Protocol J3D-MC-FNAA(i)

A Phase 1, Randomized, Participant- and Investigator-Blind, Placebo-Controlled, Single- and Multiple-Ascending Dose, Drug-Drug Interaction and Food Effect Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LY3509754 in Healthy Non-Japanese and Japanese Participants

NCT04586920

Approval Date: 01-Dec-2021

Title Page

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Protocol Number: J3D-MC-FNAA

Amendment Number: i

Compound: LY3509754

Study Phase: 1

Short Title: A Phase 1, Randomized, Participant- and Investigator-Blind, Placebo-Controlled, Single- and Multiple-Ascending Dose, Drug-Drug Interaction and Food Effect Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LY3509754 in Healthy Participants

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 151075

EudraCT: 2020-003957-30

Approval Date: Protocol Amendment (i) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-014906

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment h	*17-November-2021*
Amendment g	*10-November-2021*
Amendment f	*19-October-2021*
Amendment e	*01-October-2021*
Amendment d	*18-June-2021*
Amendment c	*02-April-2021*
Amendment b	*05-February-2021*
Amendment a	*30-December-2020*
Original Protocol	*04-September-2020*

Amendment [i]

Overall Rationale for the Amendment:

This protocol was amended to allow for sections of any liver biopsies that may be performed to be sent to Lilly for further exploratory histological evaluations, including but not limited to the detection of cytokines, immunoglobulins, and any potential cellular infiltrates. Elevated liver enzymes have been observed in some participants dosed with LY3509754. Further analysis of these samples may provide additional mechanistic understanding of elevated liver enzymes following drug discontinuation.

Section # and Name	Description of Change	Brief Rationale
10.1.9 Long-Term Sample Retention	Added Liver Biopsy Sections to table	To designate the retention period for any liver biopsy sections that Lilly receives
10.6 Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments	Added text allowing for a section of any liver biopsies that are performed to be sent to Lilly	To allow for further analysis

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Participant-and Investigator-Blind, Placebo-Controlled, Single- and Multiple-Ascending Dose, Drug-Drug Interaction and Food Effect Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LY3509754 in Healthy Non-Japanese and Japanese Participants

Short Title: A Phase 1, Randomized, Participant-and Investigator-Blind, Placebo-Controlled, Single- and Multiple-Ascending Dose, Drug-Drug Interaction and Food Effect Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LY3509754 in Healthy Participants

Rationale: LY3509754 is an oral small molecule inhibitor for IL-17A that is being developed for once-daily treatment of psoriasis (PsO) and other immune-mediated diseases.

IL-17A is a clinically validated cytokine involved in the exacerbation of PsO, psoriatic arthritis (PsA), ankylosing spondylitis (AxSpa), and related autoimmune disorders.

LY3509754 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 LY3509754 in healthy participants (including Japanese healthy participants) in a combined single-ascending dose (SAD) and multiple-ascending dose (MAD) design. The study will also evaluate the effect of food on the PK of LY3509754. LY3509754 has the potential for cytochrome P450 3A4 (CYP3A4) drug-drug interactions (DDI). As such, the study will investigate the impact of LY3509754 as a substrate and as an inducer of CYP3A4. The data generated in this study will be used to help design subsequent clinical studies.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• The primary objective is to assess the safety and tolerability following single or multiple doses of LY3509754 administered to healthy participants	• Incidence of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs)
Secondary	
• The secondary objective is to characterize the PK following single or multiple orally administered doses of LY3509754 in healthy participants	• Maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC) of LY3509754

Overall Design

Study J3D-MC-FNAA is a Phase 1, multi-center study in healthy participants to be conducted in 4 parts:

- Part A (SAD): Part A will be a participant- and investigator-blind, placebo-controlled, randomized, SAD study to evaluate the safety, tolerability, and PK of LY3509754 in healthy participants in up to 6 cohorts. One cohort (Cohort 4) will include a randomized, single-dose level, 2 period crossover food effect evaluation in participants administered LY3509754 following fasting and a high fat meal (periods 1 and 2, respectively).
- Part B (DDI – CYP3A4 victim): Part B will be a participant- and investigator-blind, placebo-controlled, single-dose-level, single-arm, drug-drug interaction (DDI) study to evaluate the multiple dose impact of the CYP3A4 inhibitor, itraconazole, on the single dose exposure of LY3509754.
- Part C (MAD): Part C will be a participant- and investigator-blind, placebo-controlled, randomized, 14-day, single-period MAD study with up to 3 cohorts to evaluate the safety, tolerability, and PK of LY3509754 in healthy participants. One cohort (Cohort 2) will include a fixed sequence, perpetrator DDI evaluation to understand the impact of LY3509754 (administered as multiple doses to steady state) on midazolam PK.
- Part D (Japanese participants): Part D will be a participant- and investigator-blind, placebo-controlled, randomized, multiple dose study to evaluate the safety, tolerability, and PK of LY3509754 in healthy Japanese participants in 2 dose levels in 2 separate cohorts (1 dose level per cohort). The 2 dose levels will be conducted concurrently.

Disclosure Statement: This is a Phase 1, randomized, participant-and investigator-blind, placebo-controlled, single- and multiple-ascending dose, DDI study to evaluate the safety, tolerability, and PK of LY3509754 in healthy non-Japanese and Japanese participants.

Number of Participants:

Approximately 105 participants will be required to complete this study, which includes the 4 parts below.

- **Part A (SAD):** Participants will be randomly assigned/enrolled into up to 6 cohorts with up to 51 participants completing this part of the study. Cohorts 1, 2, 3, and 5 will undergo the dose escalation with 6 LY3509754:2 placebo participants completing this part of the study. Cohort 4 will have a total of 11 participants completing a 2-period crossover with 9 LY3509754:2 placebo per period. Cohort 6 will have up to 8 participants completing this part of the study. This cohort may be used for additional safety, tolerability, PK, and food effect evaluation as deemed necessary by the sponsor and in discussion with the investigator following review of emerging safety, tolerability, and PK data from Cohorts 1 through 5.
- **Part B (DDI – CYP3A4 victim):** Participants will be randomly assigned/enrolled with up to 12 participants (9 LY3509754:3 placebo) completing this part of the study.

- **Part C (MAD):** Participants will be randomly assigned/enrolled into up to 4 cohorts with up to 26 participants completing this part of the study. In 1 cohort, a perpetrator DDI evaluation will be conducted. Cohorts 1 and 3 will undergo the dose escalation with 6 LY3509754:2 placebo participants completing this part of the study. Cohort 2 will have a total of 10 participants completing the fixed sequence DDI and dose escalation evaluation with 8 LY3509754:2 placebo participants.
- **Part D (Japanese participants):** Participants will be randomly assigned/enrolled into up to 2 cohorts with at least 16 participants completing this part of the study. At least 8 participants [6 LY3509754:2 placebo] are completing each dose level.

Intervention Groups and Duration:

Study J3D-MC-FNAA will be conducted in 4 parts. Participants will be screened within 28 days prior to Day 1 of dosing for each group.

The planned study interventions will be administered orally for the 4 parts as follows:

- Part A (SAD):
  - Cohort 1: 10 mg
  - Cohort 2: 30 mg
  - Cohort 3: 100 mg
  - Cohort 4: 300 mg
    - Period 1 Cohort 4 :300 mg fasted conditions
    - Period 2 Cohort 4: 300 mg fed conditions
  - Cohort 5: 1000 mg
  - Cohort 6: 2000 mg
- Part B (DDI – CYP3A4 victim):
  - 10 mg of LY3509754 on Days 1 and 10; and 200 mg itraconazole on Days 4 through 13.
- Part C (MAD):
  - Cohort 1: 100 mg/once daily (QD) × 14 days
  - Cohort 2: Fixed sequence
    - Single 1.2-mg midazolam dose followed by
    - 300 LY3509754 mg/QD × 14 days followed by
    - Single 1.2-mg midazolam dose and single 300-mg dose of LY3509754 on Day 15
  - Cohort 3: 1000 mg/QD x 14 days
- Part D (Japanese participants):
  - Cohorts 1 and 2: Once daily × 14 days. Dose level 1 will be 400 mg LY3509754; dose level 2 will be 1000 mg LY3509754 (the maximum dose evaluated in Part C).

Statistical Analysis:

Safety:

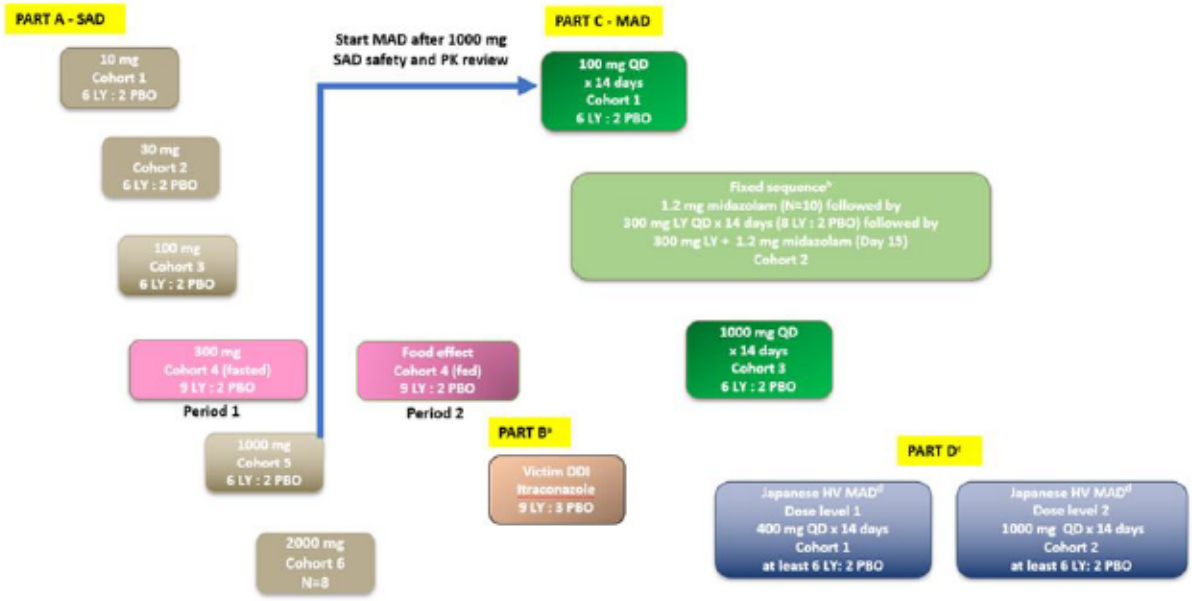
Safety parameters to be assessed include adverse events (AEs), clinical laboratory parameters, vital signs, and electrocardiogram (ECG) parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the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

Pharmacokinetic:

The primary plasma pharmacokinetic (PK) parameters to be determined for LY3509754 based on standard noncompartmental analysis are C_{max}, time to maximum concentration (t_{max}), AUC, terminal elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V/F) after single- and multiple-dose administration. Additionally, PK parameters of LY3509754 will be compared when administered alone versus in the presence of itraconazole with a high-fat meal versus in a fasted state, and between Japanese and non-Japanese participants. The C_{max} and AUC of midazolam and its hydroxylated metabolite will be assessed after administration of midazolam alone and concomitantly with LY3509754.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: DDI = drug-drug interaction; HV = healthy volunteers; LY = LY3509754; MAD = multiple-ascending dose; PBO = placebo; PK = pharmacokinetics; QD = once daily; SAD = single-ascending dose; TBD = to be determined.

Schema does not represent start or end times of each study part.

[a] Part B will begin after emerging safety, tolerability, and PK data from Part A has been reviewed.

[b] Fixed sequence cohort with 3 dosing events. In the first dosing event, all 10 participants receive midazolam. In the second dosing event, LY3509754 or placebo (8 LY3509754; 2 placebo) will be administered once daily for 14 days. In the third dosing event, both LY3509754 and midazolam will be administered on Day 15.

[c] Cohorts to run concurrently. At least 12 participants must complete Part D of the study.

[d] Dose level selected based on the results in the other parts of the study.

1.3. Schedule of Activities

1.3.1. Part A: Single-Ascending Dose, Cohorts 1, 2, 3, 5, and 6

Procedure	Screening			Treatment Period					ED	Follow-up[e]	Comments
Study Day	-28 to -3	-2	-1	1	2	3	4	5		At least 7 days after discharge	
Informed consent	X										
Admission to CRU		X									
Discharge from CRU								X			
PE/MA[a]	X	X		P				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.
COVID-19 test (PCR)	X	X						X	X	X	
Pregnancy test	X	X							X	X	Serum test at screening. Urine test at all other time points.
Urine drug screen	X	X									
Breath or urine ethanol test	X	X									Ethanol test may be repeated at other time points at the discretion of the investigator.
QuantiFERON®-TB Gold test	X										
AE/medication review	X	X	X	X	X	X	X	X	X	X	
Height/weight	X								X	X	Height at screening only.
LY3509754/Placebo administration				X							Participants will fast overnight before receiving LY3509754/placebo and for approximately 2 hours after dosing. On intensive PK days, participants may receive a light breakfast approximately 2 hours after dosing LY3509754/placebo.

Procedure	Screening			Treatment Period					ED	Follow-up[e]	Comments
Study Day	-28 to -3	-2	-1	1	2	3	4	5		At least 7 days after discharge	
Vital signs (BP, PR [supine], temperature) (hours)[a]	X	X		P, 2, 4, 8, 12	24, 36	48	72	96	X	X	Time points may be added, if clinically indicated. On Day 1, temperature will be measured at predose only. On Day 2, temperature will be measured at 24 hours only.
Clinical laboratory tests[b]	X	X						X	X	X	
12-lead ECG (hours)[a,c]	X			P, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48	72	96	X	X	
PK sampling (hours)[a]				P, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16	24, 36	48	72	96			Sampling times are relative to the time of study treatment administration (0 hour).
Exploratory blood sampling (hours)[a,d]				P, 1, 4, 12	24, 36	48	72	96		X[f]	Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).
Exploratory buccal swabs and saliva samples (hours)[a]				P, 8	24		72				Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour). Saliva only at 72 h collection (Cohort 6 only).
PGx sample				P							For storage only. Sample can be taken any time prior to dosing.
Urine collection (hours)				0-12 12-24							Urine collection time may start 20 minutes prior to actual dosing time on Day 1 and finishes within ±30 minutes of the 24-hour time point.
Serum creatinine				P							Sample can be taken any time prior to dosing in Period 1. Sent to Central Laboratory.

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; P = predose; PCR = polymerase chain reaction; PE = physical examination; PGx = pharmacogenetic; PK = pharmacokinetic; PR = pulse rate.

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.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

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

[a] Vital sign measurements, PE/MA, ECGs, may be collected within time windows depending on the collection time, as follows: Predose (within 2 hour before dosing); 0.5 h (±10 min); 1 to 4 hours (±15 min); 5 to 8 hours (±20 min); 12 hours (±30 min); 24 hours and longer (±60 min). Blood samples collected for PK, PD, or biomarker purposes may be collected within time windows depending on the collection time, as follows: Predose (within 1 hour before dosing); 0.5 h (±5 min); 1 to 4 hours (±10 min); 5 to 8 hours (±15 min); 12 hours (±30 min); 24 hours and longer (±60 min).

[b] See Section 10.2 for details. The principal investigator must review the Day -2 laboratory results before dosing on Day 1.

[c] Electrocardiograms on Day 1 will be triplicate for the first 5 hours and single for all other time points.

[d] Samples may be further processed for serum or plasma. See laboratory manual for further details.

[e] Additional follow-up visits may be conducted for safety labs and monitoring after the existing follow-up visit that is at least 7 days after discharge. Every attempt should be made to contact subjects for the follow-up visits; however, if subjects are unwilling or unable to return for the additional visits, this is not considered a protocol violation.

[f] Plasma samples should be collected for exploratory analyses at additional follow-up visits; however, if subjects are unwilling or unable to return to collect this sample, this is not considered a protocol violation.

1.3.2. Part A: Single-Ascending Dose and Food Effect Evaluation, Cohort 4 (2-Period Crossover)

Procedure	Screening			Treatment Period 1 (Fasted)					Treatment Period 2 (Fed)					ED	Follow-up[f]	Comments
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**		**At least 7 days after discharge**	
Informed consent	X															
Admission to CRU		X														
Discharge from CRU													X			
PE/MA[a]	X	X		P				X	P				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.
COVID-19 test (PCR)	X	X											X	X	X	
Pregnancy test	X	X												X	X	Serum test at screening. Urine test at all other time points.
Urine drug screen	X	X														
Breath or urine ethanol test	X	X														Ethanol test may be repeated at other time points at the discretion of the investigator.
QuantiFERON®-TB Gold test	X															
AE/medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight	X													X	X	Height at screening only.
LY3509754/Placebo administration (hours)[b]				X					X							

Procedure	Screening			Treatment Period 1 (Fasted)					Treatment Period 2 (Fed)					ED	Follow-up[f]	Comments
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**		**At least 7 days after discharge**	
Vital signs (BP, PR [supine], temperature) (hours)[a]	X	X		P, 2, 4, 8, 12	24, 36	48	72	96	P, 2, 4, 8, 12	24, 36	48	72	96	X	X	Time points may be added for each study period, if clinically indicated. For each period, on Day 1, temperature will be measured at predose only. For each period, on Day 2, temperature will be measured at 24 hours only.
Clinical laboratory tests[c]	X	X						X					X	X	X	
12-lead ECG (hours)[a,d]	X			P, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48	72	96	P, 0.5, 1, 2, 3, 4, 5, 6, 8, 12	24, 36	48	72	96	X	X	
PK sampling (hours)[a]				P, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16	24, 36	48	72	96	P, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16	24, 36	48	72	96			Sampling times are relative to the time of study treatment administration (0 hour). PK sampling will occur for both Period 1 and Period 2.

