Protocol J2D-MC-CVAA (c)

A Safety, Tolerability, Pharmacokinetic, and Pilot Food Effect Study of Single- and Multiple-Ascending Doses of LY3526318 in Healthy Participants

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Confidential Information

LY3526318

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Clinical Protocol Electronically Signed and Approved by Lilly on date provided below.

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1 Protocol Synopsis

Title of Study:
A safety, tolerability, pharmacokinetic, and pilot food effect study of single- and multiple-ascending doses 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 strong clinical and preclinical evidence for TRPA1 antagonism in the alleviation of chronic pain. In humans, exogenous TRPA1 administration induces pain and nerve hyper-excitability. TRPA1 antagonists have been safe and well tolerated in healthy participants (ODM-108; NCT02432664) and in patients with diabetic neuropathy (GRC 17536; EU Clinical Trial Register 2012-002320-33). GRC 17536 has been efficacious for pain relief in a Phase 2a trial in patients with diabetic peripheral neuropathy. LY3526318 has been shown to be effective in preclinical pain models and will be further studied in patients with chronic pain after safety and pharmacodynamics have been characterized in healthy participants.

The first-in-human Phase 1 study will evaluate the safety, tolerability, and pharmacokinetic (PK) parameters of LY3526318 in healthy participants after oral administration. The study includes a single-ascending dose (SAD/Part A) and a multiple-ascending dose (MAD/Part B).

Objectives/Endpoints:

Objectives	Endpoints
Primary (Part A)	
To evaluate safety and tolerability of LY3526318 in healthy participants following a single oral dose	• AEs • SAEs
Primary (Part B)	
To evaluate safety and tolerability of LY3526318 in healthy participants following multiple once-daily oral doses for 14 days	• AEs • SAEs
Secondary (Part A)	
To evaluate the plasma pharmacokinetics of LY3526318 in healthy participants following a single oral dose	• AUC • C_{max} • t_{max}
Secondary (Part B)	
To evaluate the plasma pharmacokinetics of LY3526318 in healthy participants following multiple once-daily oral doses for 14 days	• AUC • C_{max} • t_{max}

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; SAE = serious adverse event; t_{max} = time to C_{max}.

Summary of Study Design, Treatment Arms, and Planned Duration:

Study J2D-MC-CVAA is a single-center, randomized, double-blind, placebo-controlled, SAD (Part A) and MAD (Part B) study of LY3526318 in healthy participants.

Part A - SAD

The single-ascending doses of LY3526318 or placebo will be administered, at planned dose levels of 10, 50, 100, 400, 800, and 1000 mg, in 7 cohorts of 8 participants each, except the 100-mg cohort that will include 12 participants. The dose levels may change subject to available safety and PK data review.

Participants in the first cohort (10 mg, Cohort 1) will not be stratified by sex. A fixed number of females and males will be randomized in Cohorts 2 and 3 and the participants will be stratified to ensure equal distribution between females and males. Cohorts administered above LY3526318 100 mg are anticipated to exceed the approximate 10x margin to the projected no-observed-adverse-event-level (NOAEL)-equivalent exposure for males; for this reason, only female participants will be enrolled at dose levels higher than 100 mg. Additionally, males will only be dosed through 100 mg if exposure data from previous cohorts supports this. Randomization to LY3526318 or placebo will be 3:1 within each cohort or stratum, respectively, except for Cohort 10.

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. A sentinel dosing strategy will be utilized for the first dose level (Cohort 1, 10 mg). Two participants will receive a sentinel dose (1 each with LY3526318 and placebo) and the remaining participants will be administered after review of safety data up to 48 hours postdose. Dose escalation from the 10-mg to 50-mg cohort may occur after review of safety data from at least 6 participants in the 10-mg cohort. Dose escalations to subsequent cohorts may occur after review of safety data and available PK data through 48 hours postdose from at least 6 participants in the prior cohort.

The effect of food on LY3526318 PK will be explored in only female participants enrolled in the 100-mg cohort and in the 400-mg cohorts. The initial dose will be administered after an approximately 8-hour fast, followed by a washout period of at least 1 week, and a second dose administration following a standardized high-fat meal. To ensure a sufficient number of females for the food effect assessment at 100-mg dose level, the 100-mg cohort will be expanded to 12 participants (8 females and 4 males). An additional cohort (Cohort 10) will assess the effect of food on LY3526318 PK in 8 female participants. All participants in this cohort will receive 100 mg LY3526318 with standardized high fat meal in an open-label, 3-way crossover manner (meal administered prior to dose, at 30 minutes and at 1 hour post dose).

Except for the second dose in the food effect assessment cohorts, all other doses are planned to be administered after an approximately 8-hour fast. However, following a review of the 100-mg and/or 400-mg fed and fasted data, subsequent cohorts may be administered with food.

Participants will return to the CRU for a final follow-up visit approximately 9 days after study drug administration or after the final fed-state dose for female participants in the 100- and 400-mg cohorts.

Part B - MAD

The multiple-ascending doses of LY3526318 or placebo will be administered, at planned dose levels of 100, 400, and 1000 mg, once daily for 14 days in 3 cohorts of 8 female participants each. It is likely that 1 or more dose levels in Part B may exceed the approximate 10x margin to the projected NOAEL-equivalent exposures for males; for this

reason, only female participants will be enrolled in Part B. The planned dose levels may be updated following a review of safety and PK data from Part A and they will not exceed those studied in Part A.

The first cohort of Part B will be administered LY3526318 following a review of Part A safety and PK data. Dose escalations to subsequent cohorts may occur after review of safety data and available PK data through 14 days from at least 6 participants in the prior cohort.

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 Days 15, 18, and 19 for Cohorts 7, 8, and 9, respectively. Within each cohort, participants will be randomly assigned to receive LY3526318 or placebo in a 6:2 ratio.

LY3526318 or matching placebo is planned to be administered in an 8-hour fasting state once daily for 14 days. However, following a review of the food effect data from Part A, all doses may be administered with food.

Participants will return to the CRU for a final visit on Day 23.

Number of Participants:
Part A: Approximately 60 participants will be randomized to achieve 8 evaluable participants per cohort (6 LY3526318:2 placebo), except for the 100-mg cohort that will include 8 evaluable females and 4 evaluable males (females: 6 LY3526318:2 placebo; males: 3 LY3526318:1 placebo) and 100-mg food assessment cohort (Cohort 10) that will include 8 evaluate females and all will receive LY3526318 in an open-label manner.

Part B: Approximately 24 participants will be randomized to achieve 8 evaluable participants per cohort (6 LY3526318:2 placebo).

