Protocol: J2D-MC-CVAC (c)

A Safety, Tolerability and Pharmacokinetic Study of Single and Multiple Doses of LY3526318 in Healthy Participants

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Title Page

Protocol Title: A Safety, Tolerability and Pharmacokinetic Study of Single and Multiple Doses of LY3526318 in Healthy Participants

Protocol Number: J2D-MC-CVAC

Amendment Number: c

Compound: LY3526318

Study Phase: 1

Short Title: A Safety, Tolerability, PK and Pilot Food Effect Study of LY3526318 in Healthy Participants

Acronym: CVAC

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

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Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	15 February 2021
Amendment (a)	08 December 2020
Original Protocol	19 October 2020

Amendment (c)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

This amendment incorporates changes to allow for a high-fat meal or a light breakfast in the fed state to understand the effect of meal types on exposure. This amendment also corrects typographical errors.

Section # and Name	Description of Change	Brief Rationale
Sections 1.1, 4.1 5.3.1, and 6.1	Amended text to allow for a high-fat meal or a light breakfast in the fed state.	To allow for testing the effect of meal type on the PK of LY3526318.
Section 5.3.1	Revised text to clarify the meal schedule for Part B.	Clarification
Section 6.1	Revised wording in Part B regarding review of data from Part A dosing to align with text in Section 4.1.	Consistency

Abbreviation: PK = pharmacokinetics.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Safety, Tolerability and Pharmacokinetic Study of Single and Multiple Doses of LY3526318 in Healthy Participants

Short Title: A Safety, Tolerability, PK and Pilot Food Effect Study of LY3526318 in Healthy Participants

Rationale:

LY3526318 is a small molecule that inhibits transient receptor protein ankyrin-1 (TRPA1), a calcium-permeable nonselective cation channel. There is healthy participant experience and preclinical evidence for TRPA1 antagonism in the alleviation of chronic pain.

In the Phase 1 study, J2D-MC-CVAA (CVAA), LY3526318 was well-tolerated at all doses. Single doses up to 300 mg and multiple doses (MDs) of 100 mg daily for 14 days were administered. Plasma exposure increased with increasing doses of up to 100 mg but did not increase further at doses of 200 or 300 mg. The lowest animal-toxicology no-observed-adverse-effect level (NOAEL) is approximately 3-fold higher than the higher human exposures achieved in Study CVAA. There were no serious adverse events (SAEs) observed in Study CVAA.

There was a high degree of interindividual variability in LY3526318 pharmacokinetics (PK). When a meal was consumed near the time of dosing, LY3526318 maximum observed drug concentration (C_{max}) and area under the concentration versus time curve from time zero to 24 hours post dose (AUC_{0-24}) decreased by approximately 80% and 86%, respectively. These exposure limitations are likely due to a conversion from a more soluble to a less soluble crystal form of LY3526318 in the gastrointestinal (GI) tract prior to absorption. CCI [redacted]

Study J2D-MC-CVAC (CVAC) will evaluate the PK parameters of the new LY3526318 formulation in healthy participants after oral administration and includes a single-ascending-dose (SAD) portion (fasted and fed) (Part A) and a 5-day MD portion (Part B). The initial single dose level is 100 mg, the dose that produced maximum exposure in Study CVAA (56 µg·h/mL). Up to 2 additional single dose levels may be administered; these doses would be selected to maintain human exposure below the lowest animal-toxicology NOAEL (154 µg·h/mL, established in a 1-month monkey study). Up to two of the single doses that were administered in a fasted state may also be administered in a fed state (a high-fat meal or a light breakfast), to determine if food affects LY3526318 PK when administered in the new formulation. Additionally, one of the single doses will be administered daily for 5 days to assess safety and exposure.

Objectives and Endpoints

Objective	Endpoints
Primary (Part A – SAD)	
• To determine the pharmacokinetics of LY3526318 after a single oral dose administration	• AUC • C_{max}
Primary (Part B – MD)	
• To determine the pharmacokinetics of LY3526318 after multiple oral dose administrations	• AUC • C_{max}
Secondary (Part A – SAD)	
• To estimate the safety and tolerability of LY3526318 after single (Part A) oral administration to healthy participants • To evaluate the effect of a meal on the pharmacokinetics of LY3526318 in fed versus fasted conditions	• AEs • SAEs • C_{max} • t_{max} • AUC
Secondary (Part B – MD)	
• To estimate the safety and tolerability of LY3526318 after multiple oral administrations to healthy participants	• AEs • SAEs

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; MD = multiple dose; SAD = single-ascending dose; SAE = serious adverse event; t_{max} = time to C_{max}.

Overall Design

Study CVAC is a Phase 1, randomized, double-blind, placebo-controlled, SAD (Part A) and MD (Part B) study of LY3526318 in healthy participants.

Disclosure Statement: This is a 2-part study with 2 arms (LY3526318:Placebo) that are participant and investigator blinded.

Number of Participants:

A maximum of 16 healthy male or female participants will be enrolled. Due to the relatively small size of the study, participants who discontinue may be replaced.

Intervention Groups and Duration:

Part A - SAD

The SAD of LY3526318 or placebo will be administered, beginning at a dose of 100 mg, the dose level that produced the highest exposure in Study CVAA. A single cohort of 8 healthy participants will be randomized to a sequence in which LY3526318 or placebo will be administered in a 3:1 ratio. In each dosing period, different participants will receive placebo. In this adaptive dose study, subsequent dose levels will be selected based on safety and PK. Doses will be selected to maintain geometric mean AUC_{0-24} below the lowest NOAEL from animal-toxicology studies (154 µg·h/mL).

Following a screening period of up to 28 days, eligible participants will be confined to the clinical research unit (CRU) from Day -1 until all study assessments are completed on Day 3.

Sentinel dosing is not planned as this is not the first clinical study for LY3526318. Dose escalations to subsequent cohorts may occur at approximately 2-week intervals after review of safety data and available PK data through 24 hours post dose from at least 4 participants on active drug from the prior period. Of the 4 treatment periods planned for Part A, up to 3 single dose levels will be assessed in a fasted state (fasting at least 8 hours prior to and at least 4 hours after dosing). Up to two of these dose levels that were assessed in a fasted state may also be assessed in a fed state (a high-fat meal or a light breakfast 30 minutes prior to dosing).

Participants will return to the CRU for a final follow-up visit approximately 10 days after the final study intervention administration.

Part B - MD

LY3526318 or placebo will be administered daily for up to 5 days at a dose level not to exceed the highest dose used in Part A. Part B will begin following a review of Part A safety and PK data. Participants will be confined to the CRU throughout this 5-day dosing period and for an additional 72 hours for PK sampling. Eight treatment-naïve participants will be randomized to receive LY3526318 or placebo in a 3:1 ratio. Part B will involve dosing in a fasted or fed state (e.g., standard meal or a light breakfast as described in site-specific manual) depending on the results from Part A. The dose regimen and fed/fasting will be selected with the intent not to exceed the AUC_{0-24} achieved in Part A.

Participants will return to the CRU for a final visit on Day 14.

