 hours to 0700 hours). All Day -1 recordings are 24 hours and will serve as baseline. The recording on dosing days will be initiated approximately 2 hours prior to the planned dosing time (baseline value) and will continue according to the Schedule of Activities (Section 2). Subjects will be encouraged to maintain light activity (e.g, walking) and keep the same routine during the ABPM study days. Ambulatory blood pressure monitoring data may not be used for subject management or dose escalation decisions.

9.4.5. Neurological Examination

A directed neurological examination will be performed by the investigator (or designee) at the time points specified in the Schedule of Activities (Section 2). If clinically significant abnormalities are noted at these time points, additional examinations should be performed as clinically necessary. Examination procedures may include inspection for tremor, extraocular movements, brachial and patellar deep tendon reflexes, finger-nose pointing, and Romberg sign.

Table HUAA.9.1 presents the scoring of neurological examination findings.

Table HUAA.9.1. Scoring of Neurological Examination Findings

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

9.4.6. Columbia-Suicide Severity Rating Scale (Part C Only)

The C-SSRS (Columbia Lighthouse Project [WWW]) captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior has occurred. The C-SSRS will be administered by appropriately trained site personnel at the time points specified in the Schedule of Activities (Section 2). Subjects with any significant change must be referred to a psychiatrist.

If the investigator determines that suicide-related behaviors have occurred, the Lilly Self-Harm Supplement Form will be used to collect additional information to allow for a more complete assessment of these behaviors. As noted above, subjects with any clinically significant change, as determined by the investigator, must be referred to a psychiatrist.

9.4.7. Exploratory Scales and Questionnaire (Part C Only)

9.4.7.1. Profile of Mood States Second Edition

The Profile of Mood States Second Edition (POMS-2) (Heuchert and McNair 2012) is a 35-item, adjective rating scale and is considered to be a standardized mood-state inventory. Subjects will be instructed to rate each adjective on the basis of how they feel at the present time on a scale with 5 response options (scored numerically from 0 to 4, respectively): "Not at all," "A little," "Moderately," "Quite a bit," and "Extremely." The POMS-2 will be completed at the time points stipulated in the Schedule of Activities (Section 2).

9.4.7.2. Physician Withdrawal Checklist

The Penn Physician Withdrawal Checklist (PWC-20) is a 20-item checklist that will be used to assess the presence and severity of withdrawal symptoms. The scale was originally developed to assess the severity of withdrawal symptoms in anxiolytic medication discontinuation (Rickels et al. 2008). The PWC-20 is a validated, shortened version of the original 35-item checklist, where the 20-items were selected based on their statistical ability to differentiate between placebo and LY3154885 (Rickels et al. 1990; Schweizer et al. 1990). The 20 items assess the subject's level of symptoms on a variety of withdrawal symptoms since last visit. Each of the 20 items are scored as 0 (not present), 1 (mild), 2 (moderate), or 3 (severe).

9.4.8. Safety Monitoring

The Lilly CP and principal investigator (PI) will monitor safety data throughout the course of the study. In the event of safety concerns, the Lilly clinical pharmacologist and PI will recommend a protocol amendment or termination of the trial and will report to the investigational review board (IRB) accordingly.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review the following data:

- trends in safety data, such as BP, PR, ECGs, and ABPM
- laboratory analytes
- adverse events

When appropriate, the Lilly CP will consult with the functionally independent Global Patient Safety therapeutic area physician or CRP.

9.4.8.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated TBL ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the

abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Additional safety data should be collected if 1 or more of the following conditions occur:

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

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 3 mL and approximately 2 mL will be collected to determine the plasma concentrations of LY3154885 and itraconazole, respectively. If indicated by emerging data, a maximum of 3 blood samples per subject may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

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

Urine samples will be collected for the characterization of renal clearance of LY3154885. Urine samples will be used to determine creatinine and LY3154885 concentration. Total urine output for the appropriate period post LY3154885 administration will be collected, pooled, and refrigerated. At the end of the collection period, the total urine volume will be recorded. Any special instructions for the collection and handling of urine samples will be provided by the sponsor. Exploratory metabolite identification of LY3154885 may be conducted using urine samples. In Part A only, venous blood samples of approximately 3.5 mL each will be collected to determine serum creatinine measurements.

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 LY3154885 and itraconazole and metabolites will be assayed using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method. Samples collected from subjects receiving placebo will be retained and only analyzed for LY3154885 if required to confirm subject dosing records.

Bioanalytical samples collected to measure investigational product concentrations (including placebo samples) will be retained for a maximum of 2 years following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism and/or protein binding work.

9.6. Exploratory Pharmacodynamics

9.6.1. Exploratory Cognition Assessments (Part C Only)

The Digital Symbol Substitution Test (DSST) and Hopkins Verbal Learning Test (HVLT) will be included in Part C to assess relevant aspects of cognition, vigilance, and working memory that may provide a pharmacodynamic signal in healthy volunteers. The tests will be completed at the time points stipulated in the Schedule of Activities (Section 2).

- *DSST*: The DSST is an assessment of complex scanning and visual tracking. The screen shows a series of 9 numbered symbols that represent a "key." The participant is then presented with a series of parallel boxes that contain a symbol in the top half of the box and must provide a "number" response for the bottom half by referring to the key. Numbers are selected using the touch screen. The participant is given 90 seconds to respond to as many symbols as possible.
- *HVLT*: The HVLT is an easily administered 12-item, 3 learning trial, verbal learning test with delayed recall and recognition memory testing. The test requires recall of a series of 12 words over 3 learning trials, free recall after a delay, and a recognition trial.

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 exposure or response to LY3154885 and to investigate genetic variants thought to play a role in neurodegenerative diseases or neurological disorders. 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/IRBs impose shorter time limits, for the study at a facility selected by Lilly. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3154885 or after LY3154885 is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. 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, pharmacodynamics, 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.