Additional cohorts of up to 8 participants each may be enrolled in either part of the study. Such additional cohorts may be enrolled in case intermediate or additional dose level(s) need to be studied or additional food effect need to be studied at other than planned dose levels.

Statistical Analysis:

Safety: The primary safety endpoints are the numbers of treatment-emergent serious adverse events and adverse events. Summary statistics for each cohort will be provided by dose level and for all placebo participants combined.

Pharmacokinetic Parameters: Plasma PK parameters for LY3526318 and metabolite(s) of interest will be calculated using noncompartmental methods after single- and multiple-dose administration. Pharmacokinetic parameters will be summarized by dose level using descriptive statistics. Mean and individual plasma concentration versus time curves for LY3526318 will be represented graphically.

2 Schedule of Activities

Table 2-1 Study Schedule Protocol J2D-MC-CVAA: Part A Cohorts 1-6 (SAD)

	S	Treatment/ In CRU				Posttreatment	ED[a]
Study Day	**≤28**	**-1**	**1**	**2**	**3**	**10**	
Visit Window (days)						**±2**	
Visits	**1[b]**	**2[c]**				**3**	
CRU admission		X					
CRU discharge					X		
Participant information (including I/E criteria)	X	X					
Informed consent	X						
Medical history	X						
Height	X						
Weight	X		X			X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	C	C
Urine drug screen and ethanol test	X	X					
Vital signs including temperature	X	X	X (predose, 2 h, 4 h, 8 h)	X	X	X	X
Hematology and clinical chemistry	X	X		X[d]	X[d]	X	X
Urinalysis[e]	X	X					
Pregnancy test (serum beta-hCG)[f]	X	X				X	X
HIV, HCV, HBsAg	X						
ECG[g]	X		X (predose, 2 h, 4 h, 8 h)			X	X
C-SSRS	X	X				X	X
Randomization			X				
Study drug administration[h]			X				
PK blood sample[i]			X	X	X		X
PK 24-hour urine collection[j]			← X →				
Adverse event	← X →						
Concomitant medications	← X →						

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hour; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; PK = pharmacokinetics; S = screening; SAD = single-ascending dose.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of the first dose being administered.

[c] All participants will remain in the CRU until completion of Day 3 procedures.

[d] Hematology and clinical chemistry sample to be taken in the morning.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest.

[h] All doses are planned to be administered in a fasting state (at least 8 hours predose and 4 hours postdose), with the exception of the 100- and 400-mg cohorts. In both cohorts, the initial dose will be administered to participants in the fasted state (at least 8 hours predose and 4 hours postdose), followed by a washout period of at least 1 week and a second dose administration after a standardized high-fat meal. Only female participants will undergo fed dose administration in the 100-mg cohort. Following a review of the 100- and 400-mg fed and fasted data, subsequent cohorts may be administered with food. The exact time study drug is administered will be recorded.

i On Day 1, PK samples will be collected at time zero (predose) and at approximately 1, 2, 4, 6, 8, and 12 hours after dosing. One PK sample will be taken at 24 and 48 hours postdose (Days 2 and 3), and if applicable, at the ED Visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time collection intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. The ±5% time window also applies to the start and end times of urine collection intervals. Post-assay remainder PK plasma samples may be stored for metabolite identification.

j Urine collection interval is 0 to 24 hours postdose. The total urine volume of the 0- to 24-hour collection will be recorded.

Table 2-2 Study Schedule Protocol J2D-MC-CVAA: Part A Cohort 10 (3-Period Food Effect Cohort)

	S	Treatment/ In CRU					Posttreatment	ED[a]
Study Day (visit window)	**≤28**	**-1**	**1**	**2**	**3**	**4**	**10 (± 2)**	
Period		**1-3**					**3**	**1-3**
Visits	**1[b]**	**2[c]**					**3**	
CRU admission		X						
CRU discharge						X		
Participant information (including I/E criteria)	X	X						
Informed consent	X							
Medical history	X							
Height	X							
Weight	X		X				X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	C	C
Urine drug screen and ethanol test	X	X						
Vital signs including temperature	X	X	X (predose, 2 h, 4 h, 8 h)	X	X		X	X
Hematology and clinical chemistry	X	X		X[d]	X[d]		X	X
Urinalysis[e]	X	X						
Pregnancy test (serum beta-hCG)[f]	X	X					X	X
HIV, HCV, HBsAg	X							
ECG[g]	X		X (predose, 2 h, 4 h, 8 h)				X	X
C-SSRS	X	X					X	X
Randomization			X[h]					
Study drug administration[i]			X					
PK blood sample[j]			X	X	X	X		X
PK 24-hour urine collection[k]			← X →					
Adverse event	← X →							
Concomitant medications	← X →							

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hour; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; PK = pharmacokinetics; S = screening; SAD = single-ascending dose.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of the first dose being administered.

[c] All participants will remain in the CRU until completion of Day 4 procedures.

[d] Hematology and clinical chemistry sample to be taken in the morning.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest.

[h] randomization will occur during first period only.

[i] Doses are planned to be administered as follows in each period:

- Period 1-Fed standardized high fat meal to start 30 minutes prior to dose administration
- Period 2-Fasted at least 8-hours predose with a standardized high fat meal administered 30 minutes post dose
- Period 3-Fasted at least 8-hours predose with a standardized high fat meal administered 1 hour post dose

Periods will be separated by a washout of at least 1 week. The meals administered in all treatment periods should be consumed within 30 minutes. The exact time study drug is administered will be recorded.

[j] In each treatment period, on Day 1, PK samples will be collected at time zero (predose) and at approximately 1, 2, 4, 6, 8, and 12 hours after dosing. One PK sample will be taken at 24, 48, and 72 hours postdose (Days 2, 3, and 4), and if applicable, at the ED Visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time collection intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. The ±5% time window also applies to the start and end times of urine collection intervals. Post-assay remainder PK plasma samples may be stored for metabolite identification.

[k] Urine collection interval is 0 to 24 hours postdose. The total urine volume of the 0- to 24-hour collection will be recorded.

Table 2-3 Study Schedule Protocol J2D-MC-CVAA: Part B (MAD)-Cohort 7

	S	Treatment/In CRU								Post treatment	ED[a]
Study Day	**≤28**	**-1**	**1**	**2**	**3**	**5**	**8**	**14**	**15**	**23**	
Visit Window (days)										**±2**	
Visits	**1[b]**	**2**								**3**	
CRU admission		X									
CRU discharge									X		
Participant information (including I/E criteria)	X	X									
Informed consent	X										
Medical history	X										
Height	X										
Weight	X		X							X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	D	D		C	C
Urine drug screen and ethanol test	X	X									
Vital signs including temperature[c]	X	X	X	X	X	X	X	X		X	X
Hematology and clinical chemistry[d]	X	X		X			X	X		X	X
Urinalysis[e]	X	X									
Pregnancy test (serum beta-hCG)[f]	X	X								X	X
HIV, HCV, HBsAg	X										
ECG[g]	X		X					X		X	X
C-SSRS	X	X							X	X	X
Randomization			X								
Study drug administration[h]			← X →								
PK blood sample[i]			X	X	X	X	X	X	X		X
Adverse event	← X →										
Concomitant medications	← X →										

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hours; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; MAD = multiple-ascending dose; PK = pharmacokinetic; S = screening.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of first dose administration.