Data Monitoring Committee: No

1.2. Schema

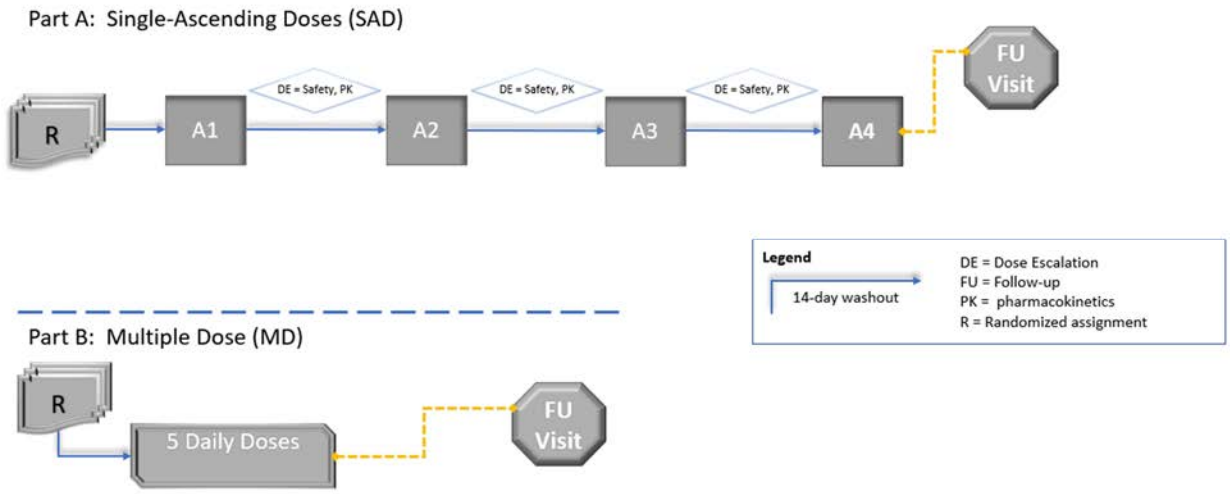

Figure 1.1. Study diagram.

Randomized to Treatment/Sequence

Treatment	SAD Periods [N=8]			
Sequence [n]	A1	A2	A3	A4
1 [2]	P	L2	L3	L4
2 [2]	L1	P	L3	L4
3 [2]	L1	L2	P	L4
4 [2]	L1	L2	L3	P

Single doses are L1, L2, L3, L4, P (Placebo); L = level for dose (mg)

Treatment	MD [N=8]
Sequence [n]	B
5 [6]	LX
5 [2]	P

Multiple Dose (MD) is dose LX that is ≤ single dose

Abbreviations: N = number of participants; n = number of participants in specific population; SAD = single ascending dose.

Figure 1.2. Study treatments for the SAD and MD cohorts.

1.3. Schedule of Activities

Table 1. Study Schedule Protocol J2D-MC-CVAC Single-Ascending Dose (SAD) – Part A

	S	Treatment Period[a]						FU	ED[b]
Visit	**1**	**2**				**3**	**4**	**5**	
Study Day	**-28**	**-1[c]**	**1**	**2**	**3**	**4**	**5**	**10 (±1 day)**	
Admit to CRU[d]		X							
Discharge from CRU					X[e]				
CRU visit	X	X				X[e]	X[e]	X	X
Informed consent	X								
Medical history	X	X							
C-SSRS	X	X						X	X
Height	X								
Weight	X	X						X	X
Physical examination	C	D	D	D	D	D	D	D	D
Urine drug screen	X	X						X	X
Hematology and clinical chemistry	X		P	X			X	X	X
Urinalysis[f]	X	X	P	X			X	X	X
β-hCG pregnancy test	X	X						X	X
HIV, HCV, HBsAg	X								
Con med		X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Vital signs	X	X	P, 2, 4, 6 h	X	X	X	X	X	X
Temperature	X	X							
ECG[g]	See Table 2								
Randomization			X						
Study intervention administration[h]			X						
PK blood sample[i]		See Table 2							

Abbreviations: C = complete physical examination; Con med = concomitant medications; COVID-19 = coronavirus disease 2019; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; FU = safety follow-up; HBsAg = hepatitis B surface antigen; β-hCG = beta subunit of human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; P = predose assessment; PK = pharmacokinetic; S = Screening; SOP = standard operating procedure.

Note: In the event that assessments are planned for the same time, assessments should be conducted in following order: ECG/vital signs/ PK sample The ECG and vital signs measurement can be obtained at least 30 minutes prior to the PK sample, which is drawn at the nominal time point.

Screening visits will be performed within 28 days before the administration of first dose.

[a] The procedures for Days -1 through 5 will be repeated for up to 4 treatment periods.

[b] Participants who discontinue the study prior to study completion will complete the ED visit procedures.

[c] Day -1 procedures can be performed on a day prior to dosing or pre-dose on day of dosing.

[d] All participants will remain in the CRU until completion of all procedures that occur that day.

[e] After participants have completed the required in-house stay, the remaining activities may be completed in house or ambulatory based upon the discretion of the investigator.

[f] A standard urine dipstick may be used.

[g] See Table 2. Triplicate 12-lead ECGs will be obtained with approximately 1 minute apart following at least 10 minutes in the supine position. Single 12-lead ECGs will be collected at the time points indicated.

[h] The exact time that study intervention is administered will be recorded.

[i] See Table 2.

Note: All local requirements regarding COVID-19 will be followed according to local/site SOP.

Table 2. Scheduled Times[b] for PK Blood Sample and ECG for Periods 1 to 4

Day[a]	Time[b]	ECG (Fasted)	ECG (Fed)	PK Sample Periods 1-4
Day -28 to -1	Screening	Single ECG		
Day 1	Predose	ECG[c]	Single ECG	X
	Dose			Dose of LY3526318
	1 h			X
	2 h	ECG[c]		X
	4 h	ECG[c]		X
	6 h	ECG[c]		X
	8 h			X
	12 h			X
Day 2	24 h	ECG[c]		X
Day 3	48 h			X
Day 4	72 h			X
Day 5	96 h			X
Follow-up visit		Single ECG	Single ECG	X
Early Discontinuation		Single ECG	Single ECG	X

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic.

[a] The procedures for Days -1 through 5 will be repeated for up to 4 treatment periods.

[b] Sampling times are given as targets to be achieved within reasonable limits. The timing of PK sample collections may be adjusted based on clinical needs. The exact sample collection dates and times must be recorded.

[c] Following at least 10 minutes in a supine position, triplicate ECG are collected with approximately 1 minute between measurements.

Table 3. Study Schedule Protocol J2D-MC-CVAC Multiple Dose (MD) – Part B

	S	Treatment Period								FU	ED[a]
Visit	**1**		**2**							**3**	
Study Day	**-28**	**-1[b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**14**	
Admit to CRU[c]		X										
Discharge from CRU										X[d]		
CRU visit	X	X									X	X
Informed consent	X											
Medical history	X	X										
C-SSRS	X	X									X	X
Height	X											
Weight	X	X									X	X
Physical examination	C	D	D	D	D	D	D	D	D	D	D	D
Urine drug screen	X	X									X	X
Hematology and clinical chemistry	X		P	P		P	P	X	X	X	X	X
Urinalysis[e]	X	X	P	X		X	X	X	X	X	X	X
β-hCG pregnancy test	X	X									X	X
HIV, HCV, HBsAg	X											
Con med		X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	P and 4 h	X	X	X	X	X	X	X	X	X
Temperature	X	X										
ECG[f]			See Table 4									
Randomization			X									
Study intervention administration[g]			X	X	X	X	X					
PK blood sample[h]			See Table 4									

Abbreviations: C = complete physical examination; Con med = concomitant medications; COVID-19 = coronavirus disease 2019; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; FU = safety follow-up; HBsAg = hepatitis B surface antigen; β-hCG = beta subunit of human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; P = predose assessment; PK = pharmacokinetic; S = Screening; SOP = standard operating procedure.

[a] Participants who discontinue the study prior to study completion will be expected to complete the ED visit procedures.

[b] Day -1 procedures can be performed on a day prior to dosing or predose on day of dosing.

[c] Participants will be confined to the CRU from Day -1 until all study assessments are completed 72 hours after the last dose

[d] After participants have completed the required in-house stay, the remaining activities may be completed in house or ambulatory based upon the discretion of the investigator.

[e] A standard urine dipstick may be used.

[f] A single 12-lead ECG will be obtained in the supine position after at least 10 minutes rest.

[g] The exact time study intervention is administered will be recorded.

[h] See Table 4 Part B Scheduled Times for PK Blood Samples.