Procedure	Screening			Treatment Period 1 (Fasted)					Treatment Period 2 (Fed)					ED	Follow-up[f]	Comments
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**		**At least 7 days after discharge**	
Exploratory blood sampling (hours)[a,e]				P, 1, 4, 12	24, 36	48	72	96							X[g]	Do not collect for Period 2 of Cohort 4. Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).
Exploratory buccal swabs and saliva samples (hours)[a]				P, 8	24											Period 1 only. Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).
PGx sample				P												For storage only. Sample can be taken any time prior to dosing in Period 1.
Urine collection (hours)				0-12 12-24												Do not collect for Period 2 of Cohort 4. Urine collection time may start 20 minutes prior to actual dosing time on Day 1 and finishes within ±30 minutes of the 24-hour time point.
Serum creatinine				P												Sample can be taken any time prior to dosing in Period 1. Sent to Central Laboratory.

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; P = predose; PCR = polymerase chain reaction; PE = physical examination; PGx = pharmacogenetic; PK = pharmacokinetic; PR = pulse rate.

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.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

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

[a] Vital sign measurements, PE/MA, ECGs, may be collected within time windows depending on the collection time, as follows: Predose (within 2 hour before dosing); 0.5 h (±10 min); 1 to 4 hours (±15 min); 5 to 8 hours (±20 min); 12 hours (±30 min); 24 hours and longer (±60 min). Blood samples collected for PK, PD, or biomarker (including buccal and saliva samples) purposes may be collected within time windows depending on the collection time, as follows: Predose (within 1 hour before dosing); 0.5 h (±5 min); 1 to 4 hours (±10 min); 5 to 8 hours (±15 min); 12 hours (±30 min); 24 hours and longer (±60 min).

[b] In Period 1, participants will fast overnight for at least 8 hours before receiving LY3509754/placebo fast for approximately 2 hours after dosing. In Period 2, fed treatments will follow a high-fat meal given 30 minutes prior to receiving LY3509754/placebo following an overnight fast of at least 8 hours (Section 5.3.1). There will be at least a 5-day washout between Periods 1 and 2. For Cohort 4 in Periods 1 and 2, 8 LY3509754: 2 placebo participants will be dosed. Subject unique IDs will remain the same for Period 1 and 2 (see Section 6.3.).

[c] See Section 10.2, for details. The PI must review the Day -2 laboratory results before dosing on Day 1 of Period 1. The PI must review the Day 5 laboratory results in Period 1 before dosing on Day 1 of Period 2.

[d] Electrocardiograms on Day 1 will be triplicate for the first 5 hours and single for all other time points in Period 1. Electrocardiograms will be singlet for all time points in Period 2.

[e] Samples may be further processed for serum or plasma. See laboratory manual for further details.

[f] Additional follow-up visits may be conducted for safety labs and monitoring after the existing follow-up visit that is at least 7 days after discharge. Every attempt should be made to contact subjects for the follow-up visits; however, if subjects are unwilling or unable to return for the additional visits, this is not considered a protocol violation.

[g] Plasma samples should be collected for exploratory analyses at additional follow-up visits; however, if subjects are unwilling or unable to return to collect this sample, this is not considered a protocol violation.

1.3.3. Part B: Drug-Drug Interaction with CYP3A4 Inhibition – Fixed Sequence

Procedure	Screening	Treatment Period																	ED	Follow-up[f]	
Study Day	-28 to -3	-2	-1	1	2	3	4	5	6	7-9	10	11	12	13	14	15	16	17		Approx 7 days after discharge	Comments
Informed consent	X																				
Admission to CRU		X																			
Discharge from CRU																		X			
PE/MA[c]	X	X		P														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.
COVID-19 test (PCR)	X	X																X	X	X	
Pregnancy test	X	X																	X	X	Serum test at screening. Urine test at all other time points.
Urine drug screen	X	X																			

Procedure	Screening			Treatment Period															ED	Follow-up[f]	
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7-9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		**Approx 7 days after discharge**	**Comments**
Breath or urine ethanol test	X	X																			Ethanol test may be repeated at other time points at the discretion of the investigator.
QuantiFERON®-TB Gold test	X																				
AE/medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight	X			X											X				X	X	Height at screening only.
LY3509754/ placebo administration a				X							X										
Administration of itraconazole[b]							X	X	X	X	X	X	X	X							Itraconazole administration to occur twice on Day 4 only.
Vital signs (BP, PR [supine],) (hours)[c,d]	X		X	P, 2, 4, 8, 12	24	48			P, 2, 4		P, 2, 4, 8, 12	X	X	X	X	X	X	X	X	X	Time points may be added, if clinically indicated.
Temperature c,d		X		P					P		P							X	X	X	

Procedure	Screening			Treatment Period															ED	Follow-up[f]	
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7-9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		**Approx 7 days after discharge**	**Comments**
Clinical laboratory tests [e]	X	X				X				X (Day 8 only)	P	X						X	X	X	
12-lead ECG (hours)[c]	X			P, 1			P				P,1				X			X	X	X	Single safety ECGs. ECGs coinciding with PK sample time points are to be conducted as close as possible prior to PK sampling.
LY3509754 PK sampling (hours)[c,d]				P, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	24, 36	48	72	96			P, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	24, 36	48	72	96	120	144	168			Sampling times are relative to the time of LY3509754 administration (0 hour).
Itraconazole and metabolite PK sampling (hours)											P, 1, 2, 5, 8, 12	24									

Procedure	Screening			Treatment Period															ED	Follow-up[f]	
Study Day	-28 to -3	-2	-1	1	2	3	4	5	6	7-9	10	11	12	13	14	15	16	17		Approx 7 days after discharge	Comments
PGx sample				P																	For storage only. Sample can be taken any time prior to dosing.

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; CYP = cytochrome P450; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; P = predose; PCR = polymerase chain reaction; PE = physical examination; PK = pharmacokinetic; PR = pulse rate.

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.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

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

[a] Participants will undergo an overnight fast (Section 5.3.1) before receiving the first dose on Day 1 and until approximately 2 hours after dosing. Participants will receive a single oral dose of LY3509754 or placebo on Day 10 after an overnight fast and approximately 1 hour after the dose of itraconazole. The washout period between LY3509754 and itraconazole dosing may be extended by up to 5 days based on emerging PK data.

[b] Itraconazole 200 mg will be administered as an oral solution twice on Day 4 (dose separated by approximately 12 hours) and once daily on Days 5 through 13. Itraconazole should be administered at approximately the same time every morning. Participants will undergo an overnight fast (Section 5.3.1) prior to the day where 2 doses of itraconazole administration occurs. On Day10, itraconazole should be administered 1 hour before LY3509754 administration (see Section 4.2.2). The timing and duration of itraconazole dosing may be adjusted based on emerging PK data from Part A.

[c] Vital sign measurements, PE/MA, ECGs, may be collected within time windows depending on the collection time, as follows: Predose (within 2 hours before dosing); 0.5 h (±10 min); 1 to 4 hours (±15 min); 5 to 8 hours (±20 min); 12 hours (±30 min); 24 hours and longer (±60 min). Blood samples collected for PK, PD, or biomarker purposes may be collected within time windows depending on the collection time, as follows: Predose (within 1 hour before dosing); 0.5 h (±5 min); 1 to 4 hours (±10 min); 5 to 8 hours (±15 min); 12 hours (±30 min); 24 hours and longer (±60 min).

[d] Predose time points refer to dosing before itraconazole and LY3509754. All postdose time points are relative to the LY3509754 dose.

[e] See Section 10.2 for details. The PI must review the Day -2 laboratory results before dosing on Day 1. LY3509754/placebo on Day 1. The PI must review Day 3 laboratory results before dosing itraconazole on Day 4.

[f] Additional follow-up visits may be conducted for safety labs and monitoring after the existing follow-up visit that is ~ 7 days after discharge. Every attempt should be made to contact subjects for the follow-up visits; however, if subjects are unwilling or unable to return for the additional visits, this is not considered a protocol violation.

1.3.4. Part C: Multiple-Ascending Dose – Cohorts 1 and 3 – Single Period

Procedure	Screening					Treatment									ED	Follow-up[d]	Comments
Study Days	-28 to -3	-2	-1	1	2	3-6	7	8-13	14	15	16	17	18	19		Approx 7 days after discharge	
Informed consent	X																
Admission to CRU		X															
Discharge from CRU														X			
PE/MA[a]	X	X		P										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.
COVID-19 test (PCR)	X	X					X							X	X	X	
Pregnancy test	X	X													X	X	Serum test at screening. Urine test at all other time points per investigator discretion.
Urine drug screen	X	X															
Breath or urine ethanol test	X	X															Ethanol test may be repeated at other time points at the discretion of the investigator.
QuantiFERON®-TB Gold test	X																
AE/medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight	X		X											X	X		Height at screening only.

Procedure	Screening					Treatment									ED	Follow-up[d]	Comments
Study Days	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3-6**	**7**	**8-13**	**14**	**15**	**16**	**17**	**18**	**19**		**Approx 7 days after discharge**	
LY3509754/ placebo administration				X	X	X	X	X	X								Participants will fast overnight before receiving LY3509754/placebo and for approximately 2 hours after dosing. On intensive PK day, participants may receive a light meal at least 2 hours after dosing.
Vital signs (BP, PR [supine], temperature) (hours)[a]	X		X	P, 2, 4, 8, 12	P, 2	P, 2	P, 2, 4, 8, 12	P, 2	P, 2, 4, 8, 12	X	X	X	X	X	X	X	On Days 1 to 14, temperature will be measured at predose only.
Clinical laboratory tests[b]	X	X					P							X	X	X	
12-lead ECG (hours)[a]	X			P, 1, 2, 3		P, 1, 2, 3 (Day 3 only)	P, 1, 2, 3	P, 1, 2, 3 (Day 10 only)						X	X	X	Single safety ECGs. ECGs coinciding with PK sample time points are to be conducted as close as possible prior to PK sampling.

Procedure	Screening			Treatment										ED	Follow-up[d]	Comments
Study Days	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3-6**	**7**	**8-13**	**14**	**15**	**16**	**17**	**18**	**19**		**Approx 7 days after discharge**	
PK sampling (hours)[a]				P, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	P		P, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	P (Day 8 only)	P, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	24	48	72	96				Sampling times are relative to the time of LY3509754 administration (0 hour).
Exploratory plasma blood sampling (hours)[a,c]				P, 1, 4, 12	P	P	P, 1, 4, 12	P	P, 1, 4, 12	24	48	72	96			X[e]	Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).
Exploratory serum blood sampling (hours)[a,c]				P		P (Days 3 and 6 only)		P (Days 9 and 12 only)		24							Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).
Exploratory buccal swabs and saliva samples (hours)[a]				P, 8	P		P, 8		P, 8	24							Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).

Procedure	Screening			Treatment											ED	Follow-up[d]	Comments
Study Days	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3-6**	**7**	**8-13**	**14**	**15**	**16**	**17**	**18**	**19**		**Approx 7 days after discharge**	
PGx sample				X													For storage only. Sample can be taken any time prior to dosing.

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; P = predose; PCR = polymerase chain reaction; PE = physical examination; PGx = pharmacogenetic; PK = pharmacokinetic; PR = pulse rate.

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.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

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

[a] Vital sign measurements, PE/MA, ECGs, and blood samples collected for PK, PD, or biomarker (including buccal and saliva samples) purposes may be collected within time windows depending on the collection time, as follows: Predose (within 1 hour before dosing); 0.5 h (±5 min); 1 to 4 hours (±10 min); 5 to 8 hours (±15 min); 12 hours (±30 min); 24 hours and longer (±60 min).

[b] See Section 10.2 for details. The principal investigator must review the Day -2 laboratory results before dosing on Day 1.

[c] Samples may be further processed for serum or plasma. See laboratory manual for further details.

[d] Additional follow-up visits may be conducted for safety labs and monitoring after the existing follow-up visit that is ~ 7 days after discharge. Every attempt should be made to contact subjects for the follow-up visits; however, if subjects are unwilling or unable to return for the additional visits, this is not considered a protocol violation.

[e] Plasma samples should be collected for exploratory analyses at additional follow-up visits; however, if subjects are unwilling or unable to return to collect this sample, this is not considered a protocol violation.

1.3.5. Part C: Multiple-Ascending Dose and Perpetrator DDI – Cohort 2 Fixed Sequence

Procedure	Screening	Treatment															ED	Follow-up[e]	Comments
Study Days	-26 to -5	-4	-3	-2	-1	1	2	3	4	5-8	9	10-14	15	16	17 - 18	19		Approx 7 days after discharge	
Informed consent	X																		
Admission to CRU		X																	
Discharge from CRU																X			
PE/MA[a]	X	X		P												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.
COVID-19 test (PCR)	X	X				X			X							X	X	X	
Pregnancy test	X	X															X	X	Serum test at screening. Urine test at all other time points per investigator discretion.
Urine drug screen	X	X																	

Procedure	Screening	Treatment															ED	Follow-up[e]	Comments
Study Days	**-26 to -5**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5-8**	**9**	**10-14**	**15**	**16**	**17-18**	**19**		**Approx 7 days after discharge**	
Breath or urine ethanol test	X	X																	Ethanol test may be repeated at other time points at the discretion of the investigator.
QuantiFERON®-TB Gold test	X																		
AE/medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight	X		X													X	X		Height at screening only.
LY3509754/ placebo administration						X	X	X	X	X	X	X	X						Participants will fast overnight before receiving LY3509754/placebo and for approximately 2 hours after dosing. On intensive PK days, participants may receive a light meal at least 2 hours after dosing.

Procedure	Screening	Treatment															ED	Follow-up[e]	Comments
Study Days	-26 to -5	-4	-3	-2	-1	1	2	3	4	5-8	9	10-14	15	16	17-18	19		Approx 7 days after discharge	
																			Dosing of LY3509754/placebo will occur at approximately the same time of day on each day of dosing and on Day -2 at approximately the same time of day as midazolam administration.
Administration of midazolam (oral syrup)				X									X						The dosing of midazolam will occur at least 1 hour after LY3509754/placebo dosing on Day 15.
Vital signs (BP, PR [supine], temperature) (hours)[a]	X		X	P, 2, 4		P, 2, 4, 8, 12		P, 2		P, 2 4, 8, 12 (Day 7 only)	P, 2	P,2 (Day 10-13) P,2,4,8 ,12 (Day 14)	X	X	X	X	X	X	On Days -2 to 14, temperature will be measured at predose only.
Clinical laboratory tests[b]	X	X			X				P							X	X	X	

Procedure	Screening	Treatment															ED	Follow-up[e]	Comments
Study Days	**-26 to -5**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5-8**	**9**	**10-14**	**15**	**16**	**17 - 18**	**19**		**Approx 7 days after discharge**	
12-lead ECG (hours)[a]	X					P, 1, 2, 3		P, 1, 2, 3		P, 1, 2, 3 (Day 7 only)		P, 1, 2, 3 (Day 10 only)				X	X	X	Single safety ECGs. ECGs coinciding with PK sample time points are to be conducted as close as possible prior to PK sampling.
LY3509754 PK sampling (hours)[a]						P, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16	P			P, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16 (Day 7 only) P (Day 8 only)		P, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16 (Day 14 only)	24						Sampling times are relative to the time of LY3509754 administration (0 hour). Collect 24-hour sample on Day 15 prior to dosing of LY3509754 or midazolam.
Midazolam and metabolite PK sampling (hours)[a,d]				P, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16	24								P, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16	24					

Procedure	**Screening**					**Treatment**											**ED**	**Follow-up[e]**	**Comments**
Study Days	**-26 to -5**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5-8**	**9**	**10-14**	**15**	**16**	**17 - 18**	**19**		**Approx 7 days after discharge**	
Exploratory blood sampling (hours)[a,c]						P, 1, 4, 12	P			P, 1, 4, 12 (Day 7 only) P (Day 8 only)		P, 1, 4, 12 (Day 14 only)	24					X[f]	Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).
Exploratory buccal swabs and saliva samples (hours)[a]						P, 8	P			P, 8 (Day 7 only)		P, 8 (Day 14 only)	24						Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).
PGx sample				X															For storage only. Sample can be taken any time prior to dosing.

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

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.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

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

[a] Vital sign measurements, PE/MA, ECGs, may be collected within time windows depending on the collection time, as follows: Predose (within 2 hour before dosing); 0.5 h (±10 min); 1 to 4 hours (±15 min); 5 to 8 hours (±20 min); 12 hours (±30 min); 24 hours and longer (±60 min). Blood samples collected for PK, PD, or biomarker (including buccal and saliva samples) purposes may be collected within time windows depending on the collection time, as follows: Predose (within 1 hour before dosing); 0.5 h (±5 min); 1 to 4 hours (±10 min); 5 to 8 hours (±15 min); 12 hours (±30 min); 24 hours and longer (±60 min).

[b] See Section 10.2 for details. The principal investigator must review the Day -2 laboratory results before dosing on Day 1.

[c] Samples may be further processed for serum or plasma. See laboratory manual for further details.

[d] Predose time points refer to dosing before midazolam. All postdose time points are relative to the midazolam dose.

[e] Additional follow-up visits may be conducted for safety labs and monitoring after the existing follow-up visit that is ~ 7 days after discharge. Every attempt should be made to contact subjects for the follow-up visits; however, if subjects are unwilling or unable to return for the additional visits, this is not considered a protocol violation.

[f] Plasma samples should be collected for exploratory analyses at additional follow-up visits; however, if subjects are unwilling or unable to return to collect this sample, this is not considered a protocol violation.

1.3.6. Part D: Multiple-Dose in Japanese Healthy Participants – Single Period

Procedure	Screening			Treatment Period										ED	Follow-up [c]	Comments
Study Day	-28 to -3	-2	-1	1	2	3-6	7	8-13	14	15	16	17	18	19		Approx 7 days after discharge	
Informed consent	X																
Admission to CRU		X															
Discharge from CRU														X			
PE/MA [a]	X	X		P										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.
COVID-19 test (PCR)	X	X					X							X	X	X	
Pregnancy test	X	X													X	X	Serum test at screening. Urine test at all other time points.
Urine drug screen	X	X															
Breath or urine ethanol test	X	X															Ethanol test may be repeated at other time points at the discretion of the investigator.