Blood samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3154885, mechanism of action of LY3154885, and/or research method, or for validating diagnostic tools or assay(s).

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. 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 LY3154885 or after LY3154885 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 is customary for Phase 1 studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Subjects who are randomized but not administered treatment or do not complete all treatment periods/doses may be replaced to ensure that enough subjects complete all parts of the study. Replacement subjects will be allocated the same treatment/sequence as the dropout subjects. 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.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

The subject's age, sex, weight, BMI, height, race, or other demographic characteristics will be recorded and may be used in the PK and safety analyses as quantitative or classification variables. These data will be summarized using standard descriptive statistics.

10.3. Statistical Analyses

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

Pharmacokinetic analyses will be conducted on data from all subjects who receive at least 1 dose of the investigational product and have evaluable PK data.

Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

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

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 enrollment 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 AEs, clinical laboratory parameters, vital signs, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data. All planned safety analyses will be detailed in the statistical analysis plan (SAP).

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3154885 will be calculated by standard noncompartmental analysis methods. Parameters for analysis will be maximum observed drug concentration (C_{max}), time to C_{max} (t_{max}), and area under the concentration versus time curve (AUC) of LY3154885 following single and multiple doses of LY3154885. Following multiple dosing, accumulation ratios based on LY3154885 AUC will be calculated as follows: AUC Day 14 / AUC Day 1 and AUC Day 7 / AUC Day 1. Other PK parameters such as half-life, apparent clearance, and apparent volume of distribution may be reported using noncompartmental analysis methods.

If appropriate data are obtained, renal clearance of LY3154885 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 clearance.

If available, plasma concentration data for itraconazole and its metabolites (if applicable) will be summarized or listed in the clinical study report, and the data may subsequently be used for exploratory model development. A noncompartmental PK analysis of itraconazole and its metabolites may be conducted if deemed valuable to the interpretation of the study results but is not required to complete the clinical study report.

10.3.2.2. Pharmacokinetic Statistical Inference

Descriptive statistics of the PK parameters calculated from Parts A, B, C, and D will be presented by treatment. The following details are noted for the respective sections.

Part A: The PK parameters C_{max} and AUC for LY3154885 will be evaluated to estimate the dose-exposure proportionality of LY3154885 using a linear-mixed-effect power model. In this model, log-transformed dose will be the independent variable and subject will be a random effect. Both C_{max} and AUC will be log-transformed prior to analysis. The least-squares (LS) means for each treatment together with the treatment differences and associated 90% confidence intervals (CIs) will be estimated from the model. These estimates will be back-transformed to present geometric means, the ratios of geometric means, and the corresponding 90% CIs.

Part B: The PK parameters C_{max} and AUC for LY3154885 when administered alone and with itraconazole will be compared using an analysis of variance (ANOVA) model. The parameters will be log-transformed prior to analysis. The model will include a fixed-effect for the treatment (LY + itraconazole : LY) and a random effect for subject. The LS means for each treatment, the

difference between the treatment LS means (LY3154885 + itraconazole – LY3154885), and the associated 90% CIs will be estimated from the ANOVA model and back-transformed from the log scale to provide estimates of the geometric means, geometric mean ratio, and corresponding 90% CIs. The t_{max} of LY3154885 for both treatments will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference and 90% CI will be calculated.

Part C: The plasma PK parameters C_{max} and AUC for LY3154885 obtained on Day 14 will be evaluated to estimate the dose-exposure proportionality of LY3154885 using a linear-mixed-effect power model. For details of the model, see Part A above.

Plasma concentrations of LY3154885 will be evaluated graphically and/or descriptively to assess the achievement of steady-state, but no formal analysis will be performed for attainment of steady-state.

Part D:

Effect of formulation: The AUC and C_{max} for LY3154885 following administration with a capsule and tablet formulation in a fasted state will be log transformed and analyzed using a mixed effects ANOVA model. The model will include fixed effects for formulation (capsule : tablet). The LS means for each formulation 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 means. The t_{max} of LY3154885 between formulations will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference and 90% CI will be calculated.

Effect of high-fat diet: The AUC and C_{max} for LY3154885 following administration with a tablet formulation in the fed state and fasted state will be log transformed and analyzed using a mixed-effects ANOVA model. The model will include fixed effects for food (fed : fasted). The LS means for fed and fasted 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 means. The t_{max} of LY3154885 between fed and fasted will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference and 90% CI will be calculated.

10.3.3. Exploratory Pharmacodynamic Analyses

Endpoints from the DSST and HVLT will be summarized by domain (as appropriate), time, and treatment. Change from baseline may be displayed as appropriate.

Further details of analyses will be provided in the SAP.

10.3.4. Exploratory Pharmacokinetic/Pharmacodynamic Analyses

No LY3154885 exposure–response analyses are planned; however, analyses may be conducted for exploratory purposes based on review of the data.

10.3.5. Data Review During the Study

Access to safety and tolerability data is scheduled to occur after every dosing session (see Sections 5.1.1, 5.1.2, 5.1.3, and 5.1.4 [study design], and 5.5 [dose justification] for further details). Pharmacokinetic data will be reviewed to guide implementation of this study (such as adjustment to blood sampling time) and to support dose escalations at the following decision points:

- In Part A, LY3154885 PK data (up to 48 hours postdose) from Doses 1 to 3 will be reviewed prior to administration of Dose 5
- In Part A, LY3154885 PK data (up to 48 hours postdose) from Dose 5 will be reviewed prior to administration of Dose 6
- In Part B, LY3154885 PK data (up to 96 hours postdose) will be reviewed to inform a decision on the conduct of Part C and D
- In Part C, LY3154885 PK data (up to 24 hours postdose on Day 15) from the low dose (Cohort 4) will be reviewed prior to administration of the high dose (Cohort 6)

The investigator and the Lilly sponsor team will make the determination regarding dose escalation based upon their review of the safety and tolerability data and any available PK data. Data reviews may be added as deemed appropriate by the sponsor without a protocol amendment.