Note: Screening visits will be performed within 28 days before the administration of first dose.

Note: In the event that assessments are planned for the same time, assessments should be conducted in following order: ECG/vital signs/PK sample. The ECG and vital signs measurement can be obtained at least 30 minutes prior to the PK sample, which is drawn at the nominal time point.

Note: All local requirements regarding COVID-19 will be followed according to local/site SOP.

Table 4. Part B Scheduled Times for PK Blood Samples and Single 12-lead ECGs

Day	Time[a]	PK Collections[b]	ECG (fasted)	ECG (fed)
Day 1	Predose	X	X	X
	Dose	Dose of LY3526318		
	1 h	X		
	2 h	X	X	
	4 h	X	X	X
	6 h	X	X	X
	8 h	X		
	12 h	X		
Day 2	Predose (24 hours after the preceding dose)	X	X	X
	Dose	Dose of LY3526318		
Day 3	Predose (24 hours after the preceding dose)	X		
	Dose	Dose of LY3526318		
Day 4	Predose (24 hours after the preceding dose)	X		
	Dose	Dose of LY3526318		
Day 5	Predose (24 hours after the preceding dose)	X	X	X
	Dose	Dose of LY3526318		
	1 h	X		
	2 h	X	X	
	4 h	X	X	X
	6 h	X	X	X
	8 h	X		
	12 h	X		
Day 6	+24 h (24 hours after the preceding dose)	X	X	X
Day 7	+ 48 h	X		
Day 8	+72 h	X		
Follow-Up		X		
Early Discontinuation		X	X	X

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic.

[a] Sampling times are given as targets to be achieved within reasonable limits.

[b] The timing of PK sample collections may be adjusted based on clinical needs. The exact sample collection dates and times must be recorded.

2. Introduction

2.1. Study Rationale

Study CVAC is designed to evaluate safety, tolerability, and PK of oral LY3526318 in healthy participants when LY3526318 is administered as a new formulation. In a prior Phase 1 study (CVAA), exposure did not increase beyond that observed at 100 mg, and the concomitant food administration reduced exposure compared to the fasted state.

In this limited SAD study, a crossover design was chosen to limit the variability of PK, especially for the comparison of PK after fed and fasted conditions. Given treatment-emergent adverse events (TEAEs) were mild in the previous SAD and MD (to 14 days) studies, participants should be able to safely tolerate a maximum of 4 single doses with 14 days of washout between dosing periods. Placebo doses are included to assess TEAEs and limit bias. Similarly, given that a Phase 1 study was previously conducted, sentinel dosing is not necessary. In addition, safety and PK will be assessed prior to each dose escalation to mitigate the possibility of more severe adverse events (AEs) and the PK exceeding the mean area under the concentration versus time curve (AUC) of the monkey NOAEL.

2.2. Background

Chronic pain is a major health issue affecting the quality of life of millions of patients. Nonsteroidal anti-inflammatory drugs are the primary choice of drugs for chronic pain treatment; however, efficacy is limited in many patients. Opioids are potent but sedating and have addictive potential, relegating them to third- and fourth-line treatment options in chronic pain (Ko et al. 2019).

The role of TRPA1 in pain and inflammation and its localization in sensory neurons have been characterized (Bodkin and Brain 2011; Ückert et al. 2017). It evokes pain and an adverse response when administered exogenously (Berta et al. 2017; Demartini et al. 2017; Maatuf et al. 2019; Wang et al. 2019). Additionally, there is genetic evidence for the contribution of TRPA1 to chronic pain.

Transient receptor protein ankyrin-1 antagonists are undergoing evaluation in clinical trials, where there is evidence of efficacy and safety (ODM-108, NCT02432664 [NIH 2017]; GRC 17536; EU Clinical Trial Register 2012-002320-33 [WWW]).

Two Phase 1 studies (CVAA and J2D-MC-CVAB [CVAB]) were conducted to assess tolerability and PK and to assess target engagement, respectively. Study CVAA included a SAD portion, a 2-week multiple ascending dose portion achieving maximum doses of 300 and 100 mg, respectively, and a pilot food-effect portion. Study CVAB assessed target engagement by measuring changes to dermal blood flow following a randomized sequence of 4-single doses: 10 mg, 30 mg, 100 mg, and placebo. There were no clinically significant adverse effects in either of these studies.

In the SAD, plasma exposure increased with increasing doses up to 100 mg, but exposure did not increase at doses of 200 or 300 mg. The geometric mean terminal elimination half-life ($t_{1/2}$) ranged from 9.72 hours to 13.5 hours without an apparent effect of dose over the range of 10 mg

to 300 mg. In addition, when a meal was consumed 30 minutes prior to a 100-mg dose, exposure was approximately 11% of that observed when participants fasted for at least 8 hours prior to and 4 hours after dosing. The new formulation being administered in the current study was developed to increase absorption and to decrease the impact of food.

2.3. Benefit/Risk Assessment

There is no benefit anticipated for healthy participants administered LY3526318.

The current study will be conducted in accordance with principles outlined in the "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products" (EMA 2017). In Study CVAA, no clinically significant safety or tolerability concerns were identified at the highest single dose administered (300 mg) or the highest multiple dose administered (100 mg once daily for 14 days). Because of the male-only AE observed in rats (seminiferous tubule degeneration), dosing in CVAA was limited to 100 mg for males, with higher doses being administered to females only. This effect was not observed in 2 subsequent male rat studies and was not observed in a 1-month monkey toxicology study, so males will be enrolled in the current study. As described in Section 4.3, subsequent dose regimens will be selected to maintain exposure below the nonclinical NOAEL exposure.

In a biomarker study (Study CVAB), there was evidence of target engagement at 3 hours, but not 24 hours after a single dose of 100 mg. Regarding the current study that uses a new formulation of LY3526318, exposure following the proposed initial dose of 100 mg is projected to be similar to or slightly greater than the exposure achieved in the prior study.

The benefit-risk for the participants treated with LY3526318 remains unchanged in relation to the coronavirus disease 2019 (COVID-19) pandemic as currently based on the results from clinical and nonclinical data. There is no evidence that administration of LY3526318 will lead to suppression or modulation of the immune system. In addition, the mode of action does not appear to have a substantial effect on the respiratory or cardiovascular system critically affected by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. As the participants to be included in this study are generally young to middle aged and healthy (without major comorbidities), the study population is not considered to be a high-risk population for serious COVID-19 disease. Only persons with a negative SARS-CoV-2 test at admission to the CRU will be allowed to participate in the study. In addition, all appropriate measures to prevent SARS-CoV-2 infection during the study will be taken as detailed in site standard operating procedures (SOPs).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3526318 may be found in the Investigator's Brochure (IB).

3. Objectives and Endpoints

Objectives	Endpoints
Primary (Part A – SAD)	
• To determine the pharmacokinetics of LY3526318 after a single oral dose administration	• AUC • C_{max}
Primary (Part B – MD)	
• To determine the pharmacokinetics of LY3526318 after multiple oral dose administrations	• AUC • C_{max}
Secondary (Part A – SAD)	
• To estimate the safety and tolerability of LY3526318 after single (Part A) oral administration to healthy participants • To evaluate the effect of a meal on the pharmacokinetics of LY3526318 in fed versus fasted conditions	• AEs • SAEs • C_{max} • t_{max} • AUC
Secondary (Part B – MD)	
• To estimate the safety and tolerability of LY3526318 after multiple oral administrations to healthy participants	• AEs • SAEs

Abbreviations: AE = adverse event; AUC = are under the drug concentration versus time curve; C_{max} = maximum observed drug concentration; MD = multiple dose; SAD = single-ascending dose; SAE = serious adverse event.