Procedure	Screening			Treatment Period											ED	Follow-up [c]	Comments
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3-6**	**7**	**8-13**	**14**	**15**	**16**	**17**	**18**	**19**		**Approx 7 days after discharge**	
QuantiFERON®-TB Gold test	X																
AE/medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight	X		X											X	X		Height at screening only.
LY3509754/ placebo administration				X	X	X	X	X	X								Participants will fast overnight before receiving LY3509754/placebo and for approximately 2 hours after dosing. On intensive PK days, participants may receive a light meal at least 2 hours after dosing.
Vital signs (BP, PR [supine], temperature) (hours)[a]	X		X	P, 2, 4, 8, 12	P, 2	P, 2	P, 2, 4, 8, 12	P, 2	P, 2, 4, 8, 12	X	X	X	X	X	X	X	On Days 1 to 14, temperature will be measured at predose only.
Clinical laboratory tests[b]	X	X					P							X	X	X	

Procedure	Screening			Treatment Period										ED	Follow-up [c]	Comments
Study Day	-28 to -3	-2	-1	1	2	3-6	7	8-13	14	15	16	17	18	19		Approx 7 days after discharge	
12-lead ECG (hours)[a,c]	X			P, 0.5 1, 2, 3, 4, 5, 6, 8, 12	P	P, 1, 2, 3 (Day 3 only all time points)	P, 1, 2, 3	P, 1, 2, 3 (Day 10 only all time points)						X	X	X	ECGs coinciding with PK sample time points are to be conducted as close as possible prior to PK sampling. ECGs must be taken prior to dosing on Day 2 but as close as possible to 24 hours following dosing on Day 1.
PK sampling (hours)[a]				P, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16	P		P, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	P (Day 8 only)	P, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	24	48	72	96				Sampling times are relative to the time of LY3509754 administration (0 hour). PK samples must be taken prior to dosing on Day 2 but as close as possible to 24 hours following LY3509754 dosing on Day 1.
Exploratory plasma blood sampling (hours)[a,d]				P, 1, 4, 12	P	P	P, 1, 4, 12	P	P, 1, 4, 12	24	48	72	96			X[f]	Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).

Procedure	**Screening**			**Treatment Period**											**ED**	**Follow-up [c]**	**Comments**
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3-6**	**7**	**8-13**	**14**	**15**	**16**	**17**	**18**	**19**		**Approx 7 days after discharge**	
Exploratory serum blood sampling (hours)[a,d]				P		P (Days 3 and 6 only		P (Days 9 and 12 only)		24							Stored sample for biomarker research. Sampling times are relative to the time of study treatment administration (0 hour).
Exploratory buccal swabs and saliva samples (hours)[a]				P, 8	P		P, 8		P, 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 PGx analysis taken prior to/on Day 1.

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; MA = medical assessment; P = predose; PCR = polymerase chain reaction; PE = physical examination; PGx = pharmacogenetic; PK = pharmacokinetic; PR = pulse rate.

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.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

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

[a] Vital sign measurements, PE/MA, ECGs, may be collected within time windows depending on the collection time, as follows: Predose (within 2 hour before dosing); 0.5 h (±10 min); 1 to 4 hours (±15 min); 5 to 8 hours (±20 min); 12 hours (±30 min); 24 hours and longer (±60 min). Blood samples collected for PK, PD, or biomarker (including buccal and saliva samples) purposes may be collected within time windows depending on the collection time, as follows: Predose (within 1 hour before dosing); 0.5 h (±5 min); 1 to 4 hours (±10 min); 5 to 8 hours (±15 min); 12 hours (±30 min); 24 hours and longer (±60 min).

[b] See Section 10.2 for details. The principal investigator must review the Day -2 laboratory results before dosing on Day 1.

[c] Electrocardiograms on Days 1 and 2 will be triplicate in Part D. On all other days, electrocardiograms will be single.

[d] Samples may be further processed for serum or plasma. See laboratory manual for further details.

[e] Additional follow-up visits may be conducted for safety labs and monitoring after the existing follow-up visit that is ~ 7 days after discharge. Every attempt should be made to contact subjects for the follow-up visits; however, if subjects are unwilling or unable to return for the additional visits, this is not considered a protocol violation.

[f] Plasma samples should be collected for exploratory analyses at additional follow-up visits; however, if subjects are unwilling or unable to return to collect this sample, this is not considered a protocol violation.

2. Introduction

LY3509754 is an oral small molecule inhibitor for IL-17A that is being developed for once-daily treatment of psoriasis (PsO) and other immune-mediated diseases.

2.1. Study Rationale

LY3509754 has not been administered to humans. This first-in-human study will investigate the safety, tolerability, and pharmacokinetics (PK) of single-ascending dose (SAD; Part A) and multiple-ascending doses of LY3509754 in healthy non-Japanese (MAD; Part C) and Japanese participants (Part D). As LY3509754 is being developed as an oral formulation and the effect of food on the PK of LY3509754 is clinically unknown, CCI [redacted]

2.2. Background

LY3509754 is an oral small molecule inhibitor for interleukin-17A (IL-17A) which is being developed for once-daily treatment of psoriasis (PsO) and other immune-mediated diseases.

IL-17A is a proinflammatory cytokine and a member of the IL-17 cytokine family, which also includes IL-17B-F. The active, homodimeric IL-17A cytokine is produced by Th17 cells and other αβ T cells as well as mast cells, γδ T cells, and innate lymphoid cells. IL-17A signals through a receptor complex consisting of IL-17RA:IL-17RC. IL-17A signaling leads to the production of proinflammatory and proliferative cytokines, chemokines and various antimicrobial peptides. Cellular targets for IL-17A include keratinocytes (among other epithelial cells, e.g., Paneth cells), fibroblasts, osteoclasts, chondrocytes, osteoblasts, endothelial cells, and neutrophils. IL-17A is a major effector cytokine that has been demonstrated to drive the pathogenesis of multiple psoriatic diseases (Blauvelt and Chiricozzi 2018).

Currently, multiple injectable monoclonal antibodies (mAbs) targeting IL-17A have been demonstrated to be safe and effective in the treatment of and approved for PsO, psoriatic arthritis (PsA), and ankylosing spondylitis (AxSpa). However, oral treatment options in PsO are limited and higher efficacy is desirable. The intent of LY3509754 development is to deliver an orally available small molecule inhibitor of IL-17A signaling to provide physicians with a complementary oral treatment option for patients with psoriatic diseases.

LY3509754 has demonstrated a favorable safety profile in good laboratory practice (GLP) compliant toxicology and safety pharmacology studies to support clinical trials. LY3509754 was evaluated in 1-month daily oral-dosing toxicity studies in Sprague Dawley rats and beagle dogs (with 1-month reversibility in high-dose rats and dogs). Safety pharmacology parameters were evaluated in an in vitro (human ether á-go-go–related gene [hERG]) assay and in vivo (rat central nervous system [CNS], rat respiratory, dog cardiovascular) studies. Genetic toxicity was evaluated in a bacterial mutation (Ames) assay, an in vitro micronucleus (MN) assay and an in vivo rat MN assay. In vitro phototoxic potential was evaluated in a Neutral Red Uptake Phototoxicity Assay in Balb/c 3T3 mouse fibroblasts.

In rats, non-adverse effects included decreased body weight and food consumption, erythrocyte effects (decreased red blood cell count, hemoglobin, and hematocrit; spherocytes and acanthocytes), increased reticulocytes, increased bilirubin, increased liver weight, stellate cell hypertrophy in the liver and hepatocellular vacuolation. The findings in erythrocyte parameters and total bilirubin were of minor magnitude and were consistent with minimal hemolysis. In rats, the 1-month no-observed-adverse-effect level (NOAEL) was 1000 mg/kg based on no adverse effects at the highest dose tested.

In dogs, non-adverse effects included vomiting, diarrhea, increased heart rate, and decreased thymic weights. In dogs, the 1-month NOAEL was 150 mg/kg based on no adverse effects at the highest dose tested. In addition to effects observed in 1-month studies, a higher dose (500 mg/kg) administered to dogs for 7 days (non-GLP dose-range finding study) was not tolerated and resulted in severe body weight loss and adverse effects in the liver, kidney, heart, and lung.

All findings in the 1-month studies were completely reversible except for liver weights, stellate cell hypertrophy and hepatocellular vacuolation, observed in rats, which were partially reversible (lower incidence and severity after the recovery phase). See Section 4.2.1 of the Investigator's Brochure (IB) for more details on nonclinical toxicology and safety pharmacology.

LY3509754 has demonstrated suitable absorption, distribution, metabolism, and excretion properties in in vitro experiments and in nonclinical in vivo studies to warrant clinical investigation. Its predicted human properties are favorable (bioavailability, F = 0.62). CCI

[redacted]

CCI [redacted]

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3509754 may be found in the IB.

The nonclinical safety information for LY3509754 adequately supports the transition from preclinical status to clinical, single- and multiple-dose evaluations. The sponsor has evaluated the risks associated with LY3509754 and does not consider it to be a high uncertainty compound, based on published criteria (Butler et al. 2017).

Namely:

1. The existence of pharmacology in vivo models that can reasonably predict intended and exaggerated pharmacologically active and excessive pharmacological responses in relation to measurable drug concentration in vivo and because the target is an endogenous human target.

2. The animal toxicity models are believed to adequately reflect human toxicity for this target in a single and repeat dose studies.
3. CCI [redacted]
4. LY3509754 has demonstrated a favorable safety profile in GLP-compliant 1-month toxicology studies in rats and dogs (with reversibility in high dose rats and dogs), safety pharmacology and genetic toxicity studies to support clinical trials.
5. Anticipated risks in the single and repeat dose studies include potential effects on erythrocytes (including decreased red blood cell count, decrease in hemoglobin, and hematocrit; spherocytes and acanthocytes), increased reticulocyte count, increase in bilirubin level, increased liver weight, and hepatocellular vacuolation, as reported in rat toxicity studies. These effects were non-adverse and are considered monitorable and measurable. Other potential risks are those associated with increased heart rate as reported in dog studies and decreased body weight as reported in the rat toxicity studies, both of which are monitorable and account for the cautious monitoring of vital signs and measurement of weight planned for this trial.

This protocol reflects the fact that LY3509754 has not been administered to humans previously, and to mitigate this risk, the study has been designed to be conducted in accordance with principles outlined in the applicable guidance, such as the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products (EMA 2017). There is no anticipated therapeutic benefit for the participants. More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY3509754 can be found in the IB.

3. Objectives and Endpoints

Objectives and Endpoints

Objectives	Endpoints
Primary	
• The primary objective is to assess the safety and tolerability following single or multiple doses of LY3509754 administered to healthy participants	• Incidence of SAEs and TEAEs
Secondary	
• The secondary objective is to characterize the PK following single or multiple orally administered doses of LY3509754 in healthy participants	• C_{max} and AUC of LY3509754
Tertiary/Exploratory	
[redacted]	

CCI

Abbreviations: AUC = area under the concentration-time curve; CCI C_{max} = maximum observed drug concentration; CCI ; PK = pharmacokinetics; CCI CCI ; SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{max} = time to maximum observed drug concentration.

4. Study Design

4.1. Overall Design

Study J3D-MC-FNAA is a Phase 1, multi-center study in healthy participants to be conducted in 4 parts:

- Part A (SAD): Part A will be a participant-and investigator-blind, placebo-controlled, randomized, SAD study to evaluate safety, tolerability, and PK of LY3509754 in healthy participants in up to 6 cohorts. One cohort (Cohort 4) will include a randomized, single-dose level, 2 period crossover [redacted]
- Part B (DDI – CYP3A4 victim): Part B will be a participant- and investigator-blind, placebo-controlled, single-dose-level, single-arm, DDI study to evaluate the multiple dose impact of the CYP3A4 inhibitor, itraconazole, on the single dose exposure of LY3509754.
- Part C (MAD): Part C will be a participant-and investigator-blind, placebo-controlled, randomized, 14-day, single-period MAD study with up to 3 cohorts to evaluate safety, tolerability, and PK of LY3509754 in healthy participants. [redacted]
- Part D (Japanese participants): Part D will be a participant-and investigator-blind, placebo-controlled, randomized, multiple dose study to evaluate the safety, tolerability, and PK of LY3509754 in healthy Japanese participants in 2 dose levels in 2 separate cohorts (1 dose level per cohort). The 2 dose levels will be conducted concurrently.

4.2. Scientific Rationale for Study Design

LY3509754 has not been administered to humans. This first-in-human study will investigate the safety, tolerability, and pharmacokinetics (PK) of single-ascending dose (SAD; Part A) and multiple-ascending doses of LY3509754 in healthy non-Japanese (MAD; Part C) and Japanese participants (Part D). As LY3509754 is being developed as an oral formulation and the effect of food on the PK of LY3509754 is clinically unknown, [redacted]

There is no anticipated therapeutic benefit for the participants in this study. Conducting the study in a healthy participant population mitigates the potential for disease state and concomitant medication use to confound the interpretation of results. In all Parts (A-D), the participants and site staff (excluding pharmacy staff) will be blinded to treatment allocation to allow for unbiased assessment of the data. The results of this study will inform the dosing tolerability range for subsequent trials, in addition to providing information on the PK and potential food and DDI effects of LY3509754.

4.2.1. Part A (Single-Ascending Dose)

Participants in Part A will be randomly assigned/enrolled into up to 6 cohorts with up to 59 participants completing this part of the study. Table FNAA.1 shows the planned LY3509754 dose and number of participants to complete each cohort in Part A.

Table FNAA.1. Planned LY3509754 Dose and Number of Participants to Complete Each Cohort (Part A)

Cohort	Dose Frequency	Planned Dose	Planned # of Completers
1	Single oral dose	10-mg LY3509754 or placebo	6 LY3509754; 2 placebo
2	Single oral dose	30-mg LY3509754 or placebo	6 LY3509754; 2 placebo
3	Single oral dose	100-mg LY3509754 or placebo	6 LY3509754; 2 placebo
4	Single oral dose (Periods 1 and 2)[a]	300-mg LY3509754 or placebo	9 LY3509754; 2 placebo
5	Single oral dose	1000-mg LY3509754 or placebo	6 LY3509754; 2 placebo
6	Single oral dose	2000 mg LY3509754[b]	Up to 8 total

[a] Participants in this cohort will be administered LY3509754 under fasted (Period 1) or fed (Period 2) conditions.

[b] Based on review of safety data from Cohorts 1 to 5.

The maximum increase in LY3509754 doses between sequential cohorts in the SAD will be no more than semi-log increases to explore the LY3509754 dose range, while providing adequate separation of the doses to characterize LY3509754 safety, tolerability, and PK. See Section 4.3.1 for dose justification.

Cohorts 1, 2, 3, 5, and 6

Participants will be admitted to the clinical research unit (CRU) on Day -2. Participants will remain in the CRU for at least 96 hours after dosing (until Day 5) according to the Schedule of Activities (SoA) (Section 1.3.1), after which they may be discharged at the discretion of the investigator.

Cohort 4

Cohort 4 will be a 2-period randomized (each period) crossover design CCI [redacted]

Participants will be admitted to the clinical research unit (CRU) on Day -2. Participants will remain in the CRU for at least 96 hours after dosing Period 2 (until Day 5 of Period 2) according to the SoA (Section 1.3.2), after which they may be discharged at the discretion of the investigator.

The washout between the LY3509754 dosing days in Period 1 and Period 2 will be at least 5 days. CCI [redacted]

Period 2 will be conducted as described for Period 1; however, participants will receive a single oral dose of LY3509754 CCI [redacted]

Cohorts 1-6 (all cohorts)

A poststudy follow-up visit for each cohort will be conducted at least 7 days after discharge.

Participants will provide total urine collections for the 24 hours postdose in each cohort (for exploratory metabolism and assessment of renal elimination); an additional blood sample will be collected to determine serum creatinine measurements.

See Section 6.6.1 for information regarding dose modifications, including dose decision and escalation.

4.2.2. Part B (CYP3A4 Inhibition)

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Part B will consist of approximately 12 participants (9 LY3509754:3 placebo) and CCI

The LY3509754 dose to be studied in Part B is 10 mg. This dose was determined based on safety, tolerability, and PK data from Part A, and will be administered as an oral formulation. See Section 4.3.1 for dose justification.

As detailed in the Schedule of Activities (SoA; Section 1.3.3), participants will be admitted to the CRU on Day -2 before receiving a single oral dose of LY3509754 or placebo on Day 1.

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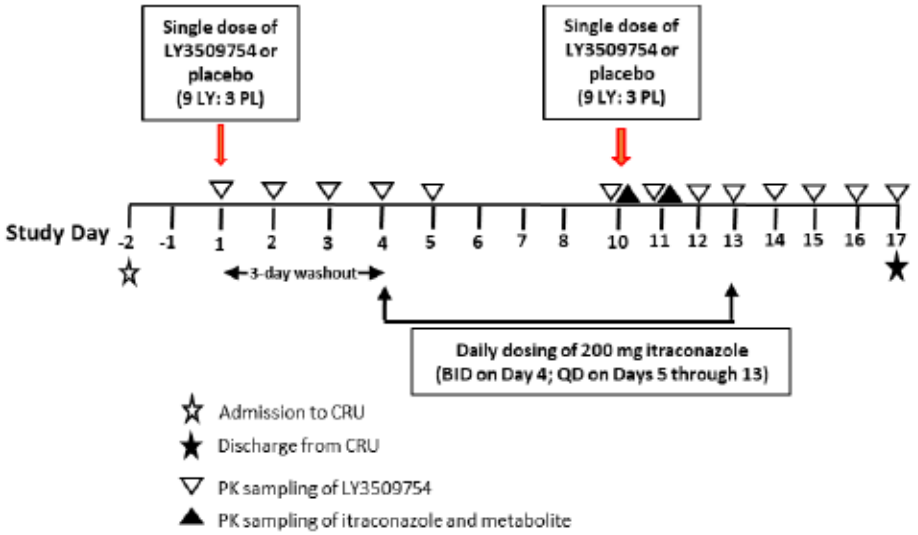
Participants will undergo an overnight fast on Day 9, before receiving a single oral dose of LY3509754 or placebo on Day 10, approximately 1 hour after the dose of itraconazole. Blood sampling for PK purposes (LY3509754 and itraconazole) and other assessments will occur according to the SoA (Section 1.3.3). The timing and duration of the itraconazole dosing may be adjusted based on emerging data from Part A.