[c] Vital signs and temperature should be measured at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose; predose on all other indicated dosing days.

[d] Hematology and chemistry sample should be collected predose on stipulated visits.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose.

[h] Study drug will be administered once daily in the CRU through Day 14, and the exact time of administration will be recorded. All doses are planned to be administered in a fasting state; however, following a review of the food effect data from Part A, all doses may be administered with food. Fasting on PK sampling days is defined as at least 8 hours predose and 4 hours postdose. Fasting on non-PK and predose only PK sampling days is defined as at least 8 hours predose and 2 hours postdose on all other indicated days.

[i] On Days 1 and Day 14, PK samples will be collected at time zero (predose) and at approximately at 1, 2, 4, 6, 8, and 12 hours after dosing. On Day 2 (at predose) and on Day 15 (prior to discharge), 1 PK sample will be taken at 24 hours postdose. Predose PK samples will also be obtained on Days 3, 5, and 8. If applicable, a sample will be collected at the ED visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. Post-assay remaining PK plasma samples may be stored for metabolite identification.

Table 2-4 Study Schedule Protocol J2D-MC-CVAA: Part B (MAD)-Cohort 8

	S	Treatment/In CRU											Post treatment	ED[a]
Study Day	**≤28**	**-1**	**1**	**2**	**3**	**5**	**8**	**14**	**15**	**16**	**17**	**18**	**23**	
Visit Window (days)													**±2**	
Visits	**1[b]**	**2**											**3**	
CRU admission		X												
CRU discharge												X		
Participant information (including I/E criteria)	X	X												
Informed consent	X													
Medical history	X													
Height	X													
Weight	X		X										X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	D	D	D	D	D		C	C
Urine drug screen and ethanol test	X	X												
Vital signs including temperature[c]	X	X	X	X	X	X	X	X					X	X
Hematology and clinical chemistry[d]	X	X		X			X	X					X	X
Urinalysis[e]	X	X												
Pregnancy test (serum beta-hCG)[f]	X	X											X	X
HIV, HCV, HBsAg	X													
ECG[g]	X		X					X					X	X
C-SSRS	X	X										X	X	X
Randomization			X											
Study drug administration[h]			← X →											
PK blood sample[i]			X	X	X	X	X	X	X	X	X	X		X
Adverse event	← X →													
Concomitant medications	← X →													

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hours; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; MAD = multiple-ascending dose; PK = pharmacokinetic; S = screening.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of first dose administration.

[c] Vital signs and temperature should be measured at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose; predose on all other indicated dosing days.

[d] Hematology and chemistry sample should be collected predose on stipulated visits.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose.

[h] Study drug will be administered once daily in the CRU through Day 14, and the exact time of administration will be recorded. All doses are planned to be administered in a fasting state; however, following a review of the food effect data from Part A, all doses may be administered with food. Fasting on PK sampling days is defined as at least 8 hours predose and 4 hours postdose. Fasting on non-PK and predose only PK sampling days is defined as at least 8 hours predose and 2 hours postdose on all other indicated days.

[i] On Day 1 and Day 14, PK samples will be collected at time zero (predose) and at approximately at 1, 2, 4, 6, 8, and 12 hours after dosing. Predose PK samples will also be obtained on Days 2, 3, 5, and 8. One PK sample will be taken at approximately 24, 48, 72, and 96 hours post Day 14 dose on Days 15, 16, 17, and 18, respectively. If applicable, a sample will be collected at the ED visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. Post-assay remaining PK plasma samples may be stored for metabolite identification.

Table 2-5 Study Schedule Protocol J2D-MC-CVAA: Part B (MAD)-Cohort 9

	S	Treatment/In CRU												Post treatment	ED[a]
Study Day	**≤28**	**-1**	**1**	**2**	**3**	**5**	**8**	**14**	**15**	**16**	**17**	**18**	**19**	**23**	
Visit Window (days)														**±2**	
Visits	**1[b]**	**2**												**3**	
CRU admission		X													
CRU discharge													X		
Participant information (including I/E criteria)	X	X													
Informed consent	X														
Medical history	X														
Height	X														
Weight	X		X											X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	D	D	D	D	D	D	D	C	C
Urine drug screen and ethanol test	X	X													
Vital signs including temperature[c]	X	X	X	X	X	X	X	X						X	X
Hematology and clinical chemistry[d]	X	X		X			X	X						X	X
Urinalysis[e]	X	X													
Pregnancy test (serum beta-hCG)[f]	X	X												X	X
HIV, HCV, HBsAg	X														
ECG[g]	X		X					X						X	X
C-SSRS	X	X											X	X	X
Randomization			X												
Study drug administration[h]			← X →												
PK blood sample[i]			X	X	X	X	X	X	X	X	X		X		X
Adverse event		← X →													
Concomitant medications		← X →													

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hours; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; MAD = multiple-ascending dose; PK = pharmacokinetic; S = screening.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of first dose administration.

[c] Vital signs and temperature should be measured at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose; predose on all other indicated dosing days.

[d] Hematology and chemistry sample should be collected predose on stipulated visits.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose.

[h] Study drug will be administered once daily in the CRU through Day 14, and the exact time of administration will be recorded. All doses are planned to be administered in a fasting state; however, following a review of the food effect data from Part A, all doses may be administered with food. Fasting on PK sampling days is defined as at least 8 hours predose and 4 hours postdose. Fasting on non-PK and predose only PK sampling days is defined as at least 8 hours predose and 2 hours postdose on all other indicated days.

[i] On Day 1 and Day 14, PK samples will be collected at time zero (predose) and at approximately at 1, 2, 4, 6, 8, and 12 hours after dosing. Predose PK samples will also be obtained on Days 2, 3, 5, and 8. One PK sample will be taken at approximately 24, 48, 72, and 120 hours post Day 14 dose on Days 15, 16, 17, and 19, respectively. If applicable, a sample will be collected at the ED visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. Post-assay remaining PK plasma samples may be stored for metabolite identification.