4. Study Design

4.1. Overall Design

This is a Phase 1, SAD (Part A) and MD (Part B) study of LY3526318 in healthy participants. Both parts are randomized, double-blind, and placebo-controlled. A maximum of 16 participants (SAD and MD cohorts of size 8, randomized 3:1) will be randomly assigned to study intervention such that approximately 16 evaluable participants complete the study.

Part A (SAD):

Single-ascending doses of LY3526318 or placebo will be administered under fasted conditions, beginning with a dose of 100 mg in a cohort of 8 participants. Up to 3 dose levels in a cohort of participants will be administered in a fasted state (fasted for at least 8 hours prior to dosing and for at least 4 hours after dosing). The dose escalation may be stopped if a projected dose may exceed the toxicology NOAEL. Each dose will be separated by at least 1 week. The initial single dose level is the equivalent of 100-mg original formulation, the dose that produced maximum $AUC_{0\text{-}inf}$ (56 µg·h/mL) in Study CVAA. This dose level was selected because it produced the highest exposure when administered using the original formulation of LY3526318, and if the new formulation produces the maximum theoretical exposure increase of 2-fold compared to the prior study, a 2-fold exposure increase is considered safe and appropriate. Up to 2 additional single dose levels may be administered in a fasted state and these doses would be selected to maintain human $AUC_{0\text{-}inf}$ below the lowest animal-toxicology NOAEL (154 µg·h/mL, established in a 1-month monkey study).

Doses that were administered in a fasted state may also be administered in a fed state to determine if food decreases exposure when LY3526318 is administered in the new formulation. For the fed state, a standardized, high-fat meal or a light breakfast (as described in site-specific manual) will be consumed prior to dosing. Approximately 50% of the total caloric content of the high-fat meal should be from fat. Study participants should eat this meal in 30 minutes or less, and the study intervention should be administered 30 minutes after the start of the meal. In all cases, study intervention should be taken with 1 glass (approximately 240 mL) of water, and no food should be allowed for at least 4 hours post dose. Water can be allowed as desired except for 1 hour before and after drug administration.

Following a screening period of up to 28 days, eligible participants will be confined to the CRU from Day -1 until all study assessments are completed on Day 3. All participants will return to the CRU after the last study period for a final visit on Study Day 10.

Part B (MD):

After a dose is identified from Part A, multiple doses of LY3526318 or placebo will be administered for up to 5 days. Additional participants will be enrolled for a total cohort size of 8 completers. The assignment to placebo or LY3526318 treatment will be determined at initial randomization to a treatment sequence.

Participants will be confined to the CRU from Day -1 until all study assessments are completed 72 hours after the last dose. Participants will begin receiving multiple once-daily doses of LY3526318 following a review of safety and PK data from Part A, and dose levels will not

exceed those administered in Part A. After review of the data from Part A, Part B doses may be administered in a fed or fasted state or either on different days.

Participants will return to the CRU for a final visit on approximately Day 14.

Safety, PK, and other assessments will be performed at time points, as prescribed in Section 1.3, during the stay at the CRU and at subsequent study visits in Part A and Part B.

Study governance considerations are described in detail in Section 10.1, Appendix 1.

4.2. Scientific Rationale for Study Design

In Study CVAA, all single doses and MDs were well tolerated, but exposure did not increase at doses above 100 mg. In addition, consumption of a meal was found to significantly decrease exposure compared to when participants fasted. This study will include dose escalation beginning with approximately 100 mg, the dose level associated with the highest exposure in the CVAA study, and will include an assessment of food effect. Residual exposure will be minimized due to a washout period of at least 1 week between doses. The PK sampling schedule is designed to measure LY3526318 concentrations over at least 5 half-lives.

Part B is a repeat-dose phase designed to assess tolerability and exposure with repeated doses.

4.3. Justification for Dose

In a prior Phase 1 study (CVAA), there were no clinically significant adverse events at the highest doses administered: 300 mg in the SAD and 100 mg/day for 14 days in the MD. These doses were administered to females only, but there was no apparent difference in exposure or tolerability at lower doses administered to males and females. 100 mg/day was selected as the highest dose for the MD, because plasma exposure did not increase with increasing dose beyond 100 mg. In addition, when a meal was consumed 30 minutes prior to a 100 mg dose, exposure was approximately 11% of that observed when participants fasted. The new formulation being administered in the current study was developed to increase absorption and to decrease the impact of food. The current formulation could produce exposures up to 2.5 times those of the prior form for any given dose level.

The NOAEL from Good Laboratory Practice toxicology studies was established in a 1-month monkey study (Study 00926044). There were no adverse effects in monkeys administered 1000 mg/kg/day, and the mean $AUC_{0\text{-}24}$ was 154 µg·h/mL. As summarized in Table 4.1, in the clinical study, CVAA, a dose of 100 mg resulted in a mean $AUC_{0\text{-}inf}$ of 56 µg·h/mL, and this is planned to be the starting dose in CVAC. The planned maximum dose of 275 mg is based on an assumption of a dose-proportional increase in exposure. The determinant of the maximum dose will be the NOAEL AUC of 154 µg·h/mL. In the event that a less-than-dose-proportional increase in exposure is observed, a unit dose higher than 275 mg may be used, as long as a mean AUC of 154 µg·h/mL is not exceeded. As a practical limit, the unit dose will not be more than 1000 mg. In addition, if a dose lower than 100 mg is needed to maintain AUC <154 µg·h/mL, de-escalation is permitted. For the multiple-dose portion of the study, the dose regimen and fed/fasting will be selected with the intent not to exceed the $AUC_{0\text{-}24}$ achieved in Part A.

Table 4.1. Margin of Safety for Oral Administration of LY3526318 Based on Administered Dose and Exposure

	Dose (mg/kg)	Dose (mg/m^2)	Dose Multiple[a]	AUC (µg·h/mL)[a]	Exposure Multiple[b]
Human					
Starting dose (100 mg)	1.67	61.7		56	
Maximum dose (275 mg)[c]	4.6	170		154	
Rat NOAEL[d]					
Male	1000	6000	97[e]	131	2.3[e]
			35[f]		0.85[f]
Female	1000	6000	97[e]	295	5.3[e]
			35[f]		1.9[f]
Monkey NOAEL[g]	1000	12000	194[e]	154	2.8[e]
			71[f]		1[f]

Abbreviations: AUC = area under the concentration versus time curve; $AUC_{0\text{-inf}}$ = area under the concentration versus time curve from time zero to infinity; AUC_{τ} = area under the concentration versus time curve during a dosing interval; NOAEL = no-observed-adverse-effect level.

a AUC for humans is $AUC_{0\text{-inf}}$ after a single dose. AUC for rat and monkey is AUC_{τ} after multiple doses.

b Dose multiple is the dose in animals/dose in humans based on mg/m^2. Exposure multiple is the calculated AUC in animals/observed or predicted AUC in humans.

c The planned maximum dose of 275 mg is based on an assumption of dose-proportional increase in exposure. The determinant of the maximum dose will be the NOAEL AUC of 154 µg·h/mL. In the event that a less-than-dose-proportional increase in exposure is observed, a unit dose higher than 275 mg may be used, as long as a mean AUC of 154 µg·h/mL is never exceeded. As a practical limit, the unit dose will not be more than 1000 mg.

d NOAELs from the 4-week, repeat-dose toxicity study (Study # 00926043).

e Based on human exposure at 100 mg using the prior formulation (Study CVAA).

f Based on the highest projected exposure (NOAEL of 154 µg·h/mL) at a 275 mg dose using the new formulation.

g NOAEL from the 4-week, repeat-dose toxicity study (Study # 00926044; no LY3526318-related effects were noted.

4.4. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the SoA (Section 1.3) for the last participant.

5. Study Population

Eligibility of participants for the study will be based on the investigator's judgment on results of screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiogram (ECG). The nature of any conditions present at the time of the physical examination and any pre-existing conditions will be documented.

Screening may occur up to 28 days prior to enrollment.