Participants will remain in the CRU until discharge on the morning of Day 17, approximately 96 hours after the final dose of itraconazole and approximately 7 days after the final dose of LY3509754. A joint sponsor and investigator safety review will be completed approximately 5 days after each LY3509754 administration. A poststudy follow-up visit will be conducted approximately 7 days after discharge. See Figure FNAA.1 for a schematic of the study design for Part B.



Abbreviations: BID = twice daily; CRU = clinical research unit; LY = LY3509754; PK = pharmacokinetic; PL = placebo; QD = once daily.

Figure FNAA.1. Part B: Drug-Drug Interaction with CYP3A4 Inhibition

4.2.3. Part C (Multiple-Ascending Dose/ CYP3A4 Perpetrator DDI)

Part C will include up to 3 cohorts and will commence once safety data has been reviewed from the 1000 mg cohort (Part A), as well as the review of PK data from interim analyses from Part A. Doses will be informed by emerging data from Part A (see Section 4.2.1 for details). The maximum increase in LY3509754 doses between sequential cohorts in the MAD will be no more than semi-log increases to explore the LY3509754 dose range, while providing adequate separation of the doses to characterize LY3509754 safety, tolerability, and PK. See Section 4.3.1 for dose justification. Table FNAA.2 shows the planned LY3509754 dose and number of participants to complete each cohort in Part C.

Table FNAA.2. Planned LY3509754 Dose and Number of Participants to Complete Each Cohort (Part C)

Cohort	Dose Frequency	Planned Dose	Planned # of Completers
1	1x daily oral for 14 days	LY3509754 100-mg	6 LY3509754; 2 placebo
2[a]	1x daily oral for 14 days[b]	LY3509754 300-mg	8 LY3509754; 2 placebo
3	1x daily oral for 14 days	LY3509754 1000-mg	6 LY3509754; 2 placebo

[a] Participants in this cohort will be administered 1.2-mg midazolam in oral syrup on Days -2 and 15. On Day 15, midazolam administration will occur at least 1 hour after participants receive a single oral dose of LY3509754.

Cohorts 1 and 3 (Single Period)

A daily dose of LY3509754 for 14 days allows for adequate duration of assessment of the safety, tolerability, and PK data at the projected LY3509754 human steady state concentrations.

Participants will remain in the CRU for greater than 96 hours following the last dose, after which they may be discharged on Day 19 at the discretion of the investigator.

Cohort 2 (Fixed Sequence)

CCI [redacted] Participants will be admitted to the CRU on Day -4. Participants will be dosed with 1.2-mg midazolam in oral syrup form on Day -2 and serial blood samples will be collected for determination of plasma midazolam concentrations (See Section 4.3.3. for dose justification). Following midazolam dosing, 8 participants will be randomly assigned to receive 300 mg of LY3509754 and 2 to receive placebo (See Section 4.3.3. for dose justification). The MAD dose escalation will begin on Day 1.

On Day 15, participants will receive another single dose of LY3509754 300-mg (see SoA [Section 1.3.5] for details). At least 1 hour following LY3509754 administration, participants will be given another 1.2 mg dose of midazolam (in oral syrup form) and serial blood samples will be collected for determination of plasma midazolam concentrations. The dosing of LY3509754 or midazolam will occur at approximately the same time each dosing day through Day 14 as detailed in the SoA (Section 1.3.5). Participants will remain in the CRU for at least 96 hours after dosing (until Day 19) according to the SoA (Section 1.3.5), after which they may be discharged at the discretion of the investigator. See Figure FNAA.2 for a schematic diagram of the study design for Part C (Cohort 2).

Cohorts 1-3 (all Cohorts)

All available PK and safety data, including AEs, vital signs (BP and PR), ECGs, and clinical laboratory tests, from at least 6 participants in each cohort will be assessed prior to escalating to the next dose level (see Section 6.6.1). Safety data must include data from at least 5 days from a minimum of 6 participants (Sections 6.6.1 and 9.3.5).

See Section 6.6.1 for information regarding dose modifications, including dose decision and escalation.

Additional cohorts may be required to safely investigate maximum exposure to LY3509754; this decision will be made between the sponsor and the investigator, following the necessary review of the safety data. The PK data emerging during the MAD part of the study will be used to assist in MAD dose-escalation decisions.

In all cohorts, PK sampling will be conducted as detailed in the SoA (Section 1.3.4 and 1.3.5) and a poststudy follow-up visit will be conducted approximately 7 days after discharge.

For additional details on the timing of study activities see Section 1.3

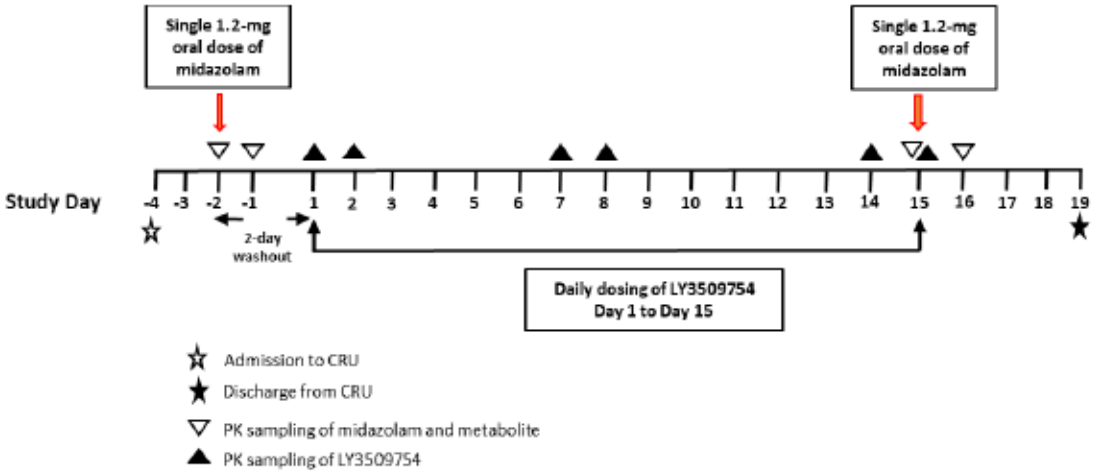


Figure FNAA.2. Part C: Multiple-Ascending Dose and Perpetrator DDI – Cohort 2 Fixed Sequence)

4.2.4. Part D (Multiple Dosing in Japanese Healthy Participants)

Part D characterizes LY3509754 safety, tolerability, and PK in a Japanese healthy population to inform the inclusion of patients of Japanese origin in future PsO and other disease state studies. Part D will be conducted after review of safety, tolerability, and PK data from other parts of the study.

Part D will explore 2 dose levels in 2 separate cohorts (see Section 4.3.1. for dose justification). Each cohort will consist of at least 8 participants (6 LY3509754:2 placebo). The 2 cohorts will be run simultaneously, and will not exceed the maximum dose evaluated in Part C (MAD in non-Japanese participants) (see Section 4.2.3 for details). For further information on the study design for Part D, refer to the Part C (MAD) describing Cohorts 1 and 3 and Cohorts 1-4 (all Cohorts) in Section 4.2.3.

See Section 5.3.1 for meals and dietary restrictions for all Parts (A-D) of the study

4.2.5. Rationale for Excluding Sentinel Dosing

While a recently published European Medicines Agency guideline (EMA 2017) recommends use of sentinel dosing in first-in-human studies, it also allows for flexibility in a proposed dosing approach based on the available scientific data and preclinical assessment of a given molecule. Based on the risk assessment of the available data, LY3509754 does not present a high uncertainty profile as described by DeGeorge et al. (2018), which would necessitate inclusion of the sentinel dosing approach.

Namely, the following characteristics of the molecule would trigger a higher level of concern, none of which is the case with LY3509754:

- Lack of nonclinical pharmacology model in vivo that can reasonably predict intended and exaggerated pharmacologically active and excessive pharmacological responses in relation to measurable drug concentration in vivo and because the target is an endogenous human target,

AND

- Animal toxicity models are understood (or expected) to poorly reflect known human toxicity for the target,

OR

- The types of toxicity that are known or can be anticipated are severe, likely irreversible, and without adequate prodromal signs.

Nonclinical pharmacology models exist for the prediction of intended and exaggerated pharmacology in conjunction with measurements of drug concentration. The intended and exaggerated pharmacological responses of LY3509754 have been well characterized in preclinical pharmacology models. The nonclinical safety profile of LY3509754, as characterized in 1-month rat and dog toxicology studies, showed all findings were completely reversible except for liver weights, stellate cell hypertrophy and hepatocellular vacuolation, observed in rats, which were partially reversible (lower incidence and severity after the recovery phase).

Section 4.3.1 provides the dose justification. The large margins of safety for the planned starting dose of 10 mg in the SAD (Part A) subjugate the need for sentinel dosing.

See Section 4.2.1 of the IB for more details on nonclinical toxicology and safety pharmacology. The types of adverse findings anticipated are mild, gradual in onset, transient, reversible and monitorable. Based on the above-summarized data, LY3509754 does not present an uncertainty profile necessitating a sentinel dosing approach. Furthermore, sentinel dosing with low-uncertainty compounds, such as LY3509754, may lead to inability to interpret data due to false positive AE findings in the absence of data from all cohorts or placebo-treated participants.

4.3. Justification for Dose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5. Study Population

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

Eligibility of participants for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECGs. 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. Participants 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.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply at screening:

Age

1. Participant must be between the ages of 18 and 65 years of age, inclusive, at the time of signing the informed consent.
    a. In Part D, Japanese participants must be between the ages of 20 and 65 years of old, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Overtly healthy males or females, as determined by medical history and physical examination.
    a. To qualify as Japanese for Part D of this study, the participant must be first-generation Japanese, defined as the participant's biological parents and all of the participant's biological grandparents must be of exclusive Japanese descent, and must have been born in Japan.
3. 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; have a urinary protein value <2+ on dipstick urinalysis.
4. Have venous access sufficient to allow for blood sampling and/or administration of study intervention for intravenous administration as per the protocol.
5. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

BMI

6. Body mass index (BMI) within the range of 18 to 35 kg/m^2 (inclusive) in Parts A, B, and C. In Part D (Japanese participants), body weight between 50 and 85 kg and BMI within the range of 18 to 28 kg/m^2.

Sex

7. Male and/or female.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants
   Please refer to Appendix 4 (Section 10.4) for definitions and additional guidance related to contraception.
b. Female participants
   1) Women of childbearing potential are excluded from the trial.
   2) Women not of childbearing potential may participate and include those who are:
      A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Müllerian agenesis; or
      B. post-menopausal – defined in Appendix 4 (Section 10.4)

Informed Consent

8. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.2), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

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

9. Are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
10. Are Lilly employees.
11. 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.
12. 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.
13. Have previously completed or withdrawn from this study or any other study investigating LY3509754, and have previously received LY3509754.

14. Have known allergies to LY3509754, related compounds or any components of the formulation, itraconazole, midazolam, or history of significant atopy.
15. Have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study.
16. Have a marked baseline prolongation of corrected QT (QTc) interval (for example, repeated demonstration of a QTcF 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.
17. 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.
18. 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.
19. Have a history of or current significant psychiatric disorders.
20. Have a history of head injury (e.g., 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.
21. Regularly use known drugs of abuse and/or show positive findings on drug screening.
22. Show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
23. Show evidence of hepatitis B and/or positive hepatitis B surface antigen.
24. Show evidence of hepatitis C and/or positive hepatitis C antibody.
25. For female participants
    a. are women who are lactating
    b. are women with a positive pregnancy test at screening

26. Have used or intend to use over-the-counter/herbal supplements (e.g., 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.
27. 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.
28. Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (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).
29. 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.
30. Consume Seville oranges or Seville orange–containing products, red wine, 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.
31. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.
32. Have a current or recent acute active infection. For at least 30 days prior to screening, patients must have no significant symptoms including fever of 100.5°F (38°C) or above, at screening or baseline, and/or signs of confirmed or suspected infection, and must have completed any appropriate anti-infective treatment.
    a. In Part D, Japanese participants with body temperature above 37.5°C will be excluded.
37. show evidence of active or latent tuberculosis (TB), based on a positive medical history, examination, and/or TB test results. QuantiFERON-TB Gold Plus test (QFT Plus or equivalent) will be used for TB testing, and participants must test negative to participate. If the initial result is indeterminate, a single repeat test is allowed. If the repeat test result is positive or indeterminate, the participant is deemed ineligible.

In addition, for Part B only:

33. Have impaired hearing or a history of hearing problems (rationale: because itraconazole has been associated with transient or permanent hearing loss).

Prior/Concurrent Clinical Study Experience

34. Are currently enrolled in a clinical trial involving a study intervention or off-label use of a drug or device, or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this trial.
35. Have been treated with biologic agents (such as mAbs, including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.

Other Exclusions

36. Are unwilling to stop alcohol consumption during study visits/time in the research unit.

5.3. Lifestyle Considerations

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

5.3.1. Meals and Dietary Restrictions

1. Refrain from consumption of red wine, Seville oranges or Seville orange–containing products, grapefruit or grapefruit-containing products, star fruits or star fruit-containing products, pomegranates, and/or pomelo from 14 days before the start of study intervention until after the final dose.
2. Part A (SAD): Participants in all cohorts will be required to fast overnight (at least 8 hours) prior to dosing on Day 1 and for at least 2 hours after dosing with LY3509754/placebo, with the exception of water, which will be freely available after dosing. LY3509754 should be administered with approximately 240 mL of room temperature water. On intensive PK days, participants may receive a light breakfast approximately 2 hours after dosing.

   SAD cohort undergoing food effect evaluation (Part A, Cohort 4): Participants will be required to fast overnight (at least 8 hours) prior to dosing on Day 1 of Periods 1 and 2. Participants will start the high-fat meal (see below) 30 minutes prior to administration of LY3509754 on Day 1 of Period 2. Participants will consume this entire meal in 30 minutes or less, and LY3509754 will be administered 30 minutes after the start of the meal. In Periods 1 and 2, LY3509754 should be administered with approximately 240 mL of room temperature water. No further food will be allowed for at least 2 hours postdose in Period 1 and at least 4 hours postdose in Period 2. Fluids will be restricted from 1 hour prior to and until 1 hour after dosing, except for fluid provided with the meal in Period 2 and water required for dose administration in both periods. On intensive PK days, participants may receive a light breakfast approximately 2 hours after dosing LY3509754/placebo in Period 1.

   The standardized high-fat, high-calorie meal (fat comprises approximately 50% of total caloric content of the meal) in Period 2 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.

3. Part B (DDI victim): Participants will be required to fast overnight (at least 8 hours) prior to each dosing day and for at least 2 hours after dosing with LY3509754, and coadministration of LY3509754 and itraconazole, with the exception of water that will be freely available after dosing. LY3509754 should be administered with approximately 240 mL of room temperature water. On the day where 2 doses of itraconazole administration occurs, participants will also need to fast for approximately 2 hours prior to the evening dose of itraconazole and at least 2 hours after dosing, with the exception of water, which will be freely available after dosing.

4. Part C (MAD): In all cohorts, participants will be required to fast overnight (at least 8 hours) on all dosing days and for at least 2 hours after dosing (on intensive PK sampling days (see SoA in Section 1.3), with the exception of water, which will be freely available 1 hour after dosing. LY3509754 should be administered with approximately 240 mL of room temperature water. On intensive PK days, participants may receive a light breakfast approximately 2 hours after dosing.

   In Part C cohort undergoing perpetrator DDI evaluation: Participants will be required to fast overnight (at least 8 hours) prior to each dosing day (including midazolam and LY3509754 dosing) and for at least 2 hours after dosing with LY3509754, and coadministration of LY3509754 and midazolam, with the exception of water that will be freely available after dosing. LY3509754 should be administered with approximately 240 mL of room temperature water. Foods that are known modulators (inhibitors or inducers) of CYP3A must be specifically excluded 14 days before the first study dosing day until the last PK sample has been obtained. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, inclusion or continuation of the participant may be at the discretion of the investigator after consultation with Lilly clinical pharmacologist. Any additional medication used during the study must be documented.

5. Part D (Japanese multiple dose): Participants will be required to fast overnight (at least 8 hours) on all dosing days and for at least 2 hours after dosing on intensive PK days, with the exception of water, which will be freely available 1 hour after dosing. LY3509754 should be administered with approximately 240 mL of room temperature water. On intensive PK days, participants may receive a light breakfast approximately 2 hours after dosing.

5.3.2. Caffeine, Alcohol, and Tobacco

1. During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final PK sample.

2. During each dosing session, participants will abstain from alcohol for 48 hours before the start of dosing until after collection of the final PK sample. During the study, while not resident at the CRU, the maximum daily alcohol intake should not exceed 2 units (see Exclusion Criterion [28], Section 5.2, for unit definition).
3. Smoking, tobacco consumption, or use of any nicotine-replacement therapy is not permitted while resident at the CRU. Participants must be willing to comply with the CRU smoking restrictions. While not resident in the CRU, smoking should not exceed 10 cigarettes per day or equivalent in nicotine use or nicotine substitutes.

5.3.3. Activity

4. Participants will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading). Participants should avoid strenuous exercise and/or activity for at least 72 hours prior to CRU admission and while resident at the CRU. Participants should remain upright for at least 2 hours after dosing, with the exception of any requirements for protocol procedures (e.g., supine for ECGs).
5. Participants are not permitted to make blood or plasma donations while participating in the study.