3 Introduction

3.1 Study Rationale

Study J2D-MC-CVAA is a first-in-human (FIH) study designed to evaluate safety, tolerability, and pharmacokinetics (PK) of oral LY3526318 in healthy participants. LY3526318 is a small molecule designed to inhibit transient receptor protein ankyrin 1 (TRPA1), a calcium-permeable nonselective cation channel, expressed by peripheral pain-sensing nociceptors, which play a pivotal role in generation of pain (Maatuf et al. 2019). A nonclinical efficacy pharmacology study using a formalin-induced flinch model in rats showed an analgesic effect after a single dose of LY3526318. The potential of LY3526318 to produce unwanted pharmacological effects associated with central nervous system (CNS), cardiovascular, or respiratory functioning was determined in rats and monkeys, and *in vitro* systems (see Section 3.2). These evaluations support advancing LY3526318 to a FIH study with the initial development focusing on chronic pain reduction.

3.2 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).

TRPA1's role 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.

TRPA1 antagonists are undergoing evaluation in clinical trials, where there is evidence of efficacy and safety (ODM-108, NCT02432664; GRC 17536, EU Clinical Trial Register 2012-002320-33).

The results of the general toxicology studies, the behavioral and cardiorespiratory safety pharmacology studies, the *in vitro* human ether-à-go-go channel assay, and the *in vitro* and *in vivo* genotoxicity/mutagenicity battery justify moving forward into human clinical studies.

The CNS safety pharmacology study in the rat and cardiovascular respiratory study (Study # 00926046) in monkeys showed no adverse findings up to the highest dose (300 mg/kg) of LY3526318 tested. No test article-related toxicity was seen at any dose in the 28-day repeat-dosing study in monkeys (Study # 00926044). CCI [redacted]

3.3 Benefit/Risk Assessment

There is no benefit anticipated for healthy participants administered LY3526318.

CCI [redacted]

Nonclinical toxicology and safety pharmacology studies with LY3526318 support the administration of LY3526318 to humans, for the primary objective of the planned study to evaluate safety and tolerability of LY3526318 in healthy participants.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3526318 is provided in the Investigator's Brochure (Lilly 2019).

Since LY3526318 has previously not been administered to humans, the study will be designed and conducted in accordance with the "*Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products*" (EMEA/CHMP/SWP/28367/07 Rev.1 - July 2017).

Additional information on scientific rationale for the study design and justification for planned LY3526318 doses are provided in Sections 5.4 and 5.5, respectively.

Taking all these findings into consideration, no additional human safety pharmacology risks are expected for healthy participants in the FIH study of LY3526318.

4 Objectives and Endpoints

Table 4-1 shows the objectives and endpoints of the study.

Table 4-1 Objectives and Endpoints

Objectives	Endpoints
Primary (Part A)	
To evaluate safety and tolerability of LY3526318 in healthy participants following a single oral dose	• AEs • SAEs
Primary (Part B)	
To evaluate safety and tolerability of LY3526318 in healthy participants following multiple once-daily oral doses for 14 days	• AEs • SAEs
Secondary (Part A)	
To evaluate the plasma pharmacokinetics of LY3526318 in healthy participants following a single oral dose	• AUC • C_{max} • t_{max}
Secondary (Part B)	
To evaluate the plasma pharmacokinetics of LY3526318 in healthy participants following multiple once-daily oral doses for 14 days	• AUC • C_{max} • t_{max}
Exploratory (Part A)	
To explore the pharmacokinetics of LY3526318 in fed versus fasted conditions	• AUC • C_{max} • t_{max}
To explore the single-dose pharmacokinetics of LY3526318 in urine	• LY3526318 urine concentration • Amount of LY3526318 excreted in 24-hour urine

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; SAE = serious adverse event; t_{max} = time to C_{max}.

5 Study Design

5.1 Overall Design

This is a Phase 1, single-ascending dose (SAD, Part A) and multiple-ascending dose (MAD, Part B) study of LY3526318 in healthy participants. Both parts are randomized, double-blind, and placebo-controlled.

Part A (SAD):

The single-ascending doses of LY3526318 or placebo will be administered, at planned dose levels of 10, 50, 100, 400, 800, and 1000 mg, in 7 cohorts of 8 participants each, except the expanded 100-mg cohort that will include 12 participants (8 female and 4 male) to accommodate a food effect assessment in the female participants only.

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. A sentinel dosing strategy will be implemented for the first dose level (Cohort 1, 10 mg). Two participants will receive a sentinel dose (1 each with LY3526318 and placebo) and the remaining participants will be administered LY3526318 after review of safety data up to 48 hours postdose. Participants in Cohort 1 will not be stratified by sex, given that sentinel dosing coupled with stratification by sex may compromise blinding. A fixed number of females and males will be randomized in Cohorts 2 and 3 and the participants will be stratified to ensure equal distribution between females and males. The Part A stratification by sex scheme is shown in Table 5-1.

Table 5-1 Part A Stratification Based on Sex

Cohort (Planned dose level [a])	Number of Females Randomized	Number of Males Randomized	Total Participants Randomized
Cohort 1 (10 mg)	Up to 8[b]	Up to 8[b]	8
Cohort 2 (50 mg)	4	4	8
Cohort 3 (100 mg)	8[c]	4	12
Cohort 4 (400 mg)	8[c]	NA	8
Cohort 5 (800 mg)	8	NA	8
Cohort 6 (1000 mg)	8	NA	8
Cohort 10 (100 mg)	8 [d]	NA	8

Abbreviation: NA = not applicable.

[a] Doses may be adjusted based on data obtained in previous study cohorts.

[b] Cohort 1 will not have a defined stratification by sex scheme. Eight participants will be randomized including males and/or females.

[c] Female participants in Cohorts 3 and 4 will receive study drug in fasted and fed conditions, separated by a washout period of at least 1 week.

[d] All 8 female participants in Cohort 10 will receive LY3526318 in a 3-period crossover with standardized high fat meals administered prior to dose, and at 30 min and 1 hour post dose. Participants receiving meals post dose administration will receive their dose in the fasted state. Periods are separated by a washout period of at least 1 week.

Cohorts administered above LY3526318 100 mg are anticipated to exceed the approximate 10x margin to the projected no-observed-adverse-event-level (NOAEL)-equivalent exposure for males; for this reason, only female participants will be enrolled at dose levels higher than 100 mg. Additionally, if exposure data from previous cohorts does not support dose escalation in males through 100 mg, males will be discontinued from further dosing in the study.