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

5.1. Inclusion Criteria

Participants are eligible for inclusion in the study only if they meet all of the following criteria at screening. The timeframes included in the following criteria are relative to screening unless otherwise noted.

Age

1. Aged 18 to 65 years, inclusive.

Sex

2. Healthy male participants, as determined through medical history and physical examination.
   a. A nonvasectomized, male participant must agree to use a condom or abstain from sexual intercourse from start of dosing until 105 days beyond the last dose of study intervention.
   b. No restrictions are required for a vasectomized male provided his vasectomy has been performed at least 4 months or prior to screening. A male who has been vasectomized <4 months prior to screening must follow the same restrictions as a nonvasectomized male
   c. Must agree not to donate sperm from start of dosing until 105 days beyond the last dose of study intervention.
3. Healthy female participants of child-bearing potential who have a fertile male sexual partner must be willing and able to practice effective contraception from admission to 105 days beyond the last dose of study intervention. Sexually active participants must use a combination of 2 of the following methods of contraception, including at least 1 so-called 'barrier' method:
   a. hormonal contraceptives (oral, transdermal patches, vaginal, or injectable)
   b. intrauterine device with or without hormones
   c. condom, diaphragm, or cervical cap ('barrier' method), and
   d. sexual abstinence.

Contraceptive requirements do not apply for participants who are exclusively in a same-sex relationship. Additional guidance is provided in Section 10.4, Appendix 4.

Weight

4. Have a body mass index of 18 to 32 kg/m^2, inclusive.

Type of Participant and Disease Characteristics

5. Are reliable and willing to make themselves available for the duration of the study and are willing to follow CRU-specific study procedures.
6. Have clinical laboratory test results within normal reference range for the population or CRU, or results with acceptable deviations that are judged not clinically significant by the investigator.

Informed Consent

7. Capable of giving signed informed consent as described in Section 10.1.2, Appendix 1, 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 they meet any of the following criteria at screening, unless otherwise noted:

Medical Conditions

1. Have a history or presence of medical illness including, but not limited to, any cardiovascular, hepatic, respiratory, hematological, endocrine, psychiatric or neurological disease, convulsions, or any clinically significant laboratory abnormality that, in the judgment of the investigator, indicate a medical problem that would preclude study participation.
2. Any abnormalities identified following a physical examination of the participant that, in the opinion of the investigator, would jeopardize the safety of the participant or interfere with study conduct if they took part in the study.
3. Positive SARS-CoV-2 virus nasopharyngeal polymerase chain reaction test at Day -1.
4. Contact with SARS-CoV-2-positive or COVID-19 patient within the last 14 days prior to admission to the CRU.
5. In the opinion of the investigator, are considered to be a danger to themselves or who have answered “yes” to either Question 4 or Question 5 on Suicidal Ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS); or answered yes to any of the suicide-related behaviors on the Suicidal Behavior portion of C-SSRS; and the ideation and behavior occurred within the past 6 months.

6. Have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study. In addition, participants with the following findings will be excluded:

    a. Confirmed Fridericia's corrected QT (QTcF) interval >450 msec for men and >470 msec for women; one repeat ECG may be performed if required.

7. Have a history of clinically significant multiple or severe drug allergies or severe posttreatment hypersensitivity reactions, which in the opinion of the investigator, may hamper participation in the study.

8. Show evidence of human immunodeficiency virus (HIV) and/or positive human HIV antibodies, hepatitis C and/or positive hepatitis C antibody, or hepatitis B and/or positive hepatitis B surface antigen.

9. Have an abnormal blood pressure (supine) defined as a diastolic blood pressure >90 or <45 mmHg and/or a systolic blood pressure >160 or <90 mmHg. Retesting may occur once during the screening visit within 2 hours of the initial abnormal blood pressure measurement at the discretion of the investigator.

Prior/Concomitant Therapy

10. Have received treatment with biologic agents (such as monoclonal antibodies, including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.

11. Are unwilling to stop herbal supplements, over the counter, or prescription medicines, including drugs that are known inducers or inhibitors of CYP3A4 or 2C9 (see Section 10.6, Appendix 6, for a list of excluded medications), within 14 days prior to study intervention administration and for duration of study. An exception is for paracetamol at doses of ≤2 grams/day.

Prior/Concurrent Clinical Study Experience

12. Are currently enrolled in a clinical drug study or are within 30 days prior to (the first) drug administration or in more than 4 other drug studies in the 12 months prior to (the first) drug administration involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

13. Have previously completed or withdrawn from this study or any other study investigating this study intervention.

Other Exclusions

14. Participants with a history of drug abuse which, in the opinion of the investigator, is clinically significant or who test positive for drugs of abuse at screening or admission.

15. Have an average weekly alcohol intake that exceeds 21 units per males and 14 units for females per week (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).

16. Are unwilling to stop alcohol and caffeinated beverage consumption and smoking/use of tobacco while resident in the CRU.
17. Are unwilling to comply with the dietary restrictions required for this study, including the avoidance of, by 5 days prior to study intervention administration until the final ambulatory visit, the ingestion of fruits, sauces, and juices containing furanocoumarins that irreversibly inhibit CYP3A4. The following fruits, sauces, and juices are excluded: grapefruit, Seville oranges, pomelos, cranberries, Goji berries, and apples.
18. Are unable to successfully complete a capsule swallow test, which may be performed at screening for any participant assigned to a dose level where more than 3 capsules will be administered.
19. Have donated blood of more than 450 mL within 60 days prior to (the first) drug administration.
20. Are the investigator or CRU personnel directly affiliated with this study or are immediate family members of the investigator or CRU personnel. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
21. Are Eli Lilly and Company (Lilly) employees or contractors or an immediate family member of employees or contractors.

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

Standard meals, according to the CRU SOPs, will be provided during the stay at the CRU. During the fasted dosing periods, participants will fast overnight for at least 8 hours prior to the morning dose and then fast for at least 4 hours after the morning dose. During the food-effect period, a standardized high-fat meal or a light breakfast will be provided at the CRU 30 minutes prior to dose administration following an overnight fast of at least 8 hours. During Part B on Days 1 and 5, participants will fast overnight for at least 8 hours prior to the morning dose and then fast for at least 4 hours after the morning dose. On days 2 through 4 participants can eat according to site procedure for non-fasted dosing. Unless otherwise instructed by CRU personnel, participants will maintain their own dietary habit throughout the ambulatory periods of the study.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants will need to abstain from alcohol and caffeinated drinks from 48 hours prior to entry in the CRU until discharge.

Smoking outside the CRU should be restricted to 5 cigarettes a day or fewer during study participation.

5.3.3. Activity

Participants must refrain from new strenuous exercise routines 48 hours prior to each CRU confinement period and throughout their CRU stay.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the discretion of the investigator with sponsor's approval. If a participant is rescreened, that participant would be assigned a new participant number and would need to sign a new ICF.

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 Intervention(s) Administered

The study intervention, LY3526318, will be administered orally. Doses are planned to range between 100 mg and 1000 mg once daily (see Section 4.3, Dose Justification), and de-escalation is permitted.

Part A

The planned dose levels range from 100 mg to 1000 mg. LY3526318 or matching placebo will be administered to participants as a single dose by trained CRU personnel. Up to 3 single dose levels will be assessed in a fasted state (fasting at least 8 hours prior to and at least 4 hours after dosing). Up to two of these dose levels that were assessed in a fasted state will also be assessed in a fed state (a high-fat meal or a light breakfast 30 minutes prior to dosing). Dose levels may be modified based on safety and available PK but will not exceed the NOAEL.

Part B

The planned dose levels in Part B will not exceed those studied in Part A. After review of the data from Part A, Part B doses may be administered in a fed or fasted state or either on different days.

CCI

The placebo capsules will be identical in appearance to LY3526318 and are prepared extemporaneously. Placebo capsules will contain only microcrystalline cellulose.