5.3.4. Infection Risk

Participants should follow local guidance and CRU precautions to minimize risk for COVID-19 infection.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study and were not alternates.

Participants who do not qualify at screening due to a transient minor illness (such as a cold) may be rescreened once, 4 or more weeks after documented resolution of symptoms. Participants who are taking any medication or medications specified in the Exclusion Criteria (Section 5.2) may be rescreened once, following a sufficient washout period determined by the investigator based on the exclusion criteria. When rescreening is performed, the individual must sign a new ICF and will be assigned a new study identification number. Participants who were eligible for inclusion in previous cohorts, but who were not randomized for nonmedical reasons, may be reassessed for inclusion in subsequent cohorts.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Interventions Administered

Study Part Name	Parts A, B, C, D[a]	Parts A, B, C, D[a]	Parts B	Part C, Cohort 2
Intervention Name	LY3509754	Placebo	Itraconazole	Midazolam
Dose Formulation and Route of Administration	Capsule taken orally	Capsule taken orally	Oral Solution	Oral Solution (syrup)
Unit Dose Strength	Experimental/ Extemporaneous preparation	N/A	Combination drug (10 mg/mL)	Combination drug
Planned Dosage Levels	10 mg – 2000 mg	N/A	200 mg	1.2 mg
Sourcing	NA	Provided centrally by the sponsor	Provided locally by the trial site	Provided locally by the trial site

[a] Capsules of 200 mg LY3509754 dosage strength and corresponding placebo will be provided by the sponsor for Part D.

Note: Information provided in this table (dose formulation, sourcing, packaging and labeling) may change throughout the study or may vary by country.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

For any specific cohort/dosing period, the total number of capsules administered will be the same for all participants, regardless of whether assigned to placebo or LY3509754. However, the number of capsules may vary between dosing periods and cohorts.

LY3509754 will be supplied in the form of LY3509754 pure compound with no inactive ingredients for extemporaneous preparation of the study intervention at the CRU. This will be performed by trained personnel (e.g., pharmacist) within a facility at the CRU, which has been qualified to perform these types of operations. Instructions for extemporaneous preparation of the study intervention (LY3509754 pure compound filled directly into a capsule) will be provided by the sponsor. For Study Part D, an additional site has been added to recruit the required number of Japanese subjects. The sponsor is providing LY3509754 in the form of 200-mg dosage strength capsules and corresponding placebo.

Clinical trial materials will be labeled according to the country's regulatory requirements. The supplies will be stored at room temperature. Unused supply of study intervention will remain in the pharmacy archives until returned to the sponsor or destroyed with their written permission.

6.3. Measures to Minimize Bias: Randomization and Blinding

All parts of the study are blinded with an unblinded site pharmacist that will dispense the drug. On Day 1, participants will be assigned a unique number (randomization number). The randomization number encodes the participant's assignment to the study, according to the randomization schedule. Each participant will be dispensed study intervention, labeled with his/her unique randomization number, throughout the study. Participants entering Period 2 of Part A (2-period crossover) will continue with their assigned unique number from Period 1.

Participants will be sequentially enrolled to cohorts. Within the following Cohorts, participants will be randomized to receive LY3509754 or placebo as described in Section 4.2.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third pa*rty (for example a pharmacist) will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.*

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan.

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

If a participant's study treatment assignment is unblinded, the participant must be discontinued from the study, unless the investigator obtains specific approval from an Eli Lilly and Company (Lilly) clinical pharmacologist (CP) or clinical research physician (CRP) for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. Where feasible and when timing of the emergent situation permits, the investigator should attempt to contact the Lilly medical monitor before unblinding a participant's treatment assignment. 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.

6.4. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will monitor each participant to ensure that the study intervention was taken accordingly to the investigational product (IP) manual.

6.5. Concomitant Therapy

In general, concomitant medication should be avoided. CYP3A inducers, inhibitors and substrates should be avoided unless otherwise indicated as part of the DDI evaluations in Part C Cohort 4. Only vitamin/mineral supplements, HRT and occasional paracetamol/acetaminophen up to 3-g dose in a 24-hour period are allowed, at the discretion of investigator for the treatment of headaches, etc. (see Exclusion Criterion [26]). Any medication that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency for concomitant therapy of special interest

If the need for concomitant medication (other than acetaminophen or HRT) arises, inclusion or continuation of the participant 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 (Section 5.2). Any medication used during the course of the study must be documented.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6. Dose Modification

Dose levels or increments, sampling schedule, timing of procedures (e.g., PK and ECG assessments) and length of stay at the CRU may be adjusted in view of emerging safety, tolerability, or PK data during the study. If considered appropriate, dose increments may be reduced, a dose level may be repeated, or a lower/intermediate dose may be administered, but dose escalations will not exceed a semi-log (3.3-fold) increase in dose. The timing of the sampling may be adjusted and additional samples may be collected, as described in the SoA in Section 1.3. The duration of the CRU stay or the duration of safety follow-up may be increased (e.g., if the half-life of LY3509754 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.

6.6.1. 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, the highest planned dose is administered, or when discontinuation criteria are met (Section 7). No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly study team. See Sections 4.2.1 and 4.2.3 for further details.

Parts A (SAD) and C (MAD):

The highest dose level that is tolerated will be designated as the MTD for single (SAD) or multiple (MAD) doses in healthy participants. Interim access to study data is scheduled to occur during the study to inform dose escalation decisions, as specified in Section 9.3.5.

In Part A, safety data from at least 5 days after the last dose of LY3509754, in particular AEs, SAEs, vital signs (blood pressure [BP] and pulse rate [PR]), electrocardiograms (ECGs) and clinically important laboratory abnormalities, from at least 6 participants in each SAD cohort, will be the primary criteria for dose escalation decisions. Emerging PK data may also be reviewed. Available PK data from the first 2 dose levels in the SAD (Cohorts 1 and 2) will be reviewed prior to escalation to the third dose level (dosing in Cohort 3). Available PK data from the third and fourth dose levels in the SAD (Cohort 3 and Cohort 4 Period 1, respectively) will be reviewed prior to escalation to dosing in Cohort 5. Emerging data from Cohorts 1 to 5 of the SAD will be reviewed prior to escalation to the planned highest SAD dose level (dosing in Cohort 6). After review of these data, an escalation to the next dose level will be jointly decided by the investigator and sponsor.

In Part C, safety data from at least 5 days after the last dose of LY3509754, from at least 6 participants in SAD (Part A) Cohort 5, will be the primary criteria for beginning dosing Cohort 1 of the MAD. All available PK data from the SAD will be used to assist in the MAD Cohort 1

dose decision. Dose escalation will be based on safety data, in particular, AEs, SAEs, and clinically important laboratory abnormalities, from at least 6 participants in each MAD cohort. Available PK data from a lower dose cohort will be reviewed prior to escalation to the next dose level. After review of these data, an escalation to the next dose level will be jointly decided by the investigator and sponsor.

For both Parts A and C, additional participants may be dosed, if necessary, to maintain at least 6 participants completing each dose level for the safety review prior to the next dose escalation. All available PK data will be reviewed on an ongoing basis and may be used as supporting data for dose escalation decisions for both parts. Safety data, in particular AEs, SAEs, and clinically important laboratory abnormalities, will be independently assessed by the investigator (who will be blinded), as well as the sponsor, and will be considered related to study drug unless there is clear evidence that the event is not related. If dose escalation is terminated prior to reaching the next higher dose level because of tolerability issues, previous dose levels may be repeated or lower dose levels may be tested or an alternate dosing schedule (BID) may be used. For Part C, additional cohorts may be required to safely investigate maximum exposure to LY3509754; this decision will be made between the sponsor and the investigator, following the necessary review of the safety data.

Part B: LY3509754 Inhibition

The dose decision for Part B will be based on safety data, in particular AEs, SAEs, and clinically important laboratory abnormalities from Part A. All available PK data from the SAD will be used to assist in the Part B dose selection. The selected dose will be predicted to have an exposure range less than the upper limit of the MTD in Part A (SAD), based on the expected approximately 9-fold increase in LY3509754 exposure when co-administered with itraconazole. See Section 4.3 for further LY3509754 dose justification.

Part D: Multiple Dosing in Japanese Healthy Participants

The dose decision for Part D will be based on the review of safety, tolerability, and any available PK data from Part C (MAD). The dose decision for Part D will be based on safety data, in particular AEs, SAEs, and clinically important laboratory abnormalities, from at least 6 participants in the maximum dose evaluated in the MAD (Part C) from at least 5 days after the last dose of LY3509754.

Part D will explore 2 dose levels in 2 separate cohorts dosed daily for 14 days. The 2 dose levels studied will be run simultaneously. The Cohort 1 and Cohort 2 dose levels will not exceed the maximum dose evaluated in Part C (MAD in non-Japanese participants).

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation or Temporary Halt of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention or Stop of Randomization

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety and PK assessments. See the SoA for data (Section 1.3) to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Should a treatment-emergent SAE described in Appendix 3 (Section 10.3) occur, dosing and enrollment in the cohort will be suspended and the investigator will consult the medical monitor for recommendation.

Possible recommendations include:

- resume dosing/enrollment in the cohort,
- move to a lower dose, or
- pause study until further evaluation.

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

1) a single participant experiences an SAE that is related to LY3509754 administration.
2) 2 participants experience a clinically significant event (CSE) of toxicological finding that is deemed to be related to LY3509754 administration.
3) 2 participants experience clinically significant changes in scheduled vital signs and laboratory results that are deemed to be related to LY3509754 administration.
4) 2 or more participants at 1 dose level experience other moderate or severe treatment-related AEs that impair normal activities and are deemed to be related to LY3509754 administration.

If moderate or severe AEs are consistently observed across participants in a cohort, or if unacceptable pharmacological effects reasonably attributable to study intervention, in the opinion of the investigator, are observed in more than 25% of the participants in a cohort, then dose escalation will be temporarily halted and no further participants will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the Medical Monitor, other relevant personnel, and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will take place before resumption of dosing.

Furthermore, a participant will be discontinued from receiving further doses of study intervention if the investigator assesses that continuation on study intervention may pose a risk to the well-being of the participant in question. Participants may also be discontinued from the study intervention if a 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 study intervention is documented, a decision will be made between the investigator and Lilly or its designee regarding participant discontinuation. Discontinuation of

the study intervention for abnormal liver tests should be considered by the investigator when a participant meets 1 of the following conditions, after consultation with the Lilly designated medical monitor:

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

Participants discontinuing from the treatment prematurely for any reason should complete AE and other follow-up procedures per Section 1.3 of this protocol.

If a clinically significant finding is identified,including, but not limited to, changes from baseline in QT interval corrected using Fridericia's formula (QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if 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
- if the participant, 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

- temporary withholding of study intervention is allowed when the participant has positive microbial lab results or clinical signs of a confirmed or suspected infection after consultation with the sponsor's medical monitor
- temporary withholding of study intervention is required for the development of any of the following infection-related criteria during the study:
    - Serious or opportunistic infections, as defined in Exclusion Criteria (Section 5.2). Study intervention is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment (exception for latent tuberculosis infection [LTBI], noted below).
    - Participants diagnosed with LTBI during the study are to be permanently discontinued from study intervention unless a participant is a candidate for LTBI treatment, and is treated for LTBI as follows:
        - Study intervention is temporarily held for at least the first 4 weeks of LTBI treatment.
        - After receiving at least 4 weeks of appropriate LTBI therapy (as per World Health Organization and/or the United States Centers for Disease Control guidelines), if there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance, study intervention may be resumed.
        - The participant must complete appropriate LTBI therapy to remain eligible to receive study intervention.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow-up

A participant 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 participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Section 1.3 lists the SoA, 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 (i.e., outside stipulated time allowances) to perform procedures or obtain samples due to legitimate clinical issues (e.g., 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 (Section 10.2) lists the laboratory tests that will be performed and 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.

8.1. Efficacy Assessments

Not applicable. Efficacy is not evaluated in this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.2).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular (CV), respiratory, abdomen, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the CV system, respiratory system, and abdomen.

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3). Vital signs will comprise BP, PR, and body temperature.
- For supine measurements of BP and PR, participants 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, participants should be supine for at least 5 minutes and stand for at least 2 minutes for supine and standing measurements, respectively. If the participant feels unable to stand, supine vital signs only will be recorded.

8.2.3. Electrocardiograms

For each participant, ECGs should be collected according to the SoA (Section 1.3).

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

For all parts of the study, 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 participant meets entry criteria.

In Parts A, C, and Part D (based on findings in Part A and C), at the time points specified in the SoA, either single or triplicate ECG recordings will be collected (see Section 1.3 for details).

During Part B, single ECGs will be collected at specified time points (see SoA, Section 1.3, for details).

Twelve-lead ECG will be obtained (whether as a single or triplicate recording depending on the part of the study) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

Electrocardiograms should preferably be recorded before collecting any blood samples. Participants must be supine for approximately 5 minutes before ECG collection and remain supine but awake during ECG collection. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. 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 participant is still present, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant 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 participant for symptoms (e.g., palpitations, near syncope, syncope) to determine whether the participant can continue in the study. The investigator or qualified designee is responsible for determining if any change in participant 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 (e.g., 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 HR 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).

8.2.4. Clinical Safety Laboratory Assessments

Procedures for clinical safety laboratory assessments are as follows:

1. See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and see the SoA (Section 1.3) for the timing and frequency.
2. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
3. All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

8.3. Adverse Events and Serious Adverse Events

Severity and seriousness of an AE are not synonymous. Severity is grading the intensity of an event. Seriousness of an event is based on the subject/event outcome. Details about collecting SAE/AE data and SAE/AE definitions are provided in Appendix 3 (Section 10.3).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

Investigators are responsible for monitoring the safety of participants 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 participant.

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

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until participation in study has ended.

All AEs will be collected from the signing of ICF until the follow-up visit.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event CRF.

Although all AEs reported after the ICF has been signed are recorded by the site in the CRF/electronic data entry system, SAE reporting to sponsor begins after the participant has signed the ICF and has received the study intervention. However, if an SAE occurs after signing the ICF, but prior to participants receiving LY3509754, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs, and the procedures for completing and transmitting SAE reports, is provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IEC, and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and other relevant documents and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until at least 5 terminal half-lives after the last dose.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a trial intervention.

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

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

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Appendix 3 (Section 10.3) of the protocol.

8.3.6.1. Time Period for Detecting Product Complaints

- Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug/device is used.
- If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug/device provided for the study, the investigator will promptly notify the sponsor.

8.3.6.2. Prompt Reporting of Product Complaints to Sponsor

- Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.
- The Product Complaint Form will be sent to the sponsor by the method provided in the form. If the primary method is unavailable, then an alternative method as provided in the form should be used.

8.3.6.3. Follow-up of Product Complaints

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.3.6.4. Regulatory Reporting Requirements for Product Complaints

Not applicable in this study.

8.4. Treatment of Overdose

For each part in this study, any dose of study intervention greater than the dose described for that part within a 24-hour time period ±12 hours will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 7 days). Refer to Section 8.3 for reporting details.
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Plasma samples will be analyzed for LY3509754, itraconazole and its hydroxyitraconazole metabolite, and midazolam and its 1-hydroxymidzaolam metabolite. Additionally, urine samples will be analyzed for LY3509754.

- LY3509754: Plasma samples of approximately 2 mL will be collected for measurement of concentrations of LY3509754 as specified in the SoA in Section 1.3.
- Urine samples of approximately 1 mL will be collected as specified in the SoA in Section 1.3.
- Total urine output for the 24 hour period post-LY3509754 administration will be collected, pooled, and refrigerated. At the end of the collection period, the total urine volume will be recorded. Urine samples will be used to determine creatinine, quantification of LY3509754 and exploratory metabolite identification. Assessment of renal clearance will be an exploratory assessment; therefore, failure to collect samples or analyze all collected samples will not be a deviation. Samples will be analyzed using a validated fit-for-purpose liquid chromatography – tandem mass spectrometry assay.
- Itraconazole: Plasma samples of approximately 2 mL will be collected for measurement of concentrations of itraconazole and hydroxyitraconazole as specified in the SoA.
- Midazolam: Plasma samples of approximately 2 mL will be collected for measurement of concentrations of midazolam and 1-hydroxymidazolam as specified in the SoA.
- A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The remaining plasma from the samples collected for pharmacokinetics may be pooled and used for exploratory metabolism work as deemed appropriate. Aliquots of the urine will be frozen and stored until qualitatively analyzed for LY3509754 and potential metabolites. Since the urinary

work is considered exploratory, failure to obtain a urine sample for any reason will not be considered a protocol violation.

The metabolism work is considered exploratory and no quantitation will be performed on these data. Results of the exploratory work are not necessary for inclusion in the final integrated clinical study report.

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

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

A blood sample for deoxyribonucleic acid (DNA) isolation will be collected from participants.

See Appendix 5 (Section 10.5) for Information regarding genetic research and Appendix 1 (Section 10.1.9) for details about sample retention and custody.

8.8. Biomarkers

Exploratory samples (serum, plasma, saliva, and ribonucleic acid from buccal swabs) for exploratory biomarker assessment

Serum, plasma, saliva, and ribonucleic acid samples from buccal swabs will be stored and analysis may be performed on exploratory biomarker variants thought to play role in IL-17-related pathways.

This may include chemokines and chemokine receptors involved in pathogenic defense, various IL-17 molecules, their receptors and signaling molecules, and immune response genes, including but not limited to those within the major histocompatibility complex, genes related to the IL-17/23 pathway and cell subtypes producing and/or responsive to these cytokines.

Plasma samples, including those remaining when bioanalysis is complete, may be used for the analysis of exosomal markers.

A list of the maximum retention period for sample types can be found in Appendix 1 (Section 10.1.9). Refer to the laboratory manual for additional details.