The effect of food on LY3526318 PK will be explored in female participants only, in the 100-mg cohort and in the 400-mg cohort. In the 100-mg cohort, the initial dose will be administered after an approximately 8-hour fast in 8 female and 4 male participants, followed by a washout period of at least 1 week. A second dose will be administered after a standardized high-fat meal in female participants only. In the 400-mg cohort, the initial dose will be administered after an approximately 8-hour fast; following a washout period of at least 1 week, the second dose will be administered after a standardized high-fat meal. Except for the food effect assessment cohorts, all other doses are to be administered after an approximately 8-hour fast. Following a review of the 100-mg and/or 400-mg fed and fasted data, subsequent cohorts may be administered with food.

An additional cohort (Cohort 10) will assess the effect of food on LY3526318 PK in 8 female participants. All participants in this cohort will received 100 mg LY3526318 with standardized high fat meal in an open-label, 3-way crossover manner (meal administered prior to dose, at 30 minutes and at 1 hour post dose; Table 2-2). Participants receiving meals post dose administration will receive their dose after an approximately 8-hour fast. Periods will be separated by a washout period of at least 1 week.

All participants will return to the CRU for a final visit approximately 9 days after study drug administration or after the fed-state dose for female participants in 100- and 400-mg cohorts.

Part B (MAD):

The multiple-ascending doses of LY3526318 or placebo will be administered, at planned dose levels of 100, 400, and 1000 mg, once daily for 14 days in 3 cohorts of 8 female participants each.

Following a screening period of up to 28 days, eligible participants will receive once-daily treatment with study drug for 14 days. Participants will be confined to the CRU from Day -1 until all study assessments are completed on Day 15 (Cohort 7), Day 18 (Cohort 8) or Day 19

(Cohort 9). Within each cohort, eligible participants will be randomly assigned to receive LY3526318 or placebo in a 6:2 ratio. The first cohort will be administered LY3526318 following a review of safety and PK data through Part A 400-mg cohort and fed period of the 100-mg cohort.

Dose levels will not exceed those administered in Part A. Dose levels in Part B are anticipated to exceed the approximate 10x margin to the projected NOAEL-equivalent exposures for males; for this reason, only female participants will be enrolled in Part B.

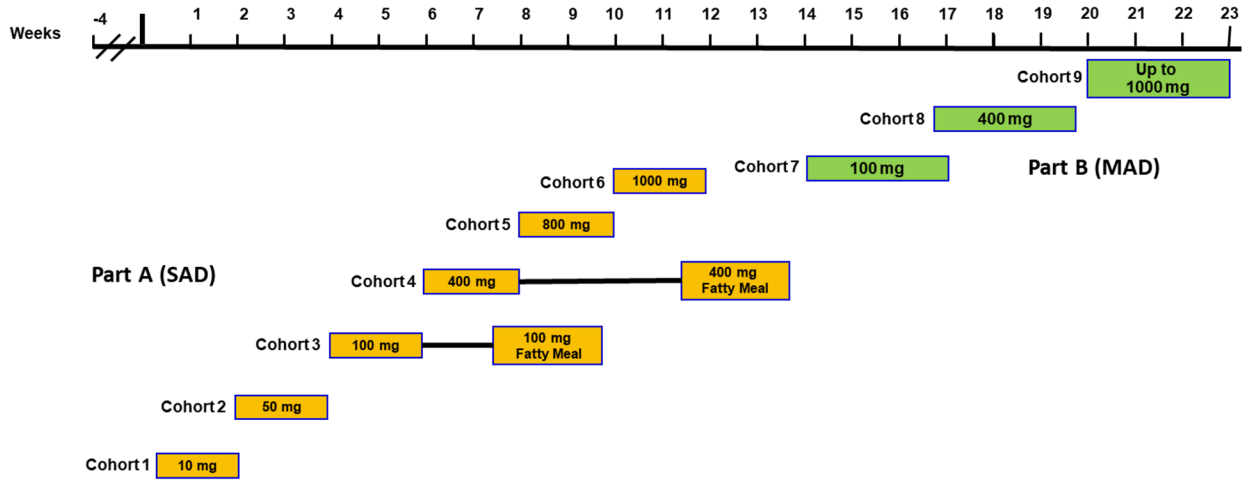
All doses are planned to be administered in an 8-hour fasting state. However, following a review of the food effect data from Part A, all doses may be administered with food.

Participants will return to the CRU for a final visit on approximately Day 23.

Safety, PK, and other assessments will be performed at time points prescribed in Section 2.

Study governance considerations are described in detail in Appendix 3.

Figure 5.1 illustrates the study design.



Abbreviations: SAD = single-ascending dose (Orange); MAD = multiple-ascending dose (Green).
Note: Doses may be adjusted based on data obtained in previous study cohorts and parts. The timeline listed is an approximation intended to illustrate relative cohort timing within and between Parts A and B. Additional cohorts may be added.

Figure 5.1 Illustration of study design for Protocol J2D-MC-CVAA.

5.2 Number of Participants

Part A: Approximately 52 participants will be randomized to achieve 8 evaluable participants per cohort, except the 100-mg cohort that will include 8 evaluable females and 4 evaluable males and 100-mg food assessment cohort (Cohort 10) that will include 8 evaluable females.

The Part A stratification by sex scheme is shown in Table 5-1 and method of treatment assignment is provided in Section 7.2.

Part B: Approximately 24 female participants will be randomized to achieve 8 evaluable participants per cohort (6 LY3526318:2 placebo).

Additional cohorts of up to 8 participants may be enrolled in either part of the study. Such additional cohorts may be enrolled in case intermediate or additional dose level(s) need to be studied or additional food effect need to be studied at other than planned dose levels.

Participants who withdraw from the study before completion of all study activities may be replaced at the discretion of the sponsor.

For purposes of this study, a participant completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been completed.

5.3 End of Study Definition

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

5.4 Scientific Rationale for Study Design

LY3526318 is a small-molecule TRPA1 inhibitor proposed for FIH dosing in a low uncertainty target and will use a clinical study design with a single cohort (Cohort 1) sentinel dosing strategy. Two oral TRPA1 inhibitors have been administered in healthy participants after being developed by other sponsors (GRC 17536 and ODM-108). Available data show that ODM-108 was well tolerated in healthy participants (NCT02432664) and GRC 17536 was well tolerated both in healthy participants and in patients with chronic pain conditions (EU Clinical Trial Register 2012-002320-33). Nonclinical pharmacology studies have demonstrated target engagement through changes in dermal blood flow for TRPA1 activation and antagonism (Aubdool et al. 2016). Cinnamaldehyde-induced dermal blood flow as measured through laser Doppler imaging (LDI) has been demonstrated to be a translationally relevant biomarker for TRPA1 activation and target engagement (Buntinx et al. 2017). Serious adverse events in this 14-day study are not anticipated based on the 28-day multiple-dose nonclinical toxicology studies.