10.3.6. Interim Analyses

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

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ABPM	ambulatory blood pressure monitoring
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
blinding	A procedure in which one or more parties to the study 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/her 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/or his/her 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
BP	blood pressure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed drug 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 study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.

CP	clinical pharmacologist
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	cardiovascular
CYP	cytochrome P450
D1 PAM	positive allosteric modulator (also called "potentiator") of the dopamine D1 receptor
DSST	Digital Symbol Substitution Test
ECG	electrocardiogram
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
GLP	good laboratory practice
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HR	heart rate
HVLT	Hopkins Verbal Learning Test
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

Investigational medicinal product (IMP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB	institutional review board
LC/MS/MS	liquid chromatography with tandem mass spectrometry
LS	least squares
MAD	multiple-ascending dose
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
open-label	A study in which there are no restrictions on knowledge of treatment allocation; therefore, the investigator and the study participant are aware of the drug therapy received during the study.
PD	Parkinson's disease
PI	principal investigator
PK	pharmacokinetic(s)
POMS-2	Profile of Mood States Second Edition
PR	pulse rate
PWC-20	Penn Physician Withdrawal Checklist
QTc	QT interval corrected for heart rate
QTCF	QT interval corrected for heart rate using Fridericia's formula
randomize	the process of assigning subjects/patients to an experimental group on a random basis
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

SRP	safety review panel
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time to C_{max}
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

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

Urinalysis[b]:
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Leukocytes
- Microscopic examination of sediment (if dipstick abnormal)[b]

Clinical Chemistry:
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Glucose (random)
- Total cholesterol
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Creatinine
- Gamma-glutamyl transferase (GGT)[a]
- Urea

- Hepatitis B surface antigen[a,c]
- Hepatitis C antibody
- HIV[a,c]

- Pregnancy test (if applicable)[d]
- FSH (if applicable)[a,e]
- Thyroid stimulating hormone (TSH)[a]

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or autocalculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Inclusion or omission of calculated values will not be considered a protocol deviation.

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

[a] Performed at screening only.

[b] If clinically indicated, per investigator's discretion.

[c] Tests may be waived if they have been performed within 6 months before screening with reports available for review.

[d] Serum test at screening and admission; urine test at all other times. Women with confirmed nonchildbearing potential status can be exempted from further pregnancy tests during the study after screening.

[e] To be performed only at screening for assessment of menopause status, if necessary.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the subject understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject 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 study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

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

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

Regulatory Considerations

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

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

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

Protocol Signatures

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

After reading the protocol, the 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 case report forms (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.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject/patient personal information collected will be provided in a written document to the subject by the Sponsor.

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 patients 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, INR
WBC	
Neutrophils	**Hepatic Serologies[a,b]**
Lymphocytes	Hepatitis A antibody, IgG
Monocytes	Hepatitis A antibody, IgM
Eosinophils	Hepatitis B surface antigen
Basophils	Hepatitis B surface antibody
Platelets	Hepatitis B core antibody, total or hepatitis B core antibody, IgM
	Hepatitis C antibody
Hepatic Chemistry[a]	Hepatitis E antibody, IgG
Total bilirubin	Hepatitis E antibody, IgM
Conjugated bilirubin	
Alkaline phosphatase	**Anti-nuclear antibody[a]**
ALT	**Alkaline phosphatase isoenzymes[a]**
AST	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
GGT	
Creatine kinase	

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

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol J1Z-MC-HUAA Sampling Summary (Part A: Ascending Dose—3 Study Periods)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	18	1	18
Clinical laboratory tests[a]	8	7	56
PK sampling[b]	2	39 (+3)	78 (+6)
Blood discard for cannula patency	1	30	30
Stored non-PGx plasma sample	10	9	90
PGx sample	10	1	10
Serum creatinine	3.5	3	10.5
Total			292.5 (298.5)
Total for clinical purposes (rounded up to nearest 10 mL)			300 (300)

Abbreviations: PGx = pharmacogenetic; PK = pharmacokinetic.

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

[b] If indicated by emerging data, a maximum of 3 blood samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor (as shown in parentheses).

Protocol J1Z-MC-HUAA Sampling Summary (Part B: CYP3A4 Inhibition—Single Study Period)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	18	1	18
Clinical laboratory tests[a]	8	5	40
PK sampling for LY3154885[b]	2	29 (+3)	58 (+6)
PK sampling for itraconazole and metabolite(s)	2	7	14
Blood discard for cannula patency	1	20	20
Total			150 (156)
Total for clinical purposes (rounded up to nearest 10 mL)			150 (160)

Abbreviation: PK = pharmacokinetic.

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

[b] If indicated by emerging data, a maximum of 3 blood samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor (as shown in parentheses).

Protocol J1Z-MC-HUAA Sampling Summary (Part C: Multiple-Ascending Dose—Single Study Period)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	18	1	18
Clinical laboratory tests[a]	8	4	32
PK sampling[b]	2	33 (+3)	66 (+6)
Blood discard for cannula patency	1	30	30
Stored non-PGx plasma sample	10	5	50
PGx sample	10	1	10
Total			206 (212)
Total for clinical purposes (rounded up to nearest 10 mL)			210 (220)

Abbreviations: PGx = pharmacogenetic; PK = pharmacokinetic.

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

[b] If indicated by emerging data, a maximum of 3 blood samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor (as shown in parentheses).