8.9. Immunogenicity Assessments

Not applicable.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Sample Size Determination

The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK, and is not powered on the basis of any a priori statistical hypothesis testing. The sample sizes for all parts of the study are based upon previous studies.

Participants who are randomized but not administered treatment may be replaced to ensure that adequate participant data will be available for safety and exposure assessments in this phase of clinical development. The replacement participant should be assigned to the same treatment arm as the discontinued participant.

9.2. Populations for Analyses

9.2.1. Study Participant Disposition

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

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

9.2.2. Study Subject Characteristics

The participant's baseline characteristics and other demographic characteristics will be recorded, listed, and summarized by treatment group and overall.

9.2.3. Treatment Compliance

The study IP will be administered at the CRU and documentation of dosing administration will occur at the CRU. Every attempt will be made by the CRU to enroll participants who have the ability to understand and comply with instructions. No doses should be missed. The time and day of study intervention administration will be accurately recorded in the electronic case report form (eCRF). Drug accountability records will be maintained by the CRU.

Any major modifications that might affect the conduct of the study, participant safety, and/or data integrity will be detailed in a protocol amendment.

9.3. Statistical Analyses

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

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

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

Summary statistics, data tabulations, and data graphs by population (Japanese and non-Japanese) will be provided as appropriate.

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.

9.3.1. Safety Analyses

9.3.1.1. Clinical Evaluation of Safety

All IP 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 IP as perceived by the investigator. Symptoms reported to occur prior to study IP dosing 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 IP-related SAEs and AEs will be reported.

9.3.1.2. 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.

9.3.2. Pharmacokinetic Analyses

9.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3509754 will be calculated by standard noncompartmental methods of analysis and summarized by dose using descriptive statistics. The primary parameters for analysis will be C_{max} and AUC of LY3509754 after single- and multiple-dose administration. Other noncompartmental parameters such as t_{max}, $t_{1/2}$, apparent clearance, apparent volume of distribution, and accumulation ratio may be calculated. Population analysis of the concentration-time data based on a compartmental model may also be performed to support PK simulations.

If appropriate data are obtained, renal clearance of LY3509754 will be estimated by dividing the amount of LY3509754 excreted in urine over a given time interval to the plasma AUC of LY3509754 over the same interval.

In Part B, if available, plasma concentration data for itraconazole and its metabolite will be listed in the study report. A PK analysis of itraconazole and its metabolite may be conducted if deemed valuable to the interpretation of the study results but is not required to complete the clinical study report.

In the perpetrator DDI portion of Part C (MAD), the primary parameters for analysis will be C_{max} and AUC of midazolam and its hydroxylated metabolite after administration of midazolam alone, and concomitantly with LY3509754. Other noncompartmental parameters such as half-life, apparent clearance, and apparent volume of distribution may be reported.

Additional analyses may be conducted as appropriate.

9.3.2.2. Pharmacokinetic Statistical Inference

In Part A (SAD) and the MAD portion of Part C of the study, pharmacokinetic parameters C_{max} and AUC for LY3509754 will be evaluated to estimate dose proportionality of LY3509754 using a linear-mixed-effect power model. Log-transformed C_{max} and AUC parameters will be evaluated using a power model (where log dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means, the ratios of geometric means and corresponding 90% confidence intervals (CIs). The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. A subinterval within the highest and lowest doses may also be considered for assessment of dose proportionality using the same approach. For the dose proportionality assessment, data from the placebo group will be excluded. For the MAD portion of Part C, LY3509754 dose proportionality will be assessed on Day 1 and Day 14.

For the food effect portion of Part A, C_{max} and AUC for LY3509754, when administered with a high-fat meal versus in a fasted state, will be compared. These comparisons will be performed using a mixed effects analysis of variance model. The model will include a fixed effect for the treatment and a random effect for participant. The ratio of least squares geometric means for the test treatment compared to reference treatment, as well as the 90% CI of the ratio will be estimated and reported. The t_{max} of LY3509754 will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference and 90% CI for the difference between treatments will be calculated.

For Part B, C_{max} and AUC for LY3509754, when administered alone versus in the presence of itraconazole, will be compared using an analysis of variance (ANOVA) model. The parameters will be log-transformed prior to analysis. The model will include a fixed effect for the treatment and a random effect for subject. The least-squares means for each treatment, the difference between the treatment least-square means (LY3509754 + itraconazole – LY3509754), 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.

For the perpetrator DDI portion of Part C, PK parameter estimates will be evaluated to delineate effects of LY3509754 on the PK of midazolam. Log-transformed C_{max} and AUC estimates for midazolam will be evaluated to estimate ratios of geometric means in the presence and absence of LY3509754 along with the corresponding 90% CIs. A mixed effects model with treatment as fixed effect and subject as random effect will be used.

For Part D, LY3509754 PK parameters will be compared between Japanese and non-Japanese participants (using SAD, MAD data for non-Japanese participants). Descriptive statistics for C_{max}, AUC, t_{max}, terminal half-life, apparent clearance, and apparent volume of distribution will be included in the tabular comparisons. Body-weight normalized PK parameters may be calculated if warranted. Graphical comparisons of C_{max}, AUC, and concentration-time profiles will also be prepared.

Additional analyses may be conducted for each part as appropriate.

9.3.3. Pharmacodynamic Analyses

9.3.3.1. Pharmacodynamic Parameter Estimation

Not applicable.

9.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

9.3.5. Interim Access to Data (IAD)

Interim access to safety and tolerability data is scheduled to occur after every dosing session. The investigator and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data. Access to PK data will also occur on a rolling basis during dose escalation as it becomes available, but will not be a requirement for selecting subsequent dose levels. The following IADs are planned to evaluate exposure data. The purpose of these reviews is to guide dose escalation, dose selection for subsequent cohorts, and/or to inform the design of subsequent studies.

In Part A (SAD), IAD is planned to occur for each cohort, when approximately 6 participants have available data up to 5 days postdose. In Part B (CYP3A4 victim DDI), IAD is planned to occur when approximately 9 participants have available data up to Day 17. In Part C (MAD and CYP3A4 perpetrator DDI), IAD is planned to occur for each cohort. For Cohorts 1 and 3, this occurs when approximately 6 participants have available data up to Day 19. For Cohort 2, this occurs when approximately 8 participants have available data up to Day 19.

After Parts A-D have been completed, a further IAD is planned to include all available safety and PK data to support Phase 2 development of the molecule.

The investigator and the Lilly sponsor team will make the determination regarding dose escalation based upon their review of the data. The investigator will remain blinded and the Lilly sponsor team will be unblinded during these reviews. Unblinding details are specified in the unblinding/blinding plan document.

The investigator and the Lilly clinical pharmacologist, Lilly CRP, and Lilly study team will make the determination regarding dose escalation.

Additional data reviews may occur during the study to support evaluation of any safety issue and/or to inform the design of future studies.

9.4. Interim Analyses

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

9.5. Data Monitoring Committee (DMC)

No DMC is planned for this study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) good clinical practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by the sponsor to all investigators (e.g., by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by the sponsor personnel prior to any further planned dosing. If a dose is planned

imminently, the sponsor personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case by case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Source data may include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system will be stored at third-party site. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Appendix 1 (Section 10.1.5).

10.1.7. Study and Site Start and Closure

10.1.7.1. Discontinuation of the Study

The study start date is the date on which the clinical study will be open for recruitment of participants.

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

Medical Oversight and Safety Review

Ongoing safety review(s) by designated sponsor personnel will occur and be documented. Such reviews will include:

- Monitoring and assessing the safety information collected during the trial both in real time and periodically, and
- Reviewing safety data for trends that need action, and
- Detecting adverse drug/device effects.

A safety investigation will be triggered to determine if the study should be terminated early based on the following criteria:

- Two study participants develop the same treatment-emergent adverse event (TEAE) or SAE considered possibly or probably related to study intervention that is severe or medically significant but not immediately life-threatening, or where hospitalization or prolongation of hospitalization is indicated, or is disabling, or limits self-care activities of daily living.
- One study participant develops any TEAE or SAE regardless of attribution to study intervention that has life-threatening consequences or requires urgent intervention.
- Death of any study participant at any time.
- Any other clinically significant safety signal.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

10.1.7.2. Discontinuation of Study Sites

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

10.1.8. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.9. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable responses that may not be observed until later in the development of LY3509754 or after LY3509754 becomes commercially available.

The retention period begins after the last participant visit for the study.

The maximum retention times may be shorter, if specified in local regulations and/or if ERBs/IRBs impose shorter time limits, or by decision of the sponsor.

Any samples remaining after the specified retention period will be destroyed.

The sample retention facility will be selected by the sponsor or its designee.

The following table lists the maximum retention period for sample types.

Sample Type	Custodian	Retention Period after Last Participant Visit
Pharmacokinetics	Sponsor or designee	2 years
Exploratory Biomarker Samples	Sponsor or designee	15 years
Liver Biopsy Sections	Sponsor or designee	15 years
Pharmacogenetics	Sponsor or designee	15 years
Immunogenicity	Sponsor or designee	15 years

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing: See Section 5.1 (Inclusion Criteria for screening pregnancy criteria) and Section 10.4 (Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information).

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Safety Laboratory Tests

Hematology[a]	Clinical Chemistry (fasting)[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphate
Leukocytes (WBC)	Magnesium
Absolute counts of	Creatinine
Neutrophils	Glucose
Lymphocytes	Urea
Monocytes	Uric acid
Eosinophils	Total protein
Basophils	Albumin
Platelets	Total bilirubin
	Direct bilirubin
Urinalysis[a]	Gamma-glutamyl transferase
Specific gravity	
pH	
Protein	Alkaline phosphatase (ALP)
Glucose	Aspartate aminotransferase (AST)
Ketones	Alanine aminotransferase (ALT)
Bilirubin	
Urobilinogen	
Nitrite	
Blood	QuantiFERON-TB Gold test[c,g]
Leukocytes	
Microscopy[b]	
WBC esterase	
	Serology
	Hepatitis B surface antigen[c,d]
	Hepatitis C virus serology[c,d]
	Human immunodeficiency virus (HIV)[c,d]
	Pregnancy test[e,f]
	FSH[c]

[a] Clinical safety laboratory tests.
[b] If clinically indicated, per investigator's discretion.
[c] Performed at screening only.
[d] Tests may be waived if they have been performed within 6 months before screening with reports available for review.
[e] For females only: A serum pregnancy test will be performed at screening and urine pregnancy test at all other time points.
[f] Refer to Section 1.3 for schedule of collection.
[g] Results will be validated by the local laboratory at the time of initial testing.

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

Note: Cockcroft-Gault prediction of creatinine clearance from serum creatinine (1976)

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}) \times 0.85 \text{ (if female), or} \times 1.0 \text{ (if male)}}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}) \times 0.85 \text{ (if female), or} \times 1.0 \text{ (if male)}}{0.81 \times \text{serum creatinine (µmol/L)}}$$

a Age in years, weight (wt) in kilograms.
Source: Cockcroft and Gault 1976.

10.2.1. 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 J3D-MC-FNAA Sampling Summary for Part A (SAD) [Cohorts 1, 2, 3, 5, and 6]

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Screening tests[a] (local laboratory)	10	1	10
Clinical laboratory tests[a] (local laboratory)			
Study visits	4.5	2	9
ED/follow up	4.5	1	4.5
LY3509754 pharmacokinetics	2	16	32
Pharmacogenetic analysis sample (stored)	10	1	10
Exploratory blood samples[b]	18.5	9	166.5
Total			232
Total rounded up to the nearest 10 mL			240

Abbreviation: ED = early discontinuation.

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

[b] Additional samples (6 mL) may be drawn during additional safety follow-up visits.

Protocol J3D-MC-FNAA Sampling Summary for Part A SAD Food Effect Evaluation [Cohort 4]

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Screening tests[a] (local laboratory)	10	1	10
Clinical laboratory tests[a] (local laboratory)			
Study visits	4.5	3	13.5
ED/follow up	4.5	1	4.5
LY3509754 pharmacokinetics	2	32	64
Pharmacogenetic analysis sample (stored)	10	1	10
Exploratory blood samples[b]	18.5	9	166.5
Total			268.5
Total rounded up to the nearest 10 mL			270

Abbreviation: ED = early discontinuation.

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

[b] Additional samples (6 mL) may be drawn during additional safety follow-up visits.

Protocol J3D-MC-FNAA Sampling Summary for Part B (DDI with CYP3A4 Inhibition – Fixed Sequence)

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Screening tests[a] (local laboratory)	10	1	10
Clinical laboratory tests[a] (local laboratory)			
Study visits	4.5	6	27
ED/follow up	4.5	1	4.5
LY3509754 pharmacokinetics	2	33	66
Itraconazole pharmacokinetics	2	7	14
Pharmacogenetic analysis sample (stored)	10	1	10
Total			131.5
Total rounded up to the nearest 10 mL			140

Abbreviations: ED = early discontinuation.

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

Protocol J3D-MC-FNAA Sampling Summary for Part C (MAD) [Cohorts 1 and 3]

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Screening tests[a] (local laboratory)	10	1	10
Clinical laboratory tests[a] (local laboratory)			
Study visits	4.5	3	13.5
ED/follow up	4.5	1	4.5
LY3509754 pharmacokinetics	2	36	72
Pharmacogenetic analysis sample (stored)	10	1	10
Exploratory blood plasma samples[b]	6	27	162
Exploratory blood serum samples	6	6	36
Total			308
Total rounded up to the nearest 10 mL			310

Abbreviation: ED = early discontinuation.

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

[b] Additional samples (6 mL) may be drawn during additional safety follow-up visits.

Protocol J3D-MC-FNAA Sampling Summary for Part C (MAD + Midazolam DDI) [Cohort 2]

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Screening tests[a] (local laboratory)	10	1	10
Clinical laboratory tests[a] (local laboratory)			
Study visits	4.5	4	18
ED/follow up	4.5	1	4.5
LY3509754 pharmacokinetics	2	36	72
Midazolam pharmacokinetics	2	26	52
Pharmacogenetic analysis sample (stored)	10	1	10
Exploratory blood samples[b]	18.5	15	277.5
Total			444
Total rounded up to the nearest 10 mL			450

Abbreviation: ED = early discontinuation.

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

[b] Additional samples (6 mL) may be drawn during additional safety follow-up visits.

Protocol J3D-MC-FNAA Sampling Summary for Part D MAD (Japanese Participants)

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Screening tests[a] (local laboratory)	10	1	10
Clinical laboratory tests[a] (local laboratory)			
Study visits	4.5	3	13.5
ED/follow up	4.5	1	4.5
LY3509754 pharmacokinetics	2	37	74
Exploratory blood plasma samples[b]	6	27	162
Exploratory blood serum samples	6	6	36
Pharmacogenetic analysis sample (stored)	10	1	10
Total			310
Total rounded up to the nearest 10 mL			310

Abbreviation: ED = early discontinuation.

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

[b] Additional samples (6 mL) may be drawn during additional safety follow-up visits.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, but not related to the progression of the underlying disease, and considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other

outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Reporting of SAEs

SAE Reporting via SAE Report
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor or designee. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE report within the designated reporting time frames. • Contacts for SAE reporting can be found in the SAE report.

10.3.4. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

Article I. Premenarchal

Article II. Premenopausal female with 1 of the following:

- Documented hysterectomy

- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

Article III. The post-menopausal state should be defined as:

1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or 2
2. A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND With a follicle-stimulating hormone >40 mIU/mL; or
3. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or
4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

* Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.

Contraception Guidance:
The table below describes contraception guidance for all men.

Topic	**Guidance**
All men	Should refrain from sperm donation for the duration of the study and for at least 30 days after the last dose for Parts A-D
Contraception for men with partners of childbearing potential	• Either remain abstinent (if this is their preferred and usual lifestyle), or • Must use condoms during intercourse for the duration of the study, and • For at least 30 days after the last dose
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception.

Examples of highly effective, effective and unacceptable methods of contraception can be found below.

Methods	Examples
Highly effective contraception	• Combination oral contraceptive pill and mini pill • Implanted contraceptives • Injectable contraceptives • Contraceptive patch (only women <198 pounds or 90 kg) • Total abstinence • Vasectomy (if only sexual partner) • Fallopian tube implants (if confirmed by hysterosalpingogram) • Combined contraceptive vaginal ring, or • Intrauterine devices
Effective contraception	• Male condoms with spermicide plus cervical sponges with spermicide
Ineffective forms of contraception	• Spermicide alone • Immunocontraceptives • Periodic abstinence • Fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • Withdrawal, • Post-coital douche • Lactational amenorrhea

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LY3509754.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported including fetal status (presence or absence of anomalies) and indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to LY3509754. They may also be used to develop tests/assays including diagnostic tests related to LY3509754. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples may be analyzed for genes involved in effects of LY3509754.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on LY3509754 continues, but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Close hepatic monitoring

Laboratory tests (Appendix 2, Section 10.2 including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms[a], or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms[a], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy. Sections of any liver biopsies that are performed may be sent to Lilly for further analysis.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in hepatic safety case report forms (CRF)s should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
   - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevated TBL to ≥ 2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline

3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
   - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be a serious adverse event (SAE)
5. Discontinuation of study drug due to a hepatic event

Note: The interval between the two consecutive blood tests should be at least 2 days

Hepatic Evaluation Testing

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)

Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA b	Anti-actin antibody[c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[b]	EBV DNA[b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[b]	HSV (Type 1 and 2) DNA[b]
Microbiology[d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

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

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

10.7. Appendix 9: Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AxSpa	ankylosing spondylitis
BID	twice daily
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
C_{max}	maximum observed drug concentration
$C_{min,ss}$	minimum observed drug concentration during a dosing interval at steady state
CL/F	apparent clearance
CMV	Cytomegalovirus
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.
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
CSE	clinically significant event
CSR	clinical study report
CTA	clinical trial agreement
CV	cardiovascular
CYP3A4	cytochrome P450 3A4
DDI	drug-drug interaction
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERCP	endoscopic retrograde cholangiopancreatography
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	good laboratory practices
HDV	hepatitis D virus
hERG	human ether- á-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act

HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HV	healthy volunteers
IAD	interim access to data
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
informed consent	A process by which a participant 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 participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IP	investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
LTBI	latent tuberculosis infection
mAb	monoclonal antibody
MAD	multiple-ascending dose
MN	Micronucleus
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
Participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PASI	Psoriasis Area and Severity Index
PBPK	physiologically based pharmacokinetic

PC	product complaint
PK	Pharmacokinetics
PR	pulse rate
PsA	psoriatic arthritis
PsO	Psoriasis
QD	once daily
QTc	corrected QT interval
QTcF	Fridericia's formula
SAD	single-ascending dose
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SERM	selective estrogen receptor modulator
SIB	suicidal ideation and behavior
SoA	Schedule of Activities
$T_{1/2}$	terminal elimination half-life
TBD	to be determined
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
T_{max}	time to maximum concentration
ULN	upper limit of normal
V/F	apparent volume of distribution
WOCBP	women of childbearing potential

10.8. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current protocol amendment is located directly before the Table of Contents (TOC).