LY3526318 and placebo capsules should be stored at 15°C to 30°C.

6.2. Preparation/Handling/Storage/Accountability

- 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, monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual. Note: in some cases, sites may destroy the study intervention if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of study intervention.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Method of Treatment Assignment

On Day 1 participants will be assigned a unique number (randomization number). Participants who meet all criteria for enrollment will be randomly assigned to receive either LY3526318 or placebo. A randomization table will be created using a computer software program. The randomization list will be provided to the designated unblinded CRU staff for participant randomization and dispensing purposes and kept in a secure location, accessible to the designated unblinded CRU staff only.

Participants, investigators, and CRU personnel performing trial-related activities or with the ability to influence study outcomes will be blinded with regards to LY3526318 and placebo treatment (Figure 1.2). To preserve the blinding of the sponsor, only a minimum number of Lilly personnel may have access to the randomization table and codes before the study is complete. Clinical research unit personnel who are responsible for participant-specific study intervention preparation will not be blinded; laboratory personnel, including bioanalytical laboratory personnel, will also not be blinded.

A sealed envelope that contains the study intervention assignment for each participant will be provided to the investigator. The investigator (or representative) will retain the sealed envelope in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the sponsor.

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

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician (CRP) for the participant to continue in the study.

6.3.2. Selection and Timing of Doses

All doses of the study intervention will be administered at the CRU approximately between 0800 hours and 1100 hours.

A trained CRU personnel member will administer all doses of the study intervention at the CRU.

6.4. Study Intervention Compliance

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 electronic case report form (eCRF). 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 examine each participant's hands and mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Drugs that are known inducers or inhibitors of CYP3A4 or 2C9 are to be specifically excluded (see Section 10.6, Appendix 6, for a list of excluded medications). Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) 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, and
- dosage information, including dose and frequency for concomitant therapy of special interest.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol, at doses of ≤2 grams/day, is permitted for use at any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

6.6. Dose Modification

6.6.1. Dose Escalation

The decision to proceed to the next dose level (either an increase or a decrease) will be made by the study team and the investigator based on safety, tolerability, and preliminary PK data obtained at the prior dose level.

By nature of being a dose escalation study, data will be evaluated on an ongoing basis until the mean LY3526318 exposure is projected to reach the NOAEL.

No dose decision can occur without prior discussion and agreement between the investigator and the sponsor's medical monitor.

In the SAD, the decision to escalate to the next dose will be based on vital signs, AEs, ECGs, and clinical laboratory assessments from predose to Day 4 from at least 4 individuals randomized to LY3526318. Pharmacokinetics data through at least 24 hours after the current dose will be used to inform the dose escalation decision.

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

After review of these data, the investigator and sponsor will make an agreement on the appropriate dose for the next cohort/dose level. The magnitude of dose escalations may be reduced following data review, but subsequent escalations cannot be increased by more than approximately 3-fold (a half-log increment). Doses lower than the initial dose of 100 mg may also be administered.

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

1. a single participant experiences a SAE or clinically significant event that is related to LY3526318 administration, or
2. if >3 participants at 1 dose level experience moderate treatment-related AEs that impair normal activities.

6.7. Intervention after the End of the Study

Study intervention will not be made available after completion of the study to participants.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

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 early discontinuation procedures. See the SoA, Section 1.3, for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Discontinuation due to a hepatic event or liver test abnormality:

Laboratory tests (Section 10.2, Appendix 2), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin, gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 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 participants 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 ≥2x baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; 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 (eg, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, and 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.

If a clinically significant finding is identified (including, but not limited to clinically significant changes from baseline in 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.

If a participant becomes pregnant during the study, refer to Section 8.3.5.

See the SoA (Section 1.3) 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 (eg, 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 enrolled in any other clinical study involving an investigational product or enrolled 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, or
- receives a positive SARS-CoV-2 virus test or evidence of COVID-19 during the study

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 the SoA (Section 1.3) 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 identify 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 (Schedule of Activities), 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, or an independent third party, 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 (see Section 10.1.7).

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3.). 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 10.2 lists the laboratory tests that will be performed for this study.

Section 10.2.1 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.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

A complete or directed physical examination will be conducted according to the SoA (Section 1.3).

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded at times noted in the SoA (Section 1.3).

A directed physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

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) and as clinically indicated.

It is suggested that systolic and diastolic blood pressure and heart rate should be measured in a supine position just after the ECG (if the ECG is recorded at the same time point) and for a

minimum of 10 minutes before any other procedures according to the SoA, (Section 1.3). These procedures should be performed prior to collection of blood samples if scheduled at the same time.

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.

8.2.3. Electrocardiograms

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

Participants must be supine for approximately 10 minutes before ECG collection and remain supine but awake during ECG collection. Triplicate ECG's should be obtained approximately 1 minute between tracings. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

All ECGs recorded should be stored at the CRU.

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 as an AE in the electronic data capture (EDC) system.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the CRU 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 (eg, 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 replicate ECGs from each time point.

8.2.4. Clinical Safety Laboratory Assessments

Refer to Section 10.2, Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

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 case report form (eCRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 72 hours after the last dose of study intervention 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 (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF on the AEs page. Serious Adverse events will be reported on the Sponsor Form and faxed to Lilly Global Patient Safety.

8.2.5. Safety Monitoring

The sponsor will monitor safety data throughout the course of the study.

Lilly will review SAEs within the time frames mandated by company procedures. The medical monitor will periodically review the following data:

- trends in safety data
- laboratory analytes, and
- SAEs and non-SAEs, including monitoring of GI events, hypoglycemia, injection-site reactions, hypersensitivity reactions, and reported and adjudicated pancreatitis.

When appropriate, the Lilly medical monitor will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

8.2.5.1. Hepatic Monitoring

Laboratory tests (Section 10.5, Appendix 5), including ALT, AST, ALP, TBL, direct bilirubin, 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 1 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 participants 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 ≥2x baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; 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 (eg, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, and 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.

8.3. Adverse Events and Serious Adverse Events

Adverse events 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 they 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 or study (see Section 7).

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

All SAEs will be actively collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3) and until 30 days after the last dose for spontaneously reported SAEs.

All AEs will be collected from the signing of the ICF until the follow-up visit OR participation in the study has ended.

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

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study intervention. However, if an SAE occurs after signing the ICF, but prior to receiving study intervention, 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.

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

The designated medical monitor of the sponsor will monitor safety data throughout the course of the study. The sponsor and/or its designee will review SAEs within appropriate timeframes to meet reporting obligations imposed by regulatory authorities. All SAEs and unexpected AEs for this study will be reported to regulatory authorities in accordance with local laws, directives, and regulations (Section 8.3.4).

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, assessing causality of AE and SAE, and the procedures for completing and transmitting SAE reports are 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 of an SAE by the investigator to the sponsor 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, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 30 days after the final visit, which corresponds to more than 5 terminal half-lives after the last dose of LY3526318.

Details of all pregnancies in female partners of male participants will be collected until 90 days after last administration of LY3526318.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning about the pregnancy and should follow the procedures outlined Appendix 4 (Section 10.4).

Abnormal pregnancy outcomes (eg, 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.

The sponsor collects product complaints on investigational products 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 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 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 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 provided in the form should be utilized.

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.

8.4. Treatment of Overdose

An overdose is not anticipated in the study, as a trained CRU member will administer all study intervention.

In case of overdose, use supportive therapy. There is no known antidote to LY3526318 therapy.

Any dose of LY3526318 greater than the daily dose assigned through randomization will be considered an overdose. Treatment for overdose is supportive care.

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 LY3526318 can no longer be detected systemically (at least 14 days)
3. obtain a plasma sample for PK analysis within 14 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis), and
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

For all participants, blood samples of up to 3 mL each for the determination of concentrations in plasma of LY3526318 and metabolite(s) of interest will be collected at time points specified in the SoA (Section 1.3). Instructions for the collection and handling of blood samples will be provided by the sponsor.