Protocol J1Z-MC-HUAA Sampling Summary (Part D: Formulations/Food Effect—3 Study Periods)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	18	1	18
Clinical laboratory tests[a]	8	16	128
PK sampling[b]	2	117 (+3)	234 (+6)
Blood discard for cannula patency	1	90	90
PGx sample	10	1	10
Total			480 (486)
Total for clinical purposes (rounded up to nearest 10 mL)			480 (490)

Abbreviations: PGx = pharmacogenetic; PK = pharmacokinetic.

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

[b] If indicated by emerging data, a maximum of 3 blood samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor (as shown in parentheses).

Appendix 6. Protocol Amendment J1Z-MC-HUAA(b) Summary
Single- and Multiple-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study with LY3154885 in Healthy Subjects

Overview

Protocol J1Z-MC-HUAA "Single- and Multiple-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study with LY3154885 in Healthy Subjects" has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

After receipt of feedback from the US Food and Drug Administration, the following changes have been made to this protocol:

- Section 5.1.3. Part C (Multiple-Ascending Dose) has been modified to extend the review period for safety data from 6 to 14 days prior to making a final decision about the dose level to be administered to the next cohort.

CCI [redacted]

  - Text within section 5.5 (Justification for Dose) has been modified to reflect the inclusion of the monkey NOEL data.

Other changes made to the protocol are as follows:

- Section 1 (Protocol Synopsis):
  - The language has been updated to state that for parts A, B, C, and D, subjects will be admitted to the CRU (Day -2, first period) in the afternoon.
  - Evening admission has been deleted.

- Section 2 (Schedule of Activities – Parts A – D):
  - The comment section in the physical examination/medical assessment (PE/MA) row has been updated to state that a full PE/MA will be conducted prior to final discharge from the study.

- Section 2 (Schedule of Activities – Part A):
    - "Single safety" has been added to the description within the 12-lead ECG row.
    - Also on this row, ECG measurements at hours 2 and 4 (Day 1) have been added, and
    - measurements at hours 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 (Day 1) and 36 (Day 2) have been deleted.
    - The comments previously contained within the comment section in this row have been deleted.

- Section 2 (Schedule of Activities – Parts B and C):
    - A requirement to conduct clinical laboratory tests on Day -2 has been added. A comment has been added to state that the PI must review the Day -2 laboratory results before dosing on Day 1.

- Section 2 (Schedule of Activities – Parts B and C):
    - The comment associated with the ABPM row has been updated to include the term "predose".

- Section 2 (Schedule of Activities – Part C):
    - The comments have been updated within the admission to CRU row to reflect that admission will occur in the afternoon rather than the evening.
    - The Day -1 ECG measurement has been deleted.
    - Additional ECG measurements have been added at -45 min, -30 min, and -15 min (Days 1 and 14).
    - ECG measurements have been deleted at 1, 2, 3, 4, 5, 6, 8, and 12 hours (Days 1 and 7), and
    - the predose measurement (Day 8 only) has been deleted from the D8-13 column.

- Sections 5.1.1, 5.1.2, 5.1.3, 5.1.4 (Parts A – D):
    - Admission to the CRU on Day -2 has been changed from the evening to the afternoon.

- Section 8.1 (Discontinuation from Study Treatment):
    - The discontinuation criterion "ALT or AST >3× ULN sustained for more than 2 weeks or" has been removed. The MAD study is 14 days long and this is not applicable.

- Section 8.4.3 (Electrocardiograms):
    - Language has been added to specify that single ECGs will be collected at all time points in Part A.
    - The requirement to perform triplicate ECG measurements in Part A for all time points other than screening, early discontinuation, and follow-up has been deleted.

Revised Protocol Sections

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

1. Protocol Synopsis (Treatment Arms and Planned Duration for an Individual Subject)

Part A: Subjects will attend a screening visit up to 28 days prior to dosing in Period 1. Admission to the clinical research unit (CRU) will be ~~on~~ in the ~~evening~~ afternoon of Day -2 of the first period and on Day -1 for Periods 2 and 3. After an overnight fast, subjects will receive either LY3154885 or placebo as a single oral dose on Day 1 and will remain inpatient for at least 48 hours after dosing (until Day 3), after which they may be discharged at the discretion of the investigator. The washout time between doses for a given subject will be at least 7 days. A poststudy follow-up visit will be conducted at least 7 days after the final dose.
Part B: Subjects will attend a screening visit up to 28 days before dosing. Subjects will be admitted to the CRU i~~o~~n the ~~evening~~ afternoon of Day -2 and will receive a single oral dose of LY3154885 or placebo on Day 1 after an overnight fast. There will be a 7-day washout period followed by 10 days of dosing with 200 mg itraconazole (twice daily on Day 8 [dose separated by 12 hours], then once daily on Days 9 through 17). Subjects will receive LY3154885 or placebo on Day 14, approximately 1 hour after the dose of itraconazole.

Part C: Subjects will receive either LY3154885 or placebo as a single oral once-daily dose from Days 1 through 14. Study drug will be administered as a single oral dose in the morning under fasted conditions. Subjects will attend a screening visit up to 28 days prior to dosing and will be admitted to the CRU i~~o~~n the ~~evening~~ afternoon of Day -2. After the initial dose (Day 1), subjects will be required to remain in-house for at least 48 hours after dosing (Day 3) and at the discretion of the investigator. Subjects will attend the CRU on Days 4, 5, 6, 9, and 10 on an outpatient basis for daily dosing and will be permitted to leave the CRU at the discretion of the investigator. A poststudy follow-up visit will be conducted approximately 7 days after discharge.

Optional Part D: Subjects will attend a screening visit up to 28 days prior to dosing in Period 1; admission to the CRU will be i~~o~~n the ~~evening~~ afternoon of Day -2 (Periods 1 and 2) and on Day -1 (Period 3). In Period 1, subjects will undergo an overnight fast before receiving a single oral dose of LY3154885 (capsule formulation) on Day 1. Subjects will remain inpatient for at least 48 hours after dosing, after which they may be discharged at the discretion of the investigator. Subjects will be re-admitted to the CRU on Day 6, and will undergo an overnight fast before receiving a subsequent single oral dose of LY3154885 on Day 8 with the same formulation. Subjects will be discharged on Day 10, at least 48 hours after dosing.