Amendment h: 17 November 2021

Overall Rationale for the Amendment

This protocol was amended to allow for additional plasma samples to be collected for investigation from participants who return for additional follow-up visits. Additional follow-up visits were added to the SoA in previous amendments after elevated liver enzyme levels were observed in some Japanese participants in Part D. This amendment will allow for the collection of additional blood samples for exploratory biomarker analyses at additional follow-up visits (for all participants who had exploratory blood samples collected during the study). Exploratory analyses from blood samples collected at these additional follow-up visits may provide additional mechanistic understanding of the elevated liver enzyme levels following drug discontinuation.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added time point at follow-up to allow for exploratory blood sampling at additional follow-up visits for Parts A, C, and D	This will allow for exploratory analyses at those visits
10.2.1 Blood Sampling Summary	Added footnote to exploratory blood sampling rows to Parts A, C, and D allowing additional samples at the additional follow-up visits	Additional samples will each require 6 mL

Amendment g: 10 November 2021

Overall Rationale for the Amendment

This protocol was amended to remove Part E and to allow all participants to return for additional follow up health assessment visits following the end of study visit.

As of 05 November 2021, elevated AST and ALT have been observed in 3 Japanese participants after completing the 14-day dosing of 1000 mg LY3509754 or placebo. Initial elevated ALT and AST approximately 1.5-fold to 2.7-fold above the ULN for 2 of the patients was noted 12 days post last LY3509754 or placebo dose and remains greater than 5 times above the ULN up to 40 days post the administration. In addition, for a third Japanese participant, elevated ALT and AST greater than 5 times ULN was initially noted beginning 33 days post the last administration of LY3509754 or placebo and continuing through 44 days after the last dose. The 3 participants showed no signs of hepatic decompensation at the end of study follow-up visit (approximately 7 days post discharge from the CRU and 12 days post the last LY3509754 or placebo dose) and at unscheduled visits occurring greater than 7 days after the end of study follow-up assessments. Despite the 3 participants presenting as asymptomatic and having normal AST and ALT while taking LY3509754 or placebo (QD x14 days) and upon discharge from the CRU, the delayed elevations in AST and ALT may be related to LY3509754.

Additionally, on 02 November 2021, Eli Lilly and Company (Lilly) was informed by the site that a male participant in Part D Cohort 1 (400-mg dose of LY3509754 or placebo QD x14 days) self-reported elevated ALT and AST ULN after the end of study follow-up visit (12 days post the last LY3509754 or placebo dose). These are currently being confirmed through repeat laboratory testing.

The previous amendment (Amendment f) allowed participants who did not show elevated AST and ALT at the end of study follow-up assessment and completed Part D to be requested to participate in additional follow-up health assessments for safety monitoring, including safety labs. Based on the findings from the safety labs, additional follow-up safety assessments may be completed at the discretion of the principal investigator.

Based on the ongoing investigation of participants in Part D, this amendment will allow participants from Parts A-C to also be included in this additional safety monitoring. Given the ongoing investigation, Part E will not be implemented, and no patients will be further dosed with LY3509754.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis—Number of Participants	Changed number of participants from approximately 115 to approximately 105	Part E will no longer be implemented, which reduces number of participants
1.1 Synopsis—Number of Participants, 1.1 Synopsis—Intervention Groups and Duration, 1.1 Synopsis—Pharmacokinetic, 1.2 Schema, 1.3.7 Schedule of Activities, 2.1 Study Rationale, 3 Objectives and	Removed information relevant to Part E only	Part E will no longer be implemented

Endpoints, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design, 4.2.5 Part E (DDI: LY3509754 Victim with the CYP3A4 inducer Carbamazepine), 4.3.1 Justification for LY3509754 Dose, 4.3.4 Justification for Carbamazepine Dose, 5.1 Inclusion Criteria, 5.2 Exclusion Criteria, 5.3.1 Meals and Dietary Restrictions, 6.1 Study Interventions Administered, 6.1.1 Carbamazepine Administration Details, 6.3 Measures to Minimize Bias: Randomization and Blinding, 6.5 Concomitant Therapy, 6.6.1 Dose Decision/Escalation, 7.2 Participant Discontinuation/Withdrawal from the Study, 8.2.3 Electrocardiograms, 8.2.5 Suicidal Ideation and Behavior Risk Monitoring, 8.5 Pharmacokinetics, 9.1 Sample Size Determination, 9.3.2.1 Pharmacokinetic Parameter Estimation, 9.3.2.2 Pharmacokinetic Statistical Inference, 9.3.5 Interim Access to Data (IAD), 10.2.1 Blood Sampling Summary, 10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information, 10.7 Appendix 9: Abbreviations, 11 References There were also slight changes in heading numbering as a result of removing sections relevant to Part E only.		
1.3 Schedule of Activities	Added footnote to follow-up column for Parts A-C and modified footnote e in Part D Modified wording of footnote "e" for Part D	To allow for additional safety monitoring visits To provide clarity for consequences of missing additional follow-up visits
4.2.3 Part C (Multiple-Ascending Dose/CYP3A4 Perpetrator DDI) 4.3.3 Justification for Midazolam Dose	Changed citation for in-text references	Removed a reference
5.2 Exclusion Criteria	Removed known allergy to carbamazepine as an exclusion criteria	Carbamazepine will no longer be used in the study
10.8 Appendix 10: Protocol Amendment History	Created section	This section had been inadvertently left out in previous amendments

Amendment f: 19 October 2021

Overall Rationale for the Amendment

This protocol was amended to include the option for additional health assessment visits following the end of study visit in the completed Part D (MAD in Japanese healthy participants). Two participants in Part D Cohort 2 (1000 mg LY3509754 QD x 14 days) have shown elevated AST and ALT AEs with well-preserved hepatic function and no signs of hepatic decompensation at the end of study follow-up visit (~7 days post discharge from the CRU) and 2 unscheduled visits occurring greater than 7 days after the end of study follow-up assessments. At the unscheduled follow-up visits, both the AST and ALT showed clinically significant elevations of >5 times above the upper limit of normal. Despite the two participants presenting as asymptomatic and having normal AST and ALT while taking LY3509754 (QD x14 days) and upon discharge from the CRU, the delayed elevations in AST and ALT may possibly be related to LY3509754. This amendment will allow participants who did not show elevated AST and ALT at the end of study follow-up assessment and completed the Part D, to be requested to participate in additional follow-up health assessments for safety monitoring.

Another change includes the optionality to conduct more than one additional follow-up health assessment visit for safety monitoring in Part E.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.6. Part D SoA	Added footnote "e" to follow-up column	To allow for additional safety monitoring visits
Section 1.3.7 Part E SoA	Added footnote "c" to follow-up/ED column	To allow for additional safety monitoring visits

Amendment e: 01 October 2021

Overall Rationale for the Amendment

This protocol was amended to add an additional cohort (Part E) to the study. Emerging data from Part B of this study indicates that LY3509754 is a victim of CYP3A, as data showed there was a significant increase of LY3509754 exposure upon co-administration with a strong inhibitor of CYP3A4. The purpose of this amendment is to further evaluate the CYP3A victim profile of LY3509754 in the presence of a strong CYP3A4 inducer. The data from Part E will aid in informing LY3509754 dose(s) and recommendations for concomitant medications for future patient studies.

Other changes in the protocol include updates to some of the hepatic safety guidelines, a change to the definition of post-menopausal, corrections to fix PK volume discrepancies and incorrectly referenced exclusion criteria, and other minor editorial updates.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis (Overall Design)	Part E was added	Part E is being added for the assessment of PK of LY3509754 when dosed with carbamazepine.
Section 1.1. Synopsis (Number of Participants)	Updated number of participants required to complete the study, and the number of parts in the study, and added number of participants to be enrolled in Part E	By adding Part E there are additional participants in an additional part
Section 1.1. Synopsis (Intervention Groups and Duration)	Added an additional part and the dosing schedule associated with it, and updated the number of parts in the study	Part E will have its own dosing schedule
Section 1.1. Synopsis (Statistical Analysis — Pharmacokinetics)	Added language describing the comparison of the PK of LY when administered alone versus in the presence of carbamazepine	The addition of Part E will be looking at this
Section 1.2. Schema	Part E was added	Updated to reflect the addition of Part E

Section # and Name	Description of Change	Brief Rationale
	Deleted abbreviation "TBD" from footer	To correct error as this abbreviation is not in the schema
Section 1.3.7. Part E (DDI: LY3509754 Victim with the CYP3A4 inducer Carbamazepine)	SoA for Part E was added	The addition of this new cohort requires its own schedule
Section 2.1. Study Rationale	Added rational for Part E	Part E will evaluate LY3509754 as a substrate of CYP3A4
Section 3. Objectives and Endpoints	Added an additional tertiary/exploratory objective and endpoint	Addition of Part E allows for new objective and endpoint
Section 4.1. Overall Design	Added Design of Part E	This is a DDI: LY3509754 Victim with the CYP3A4 inducer carbamazepine cohort
Section 4.2 Scientific Rationale for Study Design	Added rationale for Part E Updated language to say that Parts A-D are blinded, and that Part E is unblinded	Part E will evaluate LY3509754 as a substrate of CYP3A4 The text previously referenced all parts as Parts A-D, which is no longer the case with the addition of Part E
Section 4.2.3. Part C (Multiple-Ascending Dose/CYP3A4 Perpetrator DDI)	Updated source reference	Differentiation is important as there are now two different FDA 2020 sources
Section 4.2.5. Part E (DDI: LY3509754 Victim with the CYP3A4 inducer Carbamazepine)	Created new sub-section: Added rationale for Part E Added figure for design of Part E	 Carbamazepine is a CYP3A4 inducer Offer visualization of design

Section # and Name	Description of Change	Brief Rationale
	Updated meal and dietary restrictions reference to include Part E	Addition of Part E necessitates inclusion
Section 4.3.1 Justification for LY3509754 Dose	Described justification for dose of LY3509754 used in Part E	300 mg of LY3509754 will be used in Part E
Section 4.3.3. Justification for Midazolam Dose	Updated source reference	Differentiation is important as there are now two different FDA 2020 sources
Section 4.3.4. Justification for Carbamazepine Dose	Created new sub-section: Described justification of dose of carbamazepine used in Part E	Dosing for carbamazepine has been selected based on recommendations from FDA and other current knowledge
Section 5.1. Inclusion Criteria	Added Part E to the BMI range described for Parts A, B, and C	To specify what BMI is acceptable for inclusion in Part E
	Removed definition of post-menopausal and referred to Appendix 4, and updated definition in Appendix 4	To correct discrepancies within the existing protocol and better align with current guidance
Section 5.2. Exclusion Criteria	Added carbamazepine to the list of allergies/atopy as an exclusion criteria	Carbamazepine will be given to participants in Part E
	Added exclusion criteria for Part E only	Nature of Part E requires additional exclusion criteria
Section 5.3.1. Meals and Dietary Restrictions	Added Part E details	Nature of Part E requires specific meal and dietary restrictions
Section 6.1. Study Interventions Administered	Added column for Part E and added E to the list of parts in which LY3509754 is administered	Part E will use carbamazepine and LY3509754

Section # and Name	Description of Change	Brief Rationale
Section 6.1.1. Carbamazepine Administration Details	Created new sub-section: Added Carbamazepine Administration Details	Provided to allow study feasibility
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	Changed wording to specify only Parts A-D instead of all parts	Part E is not subject to randomization and blinding
Section 6.5. Concomitant Therapy	Included Part E in the language regarding concomitant therapy	Part E is a DDI evaluation
	Changed Exclusion Criterion [20] to [26]	Corrected error in existing protocol
	Added language describing that HRT is not allowed in Part E	Carbamazepine is predicted to decrease the efficacy of HRT
	Clarified language to state "when applicable" after HRT	HRT is not allowed in Part E
Section 6.6.1. Dose Decision/Escalation	Described reasoning behind Part E dose of LY3509754	Dosage for LY3509754 in Part E was selected based on safety data in other parts of the study
Section 7.2. Participant Discontinuation/Withdrawal from the Study	Added additional discontinuation criteria for Part E	The use of carbamazepine requires these additional criteria
Section 8.2.3. Electrocardiograms	Included Part E as a part that would have single ECGs collected at specific time points	Part E will have single ECGs collected at specified time points
Section 8.2.5. Suicidal Ideation and Behavior Risk Monitoring	Added text under "Suicidal Ideation and Behavior Risk Monitoring" section	Carbamazepine is considered to be a central nervous system active drug and, therefore, requires monitoring

Section # and Name	Description of Change	Brief Rationale
Section 8.5. Pharmacokinetics	Added carbamazepine and its carbamazepine 10, 11-epoxide metabolite to list of what plasma samples will be analyzed for and described what size samples will be collected	These are relevant to Part E
	Changed volume of plasma samples that are collected for measurement of concentrations of LY3509754, midazolam, and itraconazole from approximately 1 to approximately 2 mL	Numbers updated to correct discrepancy between text and blood sampling summary tables in existing protocol
Section 9.1. Sample Size Determination	Added text describing reasoning for sample size determination for Part E	Sample size will allow for desired statistical analyses to be performed
Section 9.3.2.1. Pharmacokinetic Parameter Estimation	Added text describing what will occur with data from Part E	To describe handling of data collected from Part E
Section 9.3.2.2. Pharmacokinetic Statistical Inference	Added text describing what will occur with data from Part E	To describe handling of data collected from Part E
Section 9.3.5. Interim Access to Data (IAD)	Added text describing what will occur with interim access to data for Parts A-D and Part E	To update when IAD will take place
Section 10.2.1. Appendix 2: Clinical Laboratory Tests Blood Sampling Summary	Added blood sampling table for Part E	Part E will collect different blood sample amounts than other parts
Section 10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Updated definition of post-menopausal state	To better align with current standardized safety guidance

Section # and Name	Description of Change	Brief Rationale
	Added male contraceptive guidance for males in Part E and differentiated between instructions for Parts E and all other parts	Part E requires stricter contraceptive guidance due to use of carbamazepine
Section 10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments	Updated hepatic safety guidelines	To better align with current standardized safety guidance
Section 10.7 Appendix 9: Abbreviations	Added 3 additional abbreviation terms and their definitions Updated abbreviation for CYP	The added text in this amendment uses these abbreviations/terms To provide clarity
Section 11. References	Added 3 references to this section	To provide references for added text

Amendment d: 18 June 2021

Overall Rationale for the Amendment

The protocol was amended to identify the dose for Cohort 1 (400 mg LY3509754) and Cohort 2 (1000 mg LY3509754) for Part D based on safety, tolerability, and pharmacokinetic data from Parts A and C. The 400-mg dose for Cohort 1 was also chosen based on availability of a 200 mg LY3509754 capsule strength that will be provided by the sponsor for Part D only. An additional US site was added to enable enrollment of Japanese subjects required for Part D. The additional US site will be provided 200-mg LY3509754 capsules and placebo capsules as the site has not been qualified by Eli Lilly and Company for extemporaneous preparations. The optional Cohorts 7 (Part A) and 4 (Part C) have been removed as there is no plan to evaluate additional dose levels.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis (Overall Design)	The study description has been updated from "single-center" to "multi-center"	This update was made for operational/ recruitment considerations
1.1. Synopsis (Overall Design)	The number of cohorts in Part A has been updated from "up to 7" to "up to 6", and the number of cohorts in Part C has been updated from "up to 4" to "up to 3"	See overall rationale for the amendment
1.1. Synopsis (Number of Participants)	The number of participants required to complete the study has been updated from "approximately 121" to "approximately 105". The number of participants for Part A has been updated from "up to 59" to "up to 51". The optional Cohort 7 (Part A) has been removed. The number of participants for Part C has been updated from "up to 34" to "up to 26". The optional Cohort 4 (Part C) has been removed.	This update was made for operational considerations and the reasons stated in the overall rationale for the amendment
1.1. Synopsis (Intervention Groups and Duration)	Cohort 7 (Part A) and Cohort 4 (Part C) have been removed. Planned doses for Cohorts 1 and 2 (Part D) have been added.	See overall rationale for the amendment
1.2. Schema	The optional Cohorts 7 (Part A) and 4 (Part C) have been removed, and planned doses for Cohorts 1 and 2 (Part D) have been added	See overall rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
1.3.1. Schedule of Activities (Part A)	The optional Cohort 7 has been removed	See overall rationale for the amendment
1.3.4. Schedule of Activities (Part C)	The optional Cohort 4 has been removed	See overall rationale for the amendment
1.3.6. Schedule of Activities (Part D)	Additional ECG collection time points have been added to Days 1 and 2 of the treatment period. ECGs on Days 1 and 2 of the treatment period have been changed from single to triplicate. An additional PK sample has been added to Day 1 of the treatment period.	Update made to collect additional safety/ tolerability information
4.1. Overall Design	Text has been updated to state that Study J3D-MC-FNAA will be a multi-center, rather than single-center study	This update was made for operational/recruitment considerations
4.1. Overall Design	The number of cohorts in Part A has been updated from "up to 7" to "up to 6". The number of cohorts in Part C has been updated from "up to 4" to "up to 3"	See overall rationale for the amendment
4.1. Overall Design	Language has been updated to specify that in Part D, Cohorts 1 and 2 will be run concurrently	This update was made for operational considerations
4.2.1. Part A and Table FNAA.1.	The optional Cohort 7 has been removed	See overall rationale for the amendment
4.2.3. Part C and Table FNAA.2.	The optional Cohort 4 has been removed	See overall rationale for the amendment
4.2.4. Part D (Multiple Dosing in Healthy Japanese Participants)	The number of participants for Part D (Cohorts 1 and 2) has been updated from "approximately" 8 per cohort (6 LY:2 placebo) to "at least" 8 per cohort (6 LY:2 placebo)	This update was made for operational considerations
4.3.1. Justification for LY3509754 Dose	The optional Cohorts 7 (Part A) and 4 (Part C) have been removed, and planned doses for Cohorts 1 and 2 (Part D) have been added	See overall rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
6.1. Study Interventions Administered	A footnote has been added to note that 200 mg LY3509754 dosage strength capsules and corresponding placebo will be provided by the sponsor for Part D	See overall rationale for the amendment
6.2. Preparation/Handling/Storage/ Accountability	Language has been added to note that an additional site has been added to the study to recruit the subjects required for Part D. The sponsor will supply LY3509754 in the form of 200-mg capsules and corresponding placebo	This update was made for operational/recruitment considerations
6.6.1. Dose Decision/Escalation (Part D)	The sentence, "The decision to conduct Part D will be at the discretion of the investigator" has been deleted. Language stating that an alternate dosing paradigm may be used for Part D has been deleted.	Part D will be conducted, and the dosing paradigm has been identified
6.6.1. Dose Decision/Escalation (Part D)	Language in this section has been updated to state that the 2 dosing cohorts in Part D will be run simultaneously	This update was made for operational considerations
8.2.3. Electrocardiograms	Language has been updated to state that in the time points specified in the SoA, triplicate ECG recordings will be collected	Update made to collect additional safety/tolerability information
Table 10.2.1. Blood Sampling Summary	The optional Cohorts 7 (Part A) and 4 (Part C) have been removed	See overall rationale for the amendment
Table 10.2.1. Blood Sampling Summary	Table for Part D has been updated to include an additional PK sampling time point	The update was made to account for an added PK sample collection on Day 1 of Part D