This study will include a pilot assessment of food effect in female participants only. In the food effect cohorts, the doses will be administered in fed and fasted states, as indicated. Residual exposure will be minimized with a washout period of at least 1 week between doses. The 100- and 400-mg doses and the high-fat meal were chosen because preclinical data suggest that study drug administration with a high-fat meal may increase exposures of LY3526318 by approximately 5-fold, compared to administration in the fasted state. Having a food assessment at 2 different dose levels will help inform the mode of study drug administration in the MAD and subsequent studies. In addition, because LY3526318 preclinical PK was subproportional to dose, and the effect of food may also be nonlinear, assessing the food effect at 2 different dose levels will provide a better understanding of LY3526318 PK.

CCI [redacted]

The current study requires safety and PK data for dose escalation. However, the first dose escalation will rely on safety data only because the 10 mg dose is anticipated to result in exposures that have no clinical effect based on preclinical efficacy models that use direct TRPA1 agonists. In addition, 10 mg is anticipated to produce exposures >100x below the NOAEL in males and >1000x below the NOAEL in females.

According to the International Council for Harmonisation (ICH) guidelines (ICH 2009), women of child-bearing potential (WOCBP) can be included in early clinical trials without nonclinical developmental toxicity studies (e.g. embryo-fetal studies) in certain circumstances. In this study, participants who are WOCBP will receive 2 weeks of treatment while maintaining adherence to highly effective contraception to mitigate the risk of pregnancy.

5.5 Justification for Dose

The oral dose ranges proposed for this study are 10 mg up to 1000 mg for the SAD, and 100 mg up to 1000 mg once daily for the MAD. Cohorts in the SAD with doses higher than 100 mg and all cohorts in the MAD will only enroll female participants (see justification in Section 5.4). The planned dose levels may be modified (increased or decreased) based on an assessment of safety data and of available PK data during the study.

The proposed dose range of 10 to 1000 mg is supported by preclinical pharmacology studies. In a study in rats, doses of 3 mg/kg or greater (approximately 30 mg in humans) elicited a significant blockade of cinnamaldehyde-evoked dermal blood flow changes as measured through LDI. In addition, doses as low as 0.3 mg/kg (approximately 3 mg in humans) and up to 3 mg/kg showed efficacy in a rat complete Freund adjuvant-induced cold hyperalgesia model; and doses of 3 and 10 mg/kg (approximately 30 and 100 mg in humans) showed efficacy in a rat model of formalin-induced pain behavior. The LDI assay and formalin-induced pain model are expected to be more predictive of target engagement in humans because they use exogenous application of cinnamaldehyde and formalin that are direct agonists of TRPA1 receptor, for which LY is a direct antagonist. Based on these data, the proposed starting dose for this study is 10 mg, which is intended to be lower than the anticipated range of target engagement.

CCI [redacted]

Based on the short elimination half-life ($t_{1/2}$) observed in monkeys after administration of a capsule formulation of LY3526318 hydrate and in a 28-day cynomolgus monkey toxicokinetic study (2 to 4 hours across doses; Study # 00926044), no accumulation is expected upon multiple dosing. Therefore, the margins of safety can be expected to be similar for both single and multiple dose administrations.

Modeling of preclinical data in GastroPlus™ suggests that the bioavailability of LY3526318 may increase by approximately 3- to 5-fold when administered with a high-fat meal, relative to administration in the fasted state. Consequently, the 100-mg cohort (females only) was chosen to explore the effect of food administration, considering that even if a 5-fold increase in exposure is observed, it would not exceed the exposure at the maximum planned dose of 1000 mg. The 400-mg dose was chosen because even if there was a 5-fold increase in exposure, it would provide acceptable margins of safety of 5x and 10x for the NOAEL in female rats and monkeys respectively, based on dose multiples. Of note, there were no findings for either female rats or monkeys in the toxicology studies, hence the NOAEL is the maximum administered dose in those studies.

Thus, the proposed doses for both the SAD and MAD portions of the study are anticipated to be in the target engagement dose range, while providing adequate margins of safety to address the study objectives.

6 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.

6.1 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.

1. Aged 18 to 65 years, inclusive.

Part A Cohorts through 100 mg:

2. Healthy male participants (including self-reported surgically sterile males), as determined through medical history and physical examination, must agree to the following:
    a. When engaging in sex with a WOCBP, both the male participant and his female partner must use highly effective contraception consisting of 2 forms of birth control (1 of which must be a male barrier method such as a latex or polyurethane condom) from start of dosing throughout the clinical study period, and for 90 days after the final study drug administration.
    b. Nonsurgically sterile male participants must not donate sperm at any time from start of dosing until 90 days beyond the administration of study drug.

All Part A and Part B cohorts:

3. Female participants must be nonpregnant and not lactating, or of nonchildbearing potential (either surgically sterilized [e.g. tubal occlusion, hysterectomy, bilateral salpingectomy] or physiologically incapable of becoming pregnant, or postmenopausal with amenorrhea for at least 12 consecutive months). Nonpregnancy will be confirmed for all female participants through a serum pregnancy test at screening and at admission to the CRU and at a final study visit. Follicle-stimulating hormone will be tested at screening for all female participants.

    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 30 days after the final visit.

    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 contraceptive (oral, transdermal patches, vaginal or injectable)

b. Intrauterine device with or without hormones

c. Condom ('barrier' method)

d. Diaphragm or cervical cap

e. Sexual abstinence

Contraceptive requirements do not apply for participants who are exclusively in same-sex relationships.

4. Have a body mass index 18 to 32 kg/m^2.
5. Have given informed consent prior to any study-specific procedures.
6. Are reliable and willing to make themselves available for the duration of the study and are willing to follow CRU-specific study procedures.
7. 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.

6.2 Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria at screening, unless otherwise noted:

1. Are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
2. Have previously completed or withdrawn from this study or any other study investigating this study drug.
3. 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.
4. 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
5. 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 Frederica's corrected QT interval >450 msec for men and >470 msec for women. One repeat ECG may be performed if required.