Period 2 will be conducted as described for Period 1; however, LY3154885 will be administered as a tablet formulation. Period 3 will be conducted as described for Period 1; however, subjects will receive a single oral dose of LY3154885 (tablet formulation) after administration of a high-fat diet.

2. Schedule of Activities

Study Schedule Protocol J1Z-MC-HUAA (Part A: Single-Ascending Dose – 3 Study Periods)

	Screening	Periods 1, 2, and 3					ED	Follow-up	Comments
Procedure	-28 to -3 days prior to dosing in Period 1	Day -2	Day -1	Day 1	Day 2	Day 3		At least 7 days after final dose	
Informed consent	X								
Admission to CRU		X (Period 1)	X (Periods 2&3)						
Discharge from CRU						X			
Medical history	X								
AE/medication review			X	X	X	X	X	X	
Height/weight	X						X	X	Height at screening only.
Neurological exam (hours)	X			Predose, 4, 8	24	48	X	X	
LY3154885/Placebo administration (hours)				0					
Vital signs (BP, PR [supine], temperature) (hours)	X		X	Predose, 2, 4, 8, 12	24, 36	48	X	X	Time points may be added for each study period, if clinically indicated. On Day 1, temperature will be measured at predose only.
ABPM			X	X	X				The ABPM on Day -1 is a 24-hour collection in Period 1 only (baseline measurement). See Section 9.4.4.
Clinical laboratory tests	X	X		Predose		X	X	X	See Appendix 2, Clinical Laboratory Tests, for details. PI must review the result of Day-2 results prior to Day 1 dose in Period 1 only.
Pregnancy test	X	X					X	X	Serum test at screening and admission of Period 1 only; urine test at all other time points.
PE/MA	X			Predose			X	X	Full PE/MA at screening and prior to final discharge from the ~~CRU~~study. Symptom-directed PE/MA at all other time points and as deemed necessary by the investigator.

continued

Study Schedule Protocol J1Z-MC-HUAA (Part A: Single-Ascending Dose – 3 Study Periods) (concluded)

	Screening	Periods 1, 2, and 3					ED	Follow-up	Comments
Procedure	-28 to -3 days prior to Period 1	Day -2	Day -1	Day 1	Day 2	Day 3		At least 7 days after final dose	
Single safety 12-lead ECG (hours)	X			Predose, 2, 4 ~~0.5, 1, 2, 3, 4, 5, 6, 8, 12~~	24, ~~36~~	48	X	X	~~Single safety ECGs at screening and ED/follow-up; triplicate ECGs at all other times. ECGs coinciding with PK sample time points are to be conducted as close as possible to PK sampling.~~
PK sampling (hours)				Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48			Sampling times are relative to the time of study treatment administration (0 hour).
Stored non-PGx plasma sample (hours)				Predose, 8	24				Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).
PGx sample			X						Single sample for pharmacogenetic analysis taken prior to/on Day 1 of Period 1.
Urine collection (hours)				0-12, 12-24	24-36				Urine collection time starts from actual dosing time on Day 1 and finishes within ±30 minutes of the 36-hour time point.
Serum creatinine				Predose					To be collected at predose and sent to central laboratory.

Note: Site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: ECG, vital signs, PK samples, clinical laboratory tests, urine samples, biomarkers, and storage samples.

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; PE = physical examination; PGx = pharmacogenetic; PI = principal investigator; PK = pharmacokinetic; PR = pulse rate.

Study Schedule Protocol J1Z-MC-HUAA (Part B: Drug-Drug Interaction with CYP3A4 Inhibition – Single Period)

	Screening	Days													
Procedure	-28 to -3	-2	-1	1	2	3	4-6	7	8	9	10-11	12	13	14	15
Informed consent	X														
Admission to CRU		X						X				X			
Discharge from CRU						X				X					
PE/MA	X														
Directed MA	X			Predose					Predose					Predose	
AE/medication review		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/height	X		X												
Pregnancy test	X	X													
Neurological exam (hours)[a]	X			Predose, 4, (8)	24	48								Predose, 4, (8)	24
Clinical laboratory tests	X	X		Predose					Predose					Predose	
ABPM			X	X	X								X	X	X
LY3154885/Placebo administration				X										X	
Administration of itraconazole									X	X	Outpatient dosing		X	X	X
Vital signs (BP, PR [supine], temperature) (hours)[a]			X	Predose 2, 4, 8, 12	24	48			Predose, 2, 4, 12	24				Predose 2, 4, 8, 12	24, 36
12-lead ECG			X	Predose					Predose					Predose	
PGx sample				X											
LY3154885 PK sampling (hours)[a]				Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48								Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36
Itraconazole and metabolite(s) PK sampling (hours)									-1, 0, 1, 2, 5, 8, 12						

continued

Study Schedule Protocol J1Z-MC-HUAA (Part B: Drug-Drug Interaction with CYP3A4 Inhibition – Single Period) (concluded)