Sampling times for PK evaluation are provided as a guidance to be adhered to as closely as possible. The actual date and time (24-hour clock time) of each sample collection must be recorded. Predose samples should be obtained between waking up and dosing. The sampling schedule may be modified following a review of PK data from the initial cohorts.

A maximum of 3 additional PK samples may be drawn at other time points during the study if warranted and agreed upon by both the investigator and the sponsor. A PK sample should be obtained at the early termination visit, if applicable.

8.5.1. Bioanalysis

Samples will be analyzed for LY3526318 and LSN3528305 at Pharmaceutical Research Associates using a validated method. Placebo samples will not be analyzed.

Bioanalytical samples collected to measure study intervention concentrations will be retained for a maximum of 1 year following the last participant visit for the study.

Residual PK plasma samples may be used for LY3526318 metabolite identification.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Not applicable.

8.10. Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

No formal hypothesis testing will occur. Exposure, safety, and tolerability endpoints will be summarized for the SAD and MD portions descriptively by dose and fed status and also provided in patient listings.

9.2. Sample Size Determination

A maximum of 16 participants (SAD and MD cohorts of size 8, randomized 3:1) will be randomly assigned to study intervention such that approximately 16 evaluable participants complete the study.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis	All participants who received at least 1 dose of study treatment and have at least 1 postbaseline evaluable PK sample.

Abbreviations: ICF = informed consent form; PK = pharmacokinetic.

9.3.1. Study Participant Disposition

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

9.3.2. Study Participant Characteristics

Participant demographics (age, sex, race, ethnicity, height, and weight) will be summarized.

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of the sponsor and its designee.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan and the clinical study report. 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.

The statistical analysis plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section

is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

Pharmacokinetic analyses will be conducted on data from all participants who received a dose of LY3526318 and have evaluable PK.

Safety analyses will be conducted for all enrolled participants who received study intervention, whether or not they completed all protocol requirements.

For continuous variables, summary statistics will include the number of participants, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of participants, frequency, and percentages. Additional analyses of the data will be conducted as deemed appropriate and may be fully detailed in a statistical analysis plan.

9.4.1. Safety Analyses

All study intervention and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. Summary statistics for AEs and SAEs will be provided by treatment arm and for all placebo participants combined.

Safety assessments include laboratory tests, vital signs, ECGs, and physical examination. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed as required.

9.4.2. Pharmacokinetic Analyses

All participants who have evaluable plasma LY3526318 concentrations will be included in the PK analyses. Pharmacokinetic parameter estimates for LY3526318 and relevant metabolites will be computed using standard noncompartmental methods of analysis.

9.4.2.1. Pharmacokinetic Parameter Estimation

Primary plasma LY3526318 and relevant metabolite PK endpoints, including but not limited to the AUC from time zero to the last measurable concentration (AUC_{0-t}), AUC_{0-24}, AUC during a dosing interval (AUC_{τ}), AUC from zero to infinity (AUC_{0-inf}), C_{max}, and the time to C_{max} (t_{max}) will be calculated using noncompartmental methods. Other PK parameters, such as apparent $t_{1/2}$, apparent clearance (CL/F), apparent volume of distribution (Vz/F), and apparent volume of distribution at steady state (Vss/F) will also be calculated.

For the food-effect exploration, the geometric means of the ratios of the log-transformed exposure measures (AUC, C_{max}) between the fed and fasted conditions and the 90% confidence intervals (CIs) for the ratios will be reported. Time to C_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, approximate 90% CIs, and p-values from the Wilcoxon test will be calculated.

Pharmacokinetic parameters will be calculated individually and presented with summary statistics. Additional PK parameters may be calculated if deemed appropriate.

Mean and individual plasma concentration versus time curves will be graphically presented for LY3526318 and possibly metabolites. Population PK modeling may be performed, with or without pooling with observations from other studies.

9.4.2.2. Pharmacokinetic Statistical Inference

Dose proportionality may be assessed using the power model approach (Smith et al. 2000), as appropriate. Additional analyses, including but not limited to population PK modeling with or without data from other studies, will be performed as deemed necessary upon review of the data.

9.4.2.3. Other Pharmacokinetic Analyses

Other analyses, such as assessment of the relationship between LY3526318 concentration and QTcF, may be conducted if appropriate based on the data.

9.4.3. Other Safety Analyses

All safety analyses will be made on the Safety Population.

9.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

Although no formal interim analyses are planned to occur, interim access to safety and PK data to support dose escalation and selection will occur, as outlined in Section 4.1.

9.6. Data Monitoring Committee

A Data Monitoring Committee will not be used in 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 Harmonization (ICH) Good Clinical Practice (GCP) Guidelines, and
- applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, 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, and
- providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (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 (CTA).

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. 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 reconsented 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 must be kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the contract research organization (CRO). 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 CRO 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.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, 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, if applicable.

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 (eg, risk-based initiatives in operations and quality such as Risk Management, 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 (eg, CROs).

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 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, the 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 the sponsor, 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 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. If applicable, 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 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 from complaint forms submitted to the 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.

The definition of what constitutes source data can be found in the data management plan.

10.1.7. Study and Site Start and Closure

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

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, or
- discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(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 participant and assure appropriate participant therapy and/or follow-up.

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.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed below will be performed by a 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 10.4 (Appendix 4: Contraceptive Guidance for Men and Women).

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	**Clinical Chemistry**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Glucose (fasting)
Mean cell volume	Blood urea nitrogen (BUN)
Mean cell hemoglobin	Total cholesterol
Mean cell hemoglobin concentration	Total protein
Leukocytes (WBC)	Albumin
Platelets	Total bilirubin
Differential WBC (Absolute counts and %) of:	Alkaline phosphatase (ALP)
Neutrophils	Aspartate aminotransferase (AST)
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Creatinine
Eosinophils	Gamma-glutamyl transferase (GGT)
Basophils	
	Alcohol Urine Test
Urinalysis Dipstick	**Urine Drug Screen[a]**
Specific gravity	Amphetamine (including XTC)
pH	Barbiturates
Protein	Benzodiazepine
Glucose	Cannabinoids
Ketones	Cocaine
Bilirubin	Methadone
Urobilinogen	Opiates
Blood	
Nitrite	Hepatitis B surface antigen[b]
	Hepatitis C antibody[b]
	HIV[b]
	FSH[b]
	Pregnancy Test (Serum, Quantitative β-hCG)

Abbreviations: β-hCG = beta subunit of human chorionic gonadotropin; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cell; XTC = MDMA (methylenedioxymethamphetamine); WBC = white blood cell.

[a] Urine drug screen may be repeated prior to admission to the clinical research unit and at other times as indicated in the Schedule of Activities.

[b] Performed at screening only.

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 J2D-MC-CVAC Sampling Summary

Part A			
Purpose	**Blood Volume per Sample (mL)**	**Number of Blood Samples**	**Total Volume (mL)**
Screening tests[a]	11.5	1	11.5
Clinical laboratory tests[a]	6.5	13	84.5
Pharmacokinetics	3	45	135
Total	21	59	231
Part B			
Purpose	**Blood Volume per Sample (mL)**	**Number of Blood Samples**	**Total Volume (mL)**
Screening tests[a]	11.5	1	11.5
Clinical laboratory tests[a]	6.5	8	52
Pharmacokinetics	3	21	63
Total	21	30	126.5

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

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 <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though they 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 an overdose should be reported regardless of sequelae.
Events <u>NOT</u> 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 (eg, 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 preexisting 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 the definition above, then it cannot be an SAE even if serious conditions are met (eg, 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 the 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 preexisting 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 (eg, 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 one 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. 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 (eg, 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 the 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 the 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 the 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 and SAE reported during the study and assign it to one 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 an 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 that 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 the 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 the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one 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 the 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 the 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 the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via Paper CRF
• Facsimile transmission or secure e mail 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 CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the Clinical Trial Serious Adverse Event (SAE) Instruction Guidelines for Completion of the SAE and Pregnancy Reporting forms.