6. 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.
7. Are an investigator or CRU personnel directly affiliated with this study, or are immediate family members of investigator or CRU personnel. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
8. Are Eli Lilly and Company (Lilly) employees or contractors or an immediate family member of employees or contractors.
9. 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.
10. Have donated blood of more than 500 mL within the previous month.
11. Are unwilling to stop alcohol and caffeinated beverage consumption and smoking/use of tobacco while resident in the CRU.
12. Have an average weekly alcohol intake that exceeds 21 units 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).
13. 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. Re-testing may occur once during the screening visit within 2 hours of the initial abnormal blood pressure measurement at the discretion of the investigator.
14. Participants with a history of drug abuse which, in the opinion of the investigator, is considered to be clinically significant or who test positive for drugs of abuse at screening or admission.
15. 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.
16. Are unwilling to comply with the dietary restrictions required for this study, including the avoidance by 5 days prior to study drug administration until the final ambulatory visit the ingestion of fruits, sauces, and juices containing furanocoumarins that irreversibly inhibit cytochrome P450 (CYP)3A4. The following fruits, sauces, and juices are excluded: grapefruit, Seville oranges, pomelos, cranberry, Goji berry, and apple.
17. 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.

6.3 Lifestyle and/or Dietary Requirements

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

6.3.1 Meals and Dietary Restrictions

Standard meals, according to the CRU standard operating procedures, will be provided during the stay at the CRU. A standardized high-fat meal for the food effect assessment cohorts will be provided at the CRU prior to dose administration. Unless otherwise instructed by CRU personnel, participants will maintain their own dietary habit throughout the ambulatory phases of the study.

6.3.2 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. No smoking/tobacco use will be allowed during the stay at the CRU.

6.3.3 Activity

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

6.4 Screen Failures

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

7 Treatment

7.1 Treatment Administered

Treatment drugs will be administered orally. Doses are planned to range between 10 and 1000 mg once daily.

Part A:

The planned dose levels are 10, 50, 100, 400, 800, and up to 1000 mg. LY3526318 or matching placebo will be administered to participants as a single dose by trained CRU personnel. Dose levels may be modified based on safety and available PK, but which are not intended to exceed the NOAEL.

All doses are planned to be administered in a fasting state (at least 8 hours predose and 4 hours postdose), with the exception of the indicated doses in the food effect cohorts (100 and 400 mg), where the study drug will be administered in both the fasted and fed states, as specified. Approximately 50% of the total caloric content of the meal should be from fat. Study participants should eat this meal in 30 minutes or less; and the study drug should be administered 30 minutes after the start of the meal. In all cases, study drug should be taken with 1 glass (approximately 240 mL) of water and no food should be allowed for at least 4 hours postdose. Water can be allowed as desired except for 1 hour before and after drug administration.

Following a review of the 100- and/or 400-mg fed and fasted data, subsequent cohorts may be administered with food.

Part B:

The planned dose levels in Part B (100, 400, and up to 1000 mg) will not exceed those studied in Part A. LY3526318 or matching placebo is planned to be administered in a fasting state once daily for 14 days. However, based on the food effect data from Part A, all doses may be administered with food. Fasting on PK sampling days is defined as at least 8 hours predose and 4 hours postdose. Fasting on non-PK and predose only PK sampling days is defined as at least 8 hours predose and 2 hours postdose.

LY3526318 or matching placebo will be administered once daily by trained CRU personnel through Day 14 in the CRU.

For 800- and 1000-mg cohorts, 8 to 10 capsules of study drug will be administered. In case of administration of multiple capsules, the participant may drink extra water, as needed.

Section 7.4 details the dose-escalation strategy.

The LY3526318 drug product is supplied as a hard gelatin capsule in dosage strengths of 10 to 100 mg. Placebo capsules will be identical in size and shape.

The investigator or designee is responsible for

- explaining the correct use of the investigational product(s) to the participant
- verifying that the instructions are followed properly

- maintaining accurate records of investigational product dispensing and collection, and
- returning all unused medications to Lilly or its designee at the end of the study.

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

7.1.1 Packaging and Labeling

The drug product will be manufactured, tested, packaged, and labeled in accordance with all applicable good manufacturing practice requirements and country's regulatory requirements. A certificate of analysis will be supplied confirming that the materials are released for human use in clinical trials. LY3526318 drug products are for investigational use only and are to be used only within the context of this study.

7.2 Method of Treatment Assignment

Randomization in the first cohort (10 mg, Cohort 1) will not be stratified by sex and participants will receive either LY3526318 or placebo in a 6:2 ratio, unless otherwise indicated.

A fixed number of females and males will be randomized in Cohorts 2 and 3 and the randomization will be stratified to ensure equal distribution between females and males. Randomization to either LY3526318 or placebo will be 3:1 within each cohort or stratum, respectively.

Participants in Cohorts 4 and onwards will receive either LY3526318 or placebo in a 6:2 ratio, except for Cohort 10 where all participants will receive LY3526318.

Refer to Part A study design in Section 5.1 and Table 5-1 for stratification by sex.

In Part B, eligible participants will be randomly assigned to receive either LY3526318 or placebo in a 6:2 ratio.

A randomization table will be created by a computer software. The randomization list will be provided to the designated unblinded CRU personnel for participant randomization and dispensing purposes and kept in a secure location, accessible to the designated unblinded CRU personnel only.

7.2.1 Selection and Timing of Doses

In Part A, the single dose of the study drug will be administered at the CRU approximately between 08:00 AM and 11:00 AM.

In Part B, all doses will be administered at the CRU approximately between 08:00 AM and 11:00 AM.

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

7.3 Blinding

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. 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 drug preparation will not be blinded; laboratory personnel, including bioanalytical laboratory personnel, will also not be blinded. Drug product and placebo will be identical in appearance.

One set of sealed envelopes containing the randomization code will be provided to the investigator at the start of the trial. A code envelope, which reveals the treatment for a specific study participant, may be opened during the study only if the participant's well-being requires knowledge of the participant's treatment assignment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Unless the investigator obtains Lilly medical monitor approval stating otherwise, a participant whose study treatment assignment is unblinded must be discontinued from the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

At the end of the study, unopened envelopes will be returned to Lilly or its designee, or destroyed according to CRU procedures.

7.4 Dose Modification

Six cohorts in Part A and 3 cohorts in Part B are planned. Additional cohorts may be enrolled in either part of the study in case intermediate or additional dose level(s) need to be studied or additional food effect need to be studied at other than planned dose levels. The planned doses in each part of the study may be modified after review of the safety and PK data of each administered dose.

7.4.1 Dose Escalation

Safety data will be the primary criteria for the dose escalation within each part of the study. In addition, available PK data will be used in support of dose escalation, with the exception of the first dose in Part A (10 mg; see justification in Section 5.4). A dose-escalation report (DER) will be provided by the investigator to the independent ethics committee (IEC) following completion of each dose level. Escalation to the next higher dose will proceed only if safety and tolerability data from at least 6 participants from the previous dose level are acceptable to the investigator and the sponsor and, if deemed necessary by the IEC following their review of the protocol, after

a statement of no objection of the DER from the IEC. The planned dose levels (defined in Section 7.1) may be adjusted based on safety and PK data.