	Days			ED	Follow-up	Comments
Procedure	16	17	18		Approx 7 days after discharge	
Discharge from CRU			X			
PE/MA			X	X	X	Full PE/MA at screening and prior to final discharge from the ~~CRU~~ study. Symptom-directed PE/MA at all other time points and as deemed necessary by the investigator.
Directed MA				X	X	
AE/medication review	X	X	X	X	X	
Weight/height				X	X	Height at screening only.
Pregnancy test				X	X	Serum test at screening and admission; urine test at all other time points. Women with confirmed nonchildbearing potential status can be exempted from further pregnancy tests during the study after screening.
Neurological exam (hours)[a]	48					The 8-hour time point is optional.
Clinical laboratory tests			X	X	X	See Appendix 2, Clinical Laboratory Tests, for details. PI must review the Day -2 laboratory result before dosing on Day 1.
ABPM	X					The ABPM on Day -1 is a 24-hour collection for baseline measurement. On dosing days, the ABPM recording will be initiated approximately 2 hours prior to dosing for measurement of predose baseline.
Administration of itraconazole	X	X				Itraconazole 200 mg will be administered twice daily on Day 8 (dose separated by 12 hours) and once daily on Days 9 through 17. Itraconazole should be administered at approximately the same time every morning. For the outpatient dosing days, subjects will record the actual time of dose administration on a diary card. On Day 14, itraconazole should be administered 1 hour before LY3154885 administration (see Section 5.1.2).
Vital signs (BP, PR [supine], temperature) (hours)[a]	48, 60	72	96	X	X	Time points may be added for each study period, if clinically indicated. On Day 1, temperature will be measured at predose only.
12-lead ECG			X	X	X	Single safety ECGs.
PGx Sample						Single sample for pharmacogenetic analysis.
LY3154885 PK sampling (hours)[a]	48, 60	72	96			Sampling times are relative to the time of LY3154885 administration (0 hour).

Note: Site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: ECG, vital signs, PK samples, and clinical laboratory tests.

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; CRU = clinical research unit; CYP = cytochrome P450; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; PE = physical examination; PI = principal investigator; PK = pharmacokinetic; PR = pulse rate.

[a] Predose time points refer to dosing before itraconazole and LY3154885. All postdose time points are relative to the LY3154885 dose.

Study Schedule Protocol J1Z-MC-HUAA (Part C: Multiple-Ascending Dose – Single Period)

	Screening	Days									ED	Follow-up	Comments
Procedure	-28 to -3	-2	-1	1	2	3-6	7	8-13	14	15		Approx 7 days after discharge	
Informed consent	X												
Admission to CRU		X				D6		D10					~~Evening~~ Afternoon admission.
Discharge from CRU						D3		D8		X			
Medical history	X												
AE/medication review			X	X	X	X	X	X	X	X	X	X	
Height/weight	X		X							X			Height at screening only.
Neurological exam (hours)	X			Predose, 4, (8)	24	48	Predose, 4, (8)	24, 48		X	X		The 8-hour time point is optional.
LY3154885/ Placebo administration				X	X	X	X	X	X				On Days 4, 5, 6, 9, and 10, subjects will receive their dose of LY3154885/placebo at the CRU and then may be discharged at the discretion of the investigator.
Vital signs (BP, PR [supine], temperature) (hours)	X		X	Predose, 2, 4, 8, 12	Predose, 2, 4, 8, 12	Predose, 2	Predose, 2, 4, 8, 12	Predose, 2	Predose, 2, 4, 8, 12	X	X	X	Time points on outpatient dosing days (Days 4, 5, 6, 9, and 10) may be adjusted based on emerging data from Part A and/or if clinically indicated. On Days 1 to 14, temperature will be measured at predose only.

continued

Study Schedule Protocol J1Z-MC-HUAA (Part C: Multiple-Ascending Dose – Single Period) (continued)

	Screening	Days									ED	Follow-up	Comments
Procedure	-28 to -3	-2	-1	1	2	3-6	7	8-13	14	15		Approx 7 days after discharge	
ABPM			X	X	X		X	D11& 12	X				The ABPM on Day -1 is a 24-hour collection for baseline measurement. On dosing days, the ABPM recording will be initiated approximately 2 hours prior to dosing for measurement of predose baseline.
Clinical laboratory tests	X	X		Predose			Predose			X	X	X	See Appendix 2, Clinical Laboratory Tests, for details. PI must review Day -2 result prior to dose on Day 1.
Pregnancy test	X	X					Predose			X	X	X	Serum test at screening and admission; urine test at all other time points per investigator discretion. Women with confirmed nonchildbearing potential status can be exempted from further pregnancy tests during the study after screening.
PE/MA	X			Predose						X	X	X	Full PE/MA at screening and prior to final discharge from the ~~CRU~~ study. Symptom-directed PE/MA at all other time points and as deemed necessary by the investigator.

continued

Study Schedule Protocol J1Z-MC-HUAA (Part C: Multiple-Ascending Dose – Single Period) (concluded)

	Screening	Days									ED	Follow-up	Comments
Procedure	-28 to -3	-2	-1	1	2	3-6	7	8-13	14	15		Approx 7 days after discharge	
12-lead ECG (hours)	X		~~X~~	Predose (-45 min, -30 min, -15 min) ~~1, 2, 3, 4, 5, 6, 8, 12~~	Predose		Predose ~~1, 2, 3, 4, 5, 6, 8, 12~~	~~Predose (D8 only)~~	Predose, (-45 min, -30 min, -15 min), 2, 3, 4, 6, 8, 12	24	X	X	Single safety ECGs at screening and ED/follow-up; triplicate ECGs at all other times. ECGs coinciding with PK sample time points are to be conducted as close as possible prior to PK sampling.
PGx sample				X									Single sample for pharmacogenetic analysis taken prior to/on Day 1.
Stored non-PGx plasma sample (hours)				Predose, 8			Predose		Predose, 8				
PK sampling (hours)				Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	Predose		Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	Predose (D8 only)	Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24			Sampling times are relative to the time of LY3154885 administration (0 hour).
POMS-2®			X			D6 only		D13 only					
Exploratory cognition assessments (HVLT, DSST)			X			D6 only		D13 only					
PWC-20				Predose						X	X	X	
C-SSRS and Lilly Self-Harm Supplement Form	X	X				D3 & D6 only		D8 & D10 only		X	X	X	Administer at screening, each admission, and each discharge from the CRU.