Amendment c: 02 April 2021

Overall Rationale for the Amendment

There is uncertainty around the efficacious dose range projections for LY3509754. Current exploratory biomarker data from Cohorts 2-4 show a dose-related increase in target concentrations with no evidence of saturation up to 300 mg. Further, there is potential for an increase in exposure (up to approximately 8.8x) in the presence of a strong CYP3A4 inhibitor (Part B DDI). For these reasons, dosing at 2000 mg is necessary to provide information to support dose selection in subsequent studies, in addition to further insight regarding safety, tolerability, PK, and exploratory biomarkers.

Review of preliminary safety data up to 19 March 2021 shows there have been no study discontinuations, LY-related AEs or SAEs in the SAD up to 1000 mg. Preliminary analysis of the available PK data from 10 to 300 mg indicates that AUC is approximately dose-proportional within this dose range after single doses. Based on this information, the margin of safety at 2000 mg is estimated to be 5x for rat and 6x for dog (based on 1-month NOAEL AUCs) and supports the evaluation of the safety, tolerability, and PK of the LY3509754 dose level of 2000 mg for Cohort 6.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	The Cohort 6 LY3509754 dose level has been updated from TBD to 2000 mg	See overall rationale for the amendment
1.2. Schema	The schema has been updated to reflect the 2000-mg dose for Cohort 6	See overall rationale for the amendment
1.3.1. Part A: Single-Ascending Dose, Cohorts 1, 2, 3, 5, 6, and 7 (SoA)	An exploratory saliva sample has been added at 72 hours post-LY3509754 dosing for Cohort 6	Analysis of the preliminary exploratory biomarker data suggest an incomplete characterization of the biomarkers due to the limited nature of the sample collections in the SAD. Lilly is currently exploring the possibility of leveraging the biomarker findings as an aspect of dose selection and refinement in future patient studies. For this reason and based on the emerging

Section # and Name	Description of Change	Brief Rationale
		exploratory biomarker data from SAD Cohorts 2-4 (30, 100 and 300 mg LY3509754), additional sample collection has been added to the MAD and Cohort 6 of the SAD.
1.3.4. Part C: Multiple-Ascending Dose – Cohorts 1, 3, and 4 – Single Period (SoA)	Exploratory blood sampling has been divided into 2 rows, 1 for plasma blood sampling time points and 1 for serum blood sampling time points. Predose plasma samples have been added on Days 3-6, and Days 9-13 (predose sample on Day 8 will still be collected). Plasma collections at 48, 72, and 96 hours after the final dose have also been added. Predose serum blood samples have been added on Days 1, 3, 6, 9, and 12. A serum collection at 24 hours after the final dose has also been added.	See rationale for update in Section 1.3.1. Part A: Single-Ascending Dose, Cohorts 1, 2, 3, 5, 6, and 7 (SoA).
1.3.6. Part D: Multiple-Dose in Japanese Healthy Participants – Single Period (SoA)	Exploratory blood sampling has been divided into 2 rows, 1 for plasma blood sampling time points and 1 for serum blood sampling time points. Predose plasma samples have been added on Days 3-6, and Days 9-13 (predose sample on Day 8 will still be collected). Plasma collections at 48, 72, and 96 hours after the final dose have also been added. Predose serum samples have been added on Days 1, 3, 6, 9, and 12. A serum collection at 24 hours after the final dose has also been added.	See rationale for update in Section 1.3.1. Part A: Single-Ascending Dose, Cohorts 1, 2, 3, 5, 6, and 7 (SoA)
4.2.1. Part A (Single-Ascending Dose)	In Table FNAA.1, the planned LY3509754 dose level for Cohort 6 has been updated to 2000 mg	See overall rationale for the amendment
4.3.1. Justification for LY3509754 Dose	Language has been updated to note that the LY3509754 dose for Cohort 6 of SAD is 2000 mg, and is based on emerging data from SAD Cohorts 1-5. Language in this section and the margin of safety table (Table FNAA.3) have been also been	See overall rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
	updated based on available PK data from Cohorts 1-4 of the SAD.	
6.1. Study Interventions Administered	The planned LY3509754 dose range for Parts A-D has been updated from 10–1000 to 10–2000 mg	See overall rationale for the amendment
6.6. Dose Modification	Language has been updated to note that the dose in Cohort 6 is the planned highest SAD dose level (was previously Cohort 5), and that emerging data from Cohorts 1-5 of the SAD will be reviewed prior to escalation to this dose level.	See overall rationale for the amendment
10.2.1. Blood Sampling Summary (Part C (MAD) [Cohorts 1, 3, and 4]) and Part D MAD (Japanese Participants)	The sampling tables for Parts C (MAD) and D (MAD; Japanese participants) have been updated. Exploratory blood sampling has been divided into 2 rows, 1 for plasma blood sampling and 1 for serum blood sampling.	This division of exploratory sampling is based on emerging data from Cohorts 1-5 of the SAD and operational considerations

Amendment b: 05 February 2021

Overall Rationale for the Amendment

Preliminary data from Cohorts 1 and 2 of the SAD portion of this study indicate a terminal elimination half-life ($t_{1/2}$) for LY3509754 of approximately 14-17 hours based on noncompartmental analysis which is longer than the projected $t_{1/2}$ of approximately 5 hours. This amendment extends safety and tolerability collection times in the MAD (Parts C and D) components of the study in accordance with this finding.

Section # and Name	Description of Change	Brief Rationale
1.1.Synopsis – Intervention Groups and Duration (Part B)	The LY3509754 dose for Part B (DDI – CYP3A4 victim) has been updated to 10 mg	This dose is based on safety, tolerability, and PK data from Part A
1.2. Schema	Language has been updated in the figure to note that the MAD will start after review of safety and PK data from the 1000-mg LY3509754 SAD cohort, rather than the 300-mg cohort as previously stated	This update corrects an error in the original protocol
1.3. Schedule of Activities	The notes column for pregnancy tests in all parts of the SoA has been updated to reflect that serum pregnancy tests will be performed at screening and urine tests will be performed at all other time points.	This update was made for consistency
1.3.2. Part A: Single-Ascending Dose and Food Effect Evaluation, Cohort 4 (2-Period Crossover)	Footnote "b" has been updated to reflect that the washout between Periods 1 and 2 will be at least 5 days. Footnote "c" has been updated to reflect that the PI must review the Day 5 laboratory results in Period 1 before dosing on Day 1 of Period 2.	These updates were made to align with the increased length of stay that was included in Amendment a
1.3.3. Part B: Drug-Drug Interaction with CYP3A4 Inhibition – Fixed Sequence	PK sampling has been extended to 96 hours postdose in the LY3509754 alone arm (dosing occurs on Day 1). Discharge, PE/MA, and clinical laboratory tests have been moved from Day 14 to Day 17. COVID-19 testing and single safety ECGs have been added to Day 17. AE/medication review, vital sign assessments, and PK samples have been added for the additional days in the CRU. The 5 hour postdose LY3509754 PK samples on Days 1 and 10,	Refer to the overall rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
	and the 60 hour postdose sample on Day 12 have been removed. Footnote "a" has been updated to reflect that the washout period between LY3509754 and itraconazole dosing may be extended by up to 5 days based on emerging PK data.	
	Temperature has been removed from the vital signs row, and a row for temperature has been added. Temperature assessments will be done at check-in (Day -2), predose on Days 1, 6, and 10, and on Day 17, early discontinuation, and follow-up.	This update was made to improve clarity surrounding temperature assessments
1.3.4. Part C: Multiple-Ascending Dose – Cohorts 1, 3, and 4 – Single Period	The duration of stay for Cohorts 1, 3, and 4 of the MAD has been increased to greater than 96 hours following the last LY3509754 dose, after which participants may be discharged on Day 19 at the discretion of the investigator. Discharge, PE/MA, clinical laboratory tests, COVID-19 testing, and single safety ECGs have been moved from Day 15 to Day 19. AE/medication review, vital sign assessments, and PK sampling time points have been added for the additional days in the CRU. The 5-hour postdose PK samples on Days 1, 7, and 14 have been removed.	Refer to the overall rationale for the amendment
	The Day 15 time points for exploratory blood sampling and exploratory buccal swabs and saliva samples have been updated from "P" to "24 hours"	This update corrects an error in the original protocol
1.3.5. Part C: Multiple-Ascending Dose and Perpetrator DDI – Cohort 2 Fixed Sequence	The duration of stay for Cohort 2 of the MAD has been increased to 96 hours following the last LY3509754 dose. Discharge, PE/MA, clinical laboratory tests, COVID-19 testing, and single safety ECGs have been moved from Day 17 to Day 19. AE/medication review and vital sign assessments have been added for the additional days in the CRU. The PK sample on Day 16 has been removed.	Refer to the overall rationale for the amendment
	The Day 15 time points for exploratory blood sampling and exploratory buccal	This update corrects an error in the original protocol

Section # and Name	Description of Change	Brief Rationale
	swabs and saliva samples have been updated from "P" to "24 hours"	
1.3.6. Part D: Multiple-Dose in Japanese Healthy Participants – Single Period	The duration of stay for Part D (MAD in Japanese Healthy Participants) has been increased to greater than 96 hours following the last LY3509754 dose. Discharge, PE/MA, clinical laboratory tests, COVID-19 testing, and single safety ECGs have been moved from Day 15 to Day 19. AE/medication review, vital sign assessments, and PK sampling time points have been added for the additional days in the CRU. The 5-hour PK samples on Days 1, 7, and 14 have been removed.	Refer to the overall rationale for the amendment
	The Day 15 time points for exploratory blood sampling and exploratory buccal swabs and saliva samples have been updated from "P" to "24 hours"	This update corrects an error in the original protocol
4.2.1. Part A (Single-Ascending Dose)	Language in this section has been updated to reflect an approximate half-life of 14 to 17 hours for LY3509754.	Refer to the overall rationale for the amendment
4.2.2. Part B (CYP3A4 Inhibition)	The LY3509754 dose to be studied in this portion of the study has been identified as 10 mg.	This dose is based on safety, tolerability, and PK data from Part A.
	Language describing the washout period has been updated from "up to 3 days" to "up to 5 days".	Refer to the overall rationale for the amendment.
	Language in this section detailing length of participant stay has been updated in accordance with the changes made to the SoA in this amendment.	PK sampling duration and participant stay in the CRU has been increased to account for predicted longer half-life of LY3509754 after itraconazole inhibition of CYP3A4-mediated clearance.
	Figure FNAA.1 has been updated to reflect the increased stay and PK sampling changes made to the SoA.	
4.2.3. Part C (Multiple-Ascending Dose/ CYP3A4 Perpetrator DDI)	Language in this section detailing length of participant stay has been updated in accordance with the changes made to the SoA in this amendment	Refer to the overall rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
	Figure FNAA.2 has been updated to reflect the increased duration of stay in the CRU and to correct an error in LY3509754 PK sampling times	Refer to the overall rationale for the amendment
4.3.1. Justification for LY3509754 Dose; Table FNAA.3.	Footnotes "c" and "d" have been updated to note that exposure is predicted AUC or C_{max} at steady state	This update was made for clarity
	The LY3509754 dose to be studied in Part B (LY3509754 CYP3A4 Victim Assessment) has been identified as 10 mg	This dose was determined based on safety, tolerability, and PK data from Part A
6.6.1. Dose Decision/Escalation	The number of days following the last dose of LY3509754 (5) that safety data are required to be reviewed for SAD and MAD dose escalations has been added	This update was made for clarity
9.3.5. Interim Access to Data (IAD)	The number of days that data will be collected for participants in each cohort before IAD is planned to occur has been updated from "up to Day 14" to "up to Day 17" for Part B (CYP3A4 victim DDI), from "up to Day 15" to "up to Day 19" for Cohorts 1 and 3, and from "up to Day 16" to "up to Day 19" for Cohort 2 in the MAD component of the study.	Refer to the overall rationale for the amendment
10.2. Appendix 2: Clinical Laboratory Tests	WBC esterase testing has been added to the urinalysis	This change corrects an omission in the original protocol
	Footnote "e" has been updated to reflect that a serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at all other time points	This update was made for consistency
10.2.1. Blood Sampling Summary	The number of LY3509754 PK samples and corresponding blood volumes have been updated in the blood sampling tables for Part B (DDI with CYP3A4 Inhibition – Fixed Sequence) and Part C (MAD + Midazolam DDI [Cohort 2])	These changes were made in accordance with updates to PK sampling made in the corresponding sections of the SoA

Amendment a: 30 December 2020

Overall Rationale for the Amendment

Preliminary data from Cohort 1 of the SAD portion of this study indicate a terminal elimination half-life ($t_{1/2}$) for LY3509754 of greater than 5 hours based on non-compartmental analysis which is longer than the projected $t_{1/2}$ of approximately 5 hours. This amendment extends safety, tolerability, and PK collection times in accordance with this finding

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities; 1.3.1. Part A: Single-Ascending Dose, Cohorts 1, 2, 3, 5, 6, and 7	The duration of stay for the SAD portion of this study (Part A, Cohorts 1-3 and 5-7) has been increased to 96 hours postdose. PK, safety, and tolerability collections were added at 72 and 96 hours postdose. Follow-up will occur at least 7 days after discharge, not final dose as previously stated.	Refer to the overall rationale for the amendment
1.3. Schedule of Activities; 1.3.2. Part A: Single-Ascending Dose and Food Effect Evaluation, Cohort 4 (2-Period Crossover)	The duration of stay for the SAD portion of this study (Part A, Cohort 4) has been increased to 96 hours postdose. PK, safety, and tolerability collections were added at 72 and 96 hours postdose for Treatment Period 1 (Fasted) and Treatment Period 2 (Fed). Follow-up will occur at least 7 days after discharge, not final dose as previously stated.	Refer to the overall rationale for the amendment
4.2. Scientific Rationale for Study Design; 4.2.1. Part A (Single-Ascending Dose)	Language in this section detailing length of participant stay and timing of follow-up has been updated in accordance with the changes made to the SoA in this amendment	Refer to the overall rationale for the amendment
5.1. Inclusion Criteria	Criterion 7.b has been updated to change the FSH cutoff from >40 mIU/mL to ≥40 mIU/mL	This corrects an error in the original protocol
5.2. Exclusion Criteria	Criterion 16 has been updated to replace QTcB with QTcF for calculation of corrected QT interval	This corrects an error in the original protocol
5.2. Exclusion Criteria	Criterion 37 has been added to include testing for active or latent tuberculosis at screening	This corrects an omission in the original protocol

Section # and Name	Description of Change	Brief Rationale
8.5. Pharmacokinetics	Language has been added to describe exploratory metabolite profiling in urine and plasma	This corrects an omission in the original protocol
9.3.5. Interim Access to Data (IAD)	The number of days that data will be collected for participants in each cohort in the SAD component of the study (Part A), before IAD is planned to occur, has been updated from up to 3 days postdose to up to 5 days postdose.	Refer to the overall rationale for the amendment
10.2. Appendix 2: Clinical Laboratory Tests	QuantiFERON-TB Gold testing, and FSH testing have been added to be done at screening. Equations for calculation of creatinine clearance have been added to the footnotes.	These changes correct omissions in the original protocol
10.2.1. Blood Sampling Summary	Updates to the sampling tables for the SAD component of the study (Part A) have been made in accordance with increased participant stay in the CRU as detailed in the SoA.	Refer to the overall rationale for the amendment

11. References

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Approval	PPD 01-Dec-2021 14:35:38 GMT+0000

Approval	PPD 01-Dec-2021 15:38:49 GMT+0000

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