10.4. Appendix 4: Contraception Guidance for Men and Women

The table below describes contraception guidance for men.

Topic	Guidance
For all men	Should refrain from sperm donation for the duration of the study and for ≥90 days after the last dose of study intervention
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 duration of the study and for ≥90 days after the last dose of study intervention
Contraception for men in exclusively same-sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

The table below provides examples of highly effective, effective, and unacceptable methods of contraception.

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 the only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  o condom with spermicide
	  o diaphragm with spermicide, or
	  o female condom with spermicide
	Note: The barrier method must include the use of a spermicide (ie, condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.

Methods	Examples
Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • postcoital douche • lactational amenorrhea

- Women of childbearing potential (WOCBP) may participate in this trial.
- Women not of childbearing potential may participate in this trial.

Word/Phrase	Definition
Women of childbearing potential	Females are considered a woman of childbearing potential if • they have had at least 1 cycle of menses, or • they have Tanner 4 breast development. Any amount of spotting should be considered menarche. If Tanner Staging of breasts is performed as a part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical Trials regarding Tanner Staging.
Women not of childbearing potential	Females are considered women not of childbearing potential if • they have a congenital anomaly such as Mullerian agenesis, • they are infertile due to surgical sterilization, or • they are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral oophorectomy, tubal ligation.
Postmenopausal state	The post-menopausal state should be defined as: 1. A woman at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note 2. A woman at least 40 years of age up to 55 years old with an intact uterus, not on hormone therapy,[a] 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 3. A woman at least 55 years of age 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 [a] 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.

Please see guidance for specific participant populations below:

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle

Must…	Must not…

agree to either remain abstinent, or	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of the trial, or

stay in a same-sex relationship without sexual relationships with males, as their preferred and usual lifestyle	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle

Topic	Explanation
Pregnancy testing	Negative urine result at screening followed by a negative serum result within 24 hours prior to treatment exposure
	Note: subsequent pregnancy testing is compound specific.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective (<1% failure rate)

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with Lilly or its designee medical monitor.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	Anti-nuclear Antibody[a]
AST	Alkaline Phosphatase Isoenzymes[a]
GGT	Anti-Smooth Muscle Antibody (or anti-actin
CPK	antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; Lilly = Eli Lilly and Company; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated or local laboratory.

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

10.6. Appendix 6: List of Excluded Concomitant Medications

This is a list of moderate and strong CYP3A4 and CYP2C9 inhibitors and inducers (effectors) to inform clinical development for CYP3A4 and CYP2C9 substrates. This list is not exhaustive, and the sponsor should be consulted in the case of any questions or uncertainty.

Strong and moderate clinical inducers of CYP3A4 (Updated 04 Mar 2019)

Drug	Special Status	Inducer Category
Aminoglutethimide	VL	Strong
Apalutamide		Strong
Avasimibe		Strong
Carbamazepine		Strong
Enzalutamide		Strong
fosphenytoin (see also phenytoin)		Strong
Ivosidenib		Strong
Lumacaftor		Strong
Mitotane		Strong
Phenobarbital		Strong
Phenytoin		Strong
Rifabutin		Strong
rifampicin (rifampin)		Strong
Rifapentine		Strong
St. John′s wort	SF	Strong
Almorexant		Moderate
Bosentan		Moderate
Dabrafenib		Moderate
Daclatasvir and asunaprevir and beclabuvir		Moderate
Danshen (*Salvia miltiorrhiza*)	SF	Moderate
Efavirenz		Moderate
Encorafenib	P	Moderate
Etravirine		Moderate
Faldaprevir and efavirenz		Moderate
Genistein	SF	Moderate
Lesinurad		Moderate
Lersivirine		Moderate
Lopinavir (alone)		Moderate
Lorlatinib		Moderate
Modafinil		Moderate
Nafcillin (intravenous)	VL	Moderate
Pentobarbital	VL	Moderate
Primidone		Moderate
Telotristat ethyl		Moderate
Thioridazine	VL: available in the UK	Moderate
Tipranavir and ritonavir		Moderate
Tocilizumab (atlizumab)	NT	Moderate

Strong and moderate clinical inducers of CYP3A4 (Updated 04 Mar 2019)

Abbreviations: IL-6 = interleukin 6; NT = nontraditional mechanism reverses the IL-6-mediated suppression of CYP3A activity in patients with rheumatoid arthritis; P = probable moderate inducer based on observed autoinduction; SF = supplement or food/drink; VL = very limited use.

Strong and moderate clinical inhibitors of CYP3A4

Drug	Special status	Inhibition category
Boceprevir		Strong
Clarithromycin		Strong
Cobicistat		Strong
Conivaptan		Strong
Danoprevir and ritonavir		Strong
Diltiazem		Strong
Elvitegravir and ritonavir		Strong
Grapefruit juice	SF	Strong
Idelalisib		Strong
Indinavir and ritonavir		Strong
Itraconazole		Strong
Ketoconazole	VL	Strong
Lopinavir and ritonavir		Strong
Nefazodone	VL	Strong
Nelfinavir		Strong
Posaconazole		Strong
Ribociclib		Strong
Ritonavir		Strong
Saquinavir and ritonavir		Strong
Telithromycin		Strong
Tipranavir and ritonavir		Strong
Viekira Pak (paritaprevir and ritonavir and/or ombitasvir)		Strong
Voriconazole		Strong
Amprenavir		Moderate
Aprepitant		Moderate
Atazanavir (see atazanavir and ritonavir)		Moderate
Atazanavir and ritonavir		Moderate
Cimetidine		Moderate
Ciprofloxacin		Moderate
Clotrimazole		Moderate
Crizotinib		Moderate
Cyclosporine		Moderate
Darunavir		Moderate
Dronedarone		Moderate
Duvelisib		Moderate
Erythromycin		Moderate
Fluconazole		Moderate

Strong and moderate clinical inhibitors of CYP3A4

Drug	Special status	Inhibition category
Fluvoxamine		Moderate
Fosnetupitant and palonosetron		Moderate
Imatinib		Moderate
Indinavir		Moderate
Isavuconazole		Moderate
Ledipasvir/sofosbuvir		Moderate
Letermovir		Moderate
Magnolia vine (*Schisandra sphenanthera*)	SF	Moderate
Netupitant		Moderate
Nilotinib		Moderate
Tofisopam		Moderate
Verapamil		Moderate

Abbreviations: SF = supplement or food/drink; VL = very limited use.

Source: University of Washington Drug Interaction Database https://www.druginteractioninfo.org/ and Hansten PD, Horn JR. *Top 100 Drug Interactions of 2018: A Guide to Patient Management*. Freeland, WA: H&H Publications; 2018.

10.7. Appendix 7: Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_T	AUC during a dosing interval
AUC_{0-inf}	AUC from time zero to infinity
AUC_{0-t}	AUC from time zero to the last measurable concentration
AUC_{0-24}	AUC from time zero to 24 hours post dose
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.
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	apparent clearance
C_{max}	maximum observed drug concentration
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
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.
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization

Term	Definition
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
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.
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
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.
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 Boards

Term	Definition
Lilly	Eli Lilly and Company
MD	multiple 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
PK	pharmacokinetic(s)
QTcF	Fridericia's corrected QT interval
SAD	single-ascending dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
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.
SoA	Schedule of Activities
SOP	standard operating procedure
TBL	total bilirubin
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 C_{max}
TRPA1	transient receptor protein ankyrin-1
$t_{1/2}$	elimination half-life
Vss/F	apparent volume of distribution at steady state
Vz/F	apparent volume of distribution
WOCBP	women of childbearing potential

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