Note: Site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: ECG, vital signs, PK samples, clinical laboratory tests, biomarkers, and storage samples.

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; DSST = Digital Symbol Substitution Test; ECG = electrocardiogram; ED = early discontinuation; HVLT = Hopkins Verbal Learning Test; MA = medical assessment; PE = physical examination; PGx = pharmacogenetic; PI = principal investigator; PK = pharmacokinetic; POMS-2 = Profile of Mood States Second Edition; PR = pulse rate; PWC-20 = Penn Physician Withdrawal Checklist.

[…]

Study Schedule Protocol J1Z-MC-HUAA (Part D: Formulations/Food Effect – 3 Study Periods) (concluded)

		Periods 1, 2, and 3																
	Screening	**Days**														**ED**	**Follow-up**	**Comments**
Procedure	-28 to -3	-2	-1	1	2	3	4-6	7	8	9	10	11-13	14	15	16		Approx 7 days after discharge	
PE/MA	X															X	X	Full PE/MA at screening and prior to final discharge from the ~~CRU~~ study. Symptom-directed PE/MA at all other time points and as deemed necessary by the investigator.
12-lead ECG	X			Predose					Predose				Predose			X	X	Single safety ECGs. ECGs coinciding with PK sample time points are to be conducted as close as possible prior to PK sampling.
PK sampling (hours)				Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48			Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48		Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48			
PGx sample				Predose														Period 1 only

Note: Site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: ECG, vital signs, PK samples, clinical laboratory tests, biomarkers, and storage samples.

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; CRU = clinical research unit; D = day; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; PE = physical examination; PGx = pharmacogenetic; PK = pharmacokinetic; PR = pulse rate.

5.1.1. Part A (Single-Ascending Dose)

[…]

In Period 1, subjects will be admitted to the clinical research unit (CRU) on the ~~evening~~ afternoon of Day -2 for set up of baseline ambulatory blood pressure monitoring (ABPM) (see Section 9.4.4) and on Day -1 for Periods 2 and 3. Subjects will undergo an overnight fast (Section 6.3.1) before dosing with LY3154885 or placebo as a single oral dose on Day 1 and will remain inpatient for at least 48 hours after dosing (until Day 3), after which they may be discharged at the discretion of the investigator. The washout time between doses for a given subject will be at least 7 days. A poststudy follow-up visit will be conducted at least 7 days after the final dose.

5.1.2. Part B (CYP3A4 Inhibition)

[…]

As detailed in the Schedule of Activities (Section 2), subjects will be admitted to the CRU in the ~~evening~~ afternoon of Day -2 for set up of baseline ABPM (see Section 9.4.4) and will undergo an overnight fast (see Section 6.3.1) before receiving a single oral dose of LY3154885 or placebo on Day 1. Subjects may be discharged from the CRU on Day 3 and will be re-admitted on Day 7. There will be a 7-day washout period followed by 10 days of dosing with 200 mg itraconazole (twice daily on Day 8 [dose separated by 12 hours], then once daily on Days 9 through 17). See Section 6.3.1 for the fasting requirements for the itraconazole dosing. Subjects will be discharged from the CRU on Day 9 after receiving their dose of itraconazole and will be self-dosing on an outpatient basis from Days 10 through 12. Subjects will be asked to complete a diary card to document the actual date and time of dose administration.

5.1.3. Part C (Multiple-Ascending Dose)

[…]

Subjects will participate in a single study period consisting of 14 days of once-daily dosing with LY3154885 or placebo; study drug will be administered as a single oral dose in the morning under fasted conditions (see Section 6.3.1). Subjects will be admitted to the CRU on the ~~evening~~ afternoon of Day -2 for set up of baseline ABPM (see Section 9.4.4) and will be required to remain in-house for at least 48 hours after dosing (Day 3), and at the discretion of the investigator. As detailed in the Schedule of Activities (Section 2), subjects will attend the CRU on Days 4, 5, 6, 9, and 10 on an outpatient basis for daily dosing and will be permitted to leave the CRU at the discretion of the investigator. Pharmacokinetic sampling will be conducted as detailed in Section 2. To assess CV effects and potential accommodation over time, ABPM will be included on Day -1 (baseline) and on Days 1, 2, 7, 11 and 12, and 14. A poststudy follow-up visit will be conducted approximately 7 days after discharge.

The doses evaluated will be selected based on emerging data from Parts A and B and from the lower doses from Part C (see Section 5.5 for details). If the safety data do not support increasing the dose in subsequent cohorts, then a dose may be repeated or lower/intermediate doses may be explored. The PK data obtained during the study may be used to assist in dose-escalation decisions, but such data are not required for dose-escalation purposes. For the safety review prior to dose decisions between cohorts, all available safety data (AEs, vital signs, ECGs, and laboratory results) to ~~at least~~Day ~~6~~14 from at least 6 subjects taking LY3154885 must be reviewed by the sponsor and investigator. In addition, each cohort (including at least 6 subjects treated with LY3154885) will complete dosing to Day 14 prior to the next cohort being admitted to the CRU for dosing.

5.1.4. Optional Part D (Pharmacokinetics of Capsule and Tablet Formulations and Food Effect)

[…]

In Periods 1 and 2, subjects will be admitted to the CRU the ~~evening~~ afternoon of Day -2 for set up of baseline ABPM (see Section 9.4.4); admission for Period 3 will be on Day -1. In Period 1, subjects will undergo an overnight fast (see Section 6.3.1) before receiving a single oral dose of LY3154885 (capsule formulation) on Day 1. Subjects will remain inpatient for at least 48 hours after dosing, after which they may be discharged at the discretion of the investigator. Subjects will be re-admitted to the CRU on Day 6 and will undergo an overnight fast before receiving a subsequent single oral dose of LY3154885 on Day 8 with the same formulation. Subjects will be discharged on Day 10, at least 48 hours after dosing. Re-admission to the CRU will be on Day 13, and following an overnight fast, subjects will receive a single oral dose of LY3154885 on Day 14 with the same formulation. Final discharge from the CRU will occur on Day 16. Pharmacokinetic sampling will be conducted as detailed in the Schedule of Activities (Section 2).

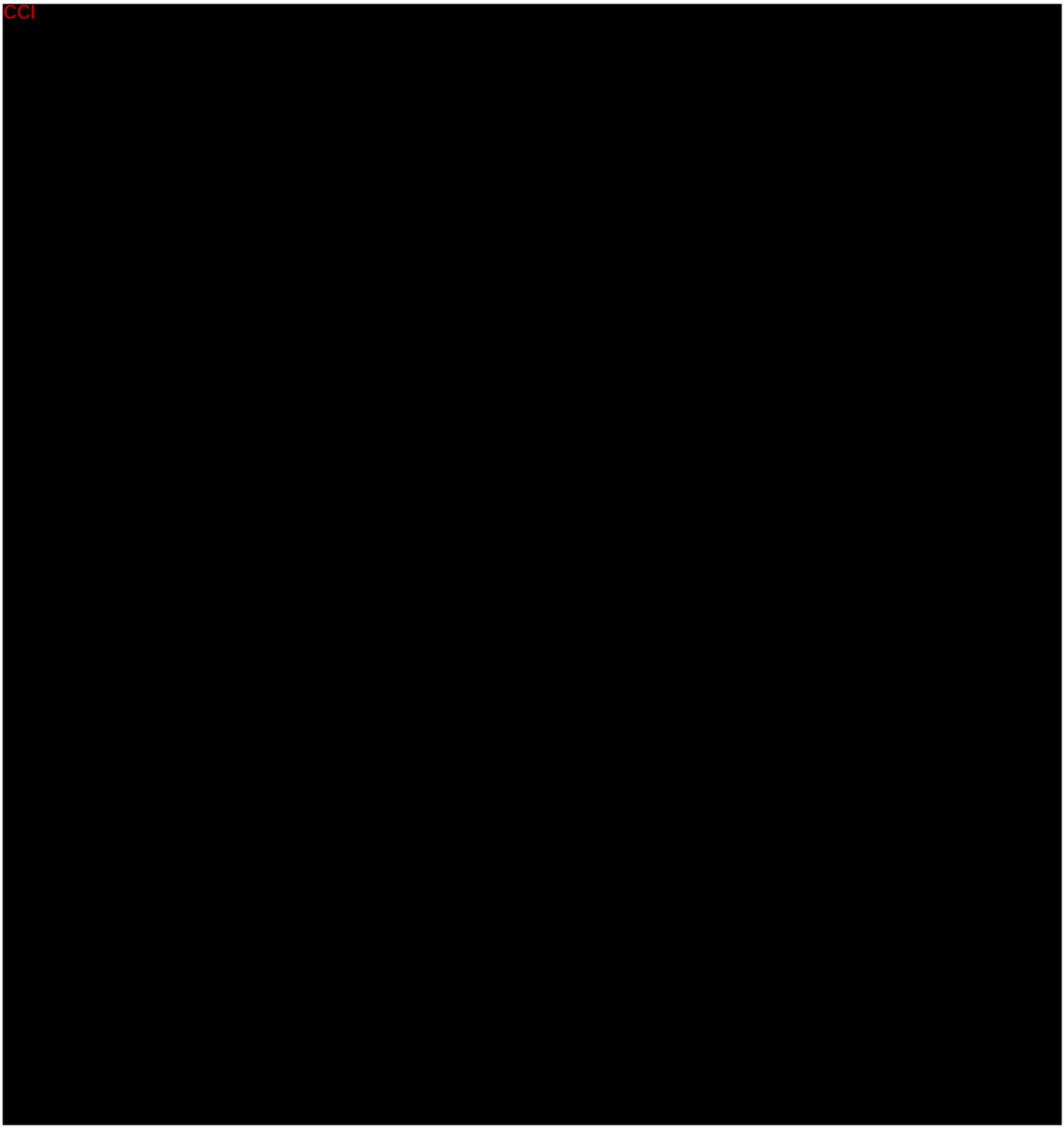
5.5 Justification for Dose

[...]

The maximum dose for this study is expected to be 500 mg based on animal toxicology studies and human PK predictions for LY3154885, CCI [redacted] 500-mg dose in humans is predicted to result in a mean plasma AUC of CCI [redacted] µg×hr/mL and C_{max} of CCI [redacted] µg/mL; these values are equivalent to 1/10th the AUC at the NOAEL in monkeys and 1/10th the C_{max} at the NOAEL in rats. The C_{max} and AUC-based multiples associated with CCI [redacted] from the non-GLP study in rats, which were not observed at similar exposures in the GLP study, are also presented in Table HUAA.5.1. To note, the predicted human C_{max} at 500 mg is CCI [redacted]-fold below the C_{max} at the NOEL for CCI [redacted] effects in both rats and monkeys. Pharmacokinetic data will be reviewed during the study to support dose escalations (see Section 10.3.5 for details) and maintain predicted drug exposures below 1/10th the AUC at the NOAEL in monkeys and 1/10th the C_{max} at the NOAEL in rats. A dose higher than 500 mg may be studied if human PK data from previous cohorts suggests the predicted exposure will be below 1/10th the AUC at the NOAEL in monkeys and 1/10th the C_{max} at the NOAEL in rats.

[...]

CCI



8.1. Discontinuation from Study Treatment

[…]

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

8.4.3. Electrocardiograms

[…]

At screening, early discontinuation, and follow-up, 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. In Parts A, B and D, single ECGs will be collected at all time points.

In Part~~s A and~~ C, at all time points other than screening, early discontinuation, and follow-up, ECGs will be collected in triplicate.

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