7.4.1.1 Part A

Dose escalation from the 10-mg cohort to the 50-mg cohort may occur after review of safety data from at least 6 participants in the 10-mg cohort. The subsequent dose escalations may occur after review of safety and available PK data through 48 hours postdose from at least 6 participants in the prior cohort. The second dose of the 100-mg cohort, food effect assessment, may occur after review of safety and available PK data from the first 3 days of fasted dose in at least 6 participants in Cohort 4 (400-mg dose). The second dose of the 400-mg cohort, in the fed state, may occur after review of Cohort 6 (1000-mg dose) safety and available PK data for at least 6 participants through 48 hours postdose.

7.4.1.2 Part B

Part A safety and PK data will be reviewed to support initiation of Part B. Based on a review of these data, it will also be decided if the study drug should be administered in the fasted or fed state, and if adjustments to higher dose levels and/or sample collection times in the Part B are deemed necessary.

Dose escalation to Cohort 8 may occur after review of safety and available PK data through 15 days from at least 6 participants of Cohort 7.

Dose escalation to Cohort 9 may occur after review of safety and available PK data through 15 days from at least 6 participants of Cohort 8.

7.4.2 Stopping Rules

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

1. a participant experiences an SAE or a clinically significant event that is related to LY3526318 administration, or
2. 3 or more participants develop AEs within 14 days of dosing that are considered to be related to study drug and graded as at least moderate, clinically significant, and not responsive to supportive care.

Dosing may be resumed at a lower dose level, with prior discussion and agreement between the investigator and the sponsor.

Individual participants or study discontinuation criteria are provided in Section 8.

7.5 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm that appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all investigational products received and any discrepancies are reported and resolved before use of the study drug. Detailed records of the amounts of study drug received, dispensed and remaining at the end of the study will be maintained.

The LY3526318 drug products are used in accordance with the protocol and will be stored in a secure and locked area with strictly limited access and monitored for temperature (manual or automated) in accordance with the labeled storage conditions. LY3526318 drug products are allocated and dispensed by appropriately trained personnel.

Unblinded pharmacy personnel will be responsible for providing either LY3526318 or placebo to the blinded study personnel for administration based on the randomization schedule. Unblinded pharmacy personnel will follow detailed pharmacy instructions for the preparation and handling of LY3526318 drug products for both Parts A and B.

LY3526318 capsules are stable when stored refrigerated between 2°C and 8°C.

7.6 Treatment Compliance

The study drug will be administered at the CRU, and documentation of study drug administration will occur at the CRU.

A qualified designee will be responsible for monitoring the administration of the timed oral doses. A mouth check will be performed by the qualified designee to ensure that the participants have swallowed the study drug.

Participants' hands will also be verified to ensure that the study drug was ingested. Dose administration will be documented in the electronic case report form (CRF).

7.7 Concomitant Therapy

Drugs that are known inducers or inhibitors of CYP3A4 or 2C9 are to be specifically excluded (see 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.

In general, concomitant medication should be avoided; however, over-the-counter medications may be administered at the investigator's discretion (e.g. acetaminophen for treatment of headache). If the need for concomitant medication (other than over-the-counter medications) arises, inclusion or continuation of the participant may be at the discretion of the investigator after consultation with the sponsor. Any medication used during the course of the study must be documented.

7.8 Treatment after the End of the Study

Not applicable.

8 Discontinuation Criteria

Participants may be withdrawn from the study if any of the following criteria are observed:

- Enrollment in any other clinical study involving an investigational product or other medical research judged not to be scientifically or medically compatible with this study.
- **Investigator's decision**: the investigator may decide that the participant should be discontinued from the study for the following reasons:

    - If, in the investigator's opinion, continuation in the study would be detrimental to the participant's well-being, in particular in case of an AE
    - Lost to follow up after 3 attempts to contact the participant through phone, text message, or mail.

If the investigator withdraws a participant for a study drug-related reason (according to the judgment of the investigator), he/she is considered a dropout. Dropouts may be replaced, where the sponsor deems this necessary.

- **Participant's Decision**: the participant requests to be discontinued from the study.
- **Sponsor's Decision**: Lilly stops the study or stops the participant's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- **Discontinuation due to a hepatic event of liver test abnormality**: Participants who are discontinued from using study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected. Discontinuation of the study drug for abnormal liver tests should be considered by the investigator when a participant meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

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

- **Pregnancy**: If the pregnancy test (planned or unplanned) of female participant of child-bearing potential is positive at any time during the stay at CRU, the female participant will be discontinued from the study.
- Requirement of prohibited concomitant medication
- Participant's failure to comply with protocol requirements or study-related procedures
- Termination of the study by the sponsor or regulatory authorities

Participants discontinuing from the study prematurely for any reason should complete AE and other follow-up procedures (Early Discontinuation Visit) per Section 2 (Schedule of Activities) of this protocol.

Every effort must be made to contact participants who do not return for a planned visit and the reason for withdrawal should be documented in the electronic data capture (EDC). The participant can only be declared as 'lost to follow-up' if the investigator has had no success in contacting the participant. Participants who withdraw from the study before completion of all study activities may be replaced at the discretion of the sponsor.

9 Study Assessments and Procedures

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

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

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

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

9.1 Efficacy Assessments

Not applicable.

9.2 Adverse Events

A clinical trial AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to that drug or drug delivery system.

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

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

Investigators must document their review of each laboratory safety report.

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

After the ICF is signed, the CRU personnel will record, via EDC, the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, CRU personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

If a participant's study drug is discontinued because of an AE, CRU personnel must report this to Lilly or its designee via EDC.

9.2.1 Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e. immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

The CRU personnel must alert the Lilly medical monitor, or its designee, of any SAE as soon as practically possible.

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

Although all AEs are recorded in the case report form or EDC after signing informed consent, SAE reporting to the sponsor begins after the participant has signed informed consent and has received the study drug. However, if an SAE occurs after signing informed consent, but prior to receiving the study drug, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in participants once they have discontinued from and/or completed the study. Serious adverse events will be collected for 30 days after the last dose of study drug. 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 reasonably possibly related to the study drug or study participation, the investigator must promptly notify Lilly within 24 hours.

Pregnancy (maternal or paternal exposure to the study drug) 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 serious and unexpected AEs for this study will be reported to regulatory authorities in accordance with local laws, directives, and regulations.

9.2.1.1 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB (Lilly 2019) and that the investigator reports as related to investigational product or

procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

9.2.2 Complaint Handling

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

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

9.3 Treatment of Overdose

An overdose is not anticipated in the study, as all study drugs will be administered by a trained CRU member.

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

9.4 Safety

9.4.1 Laboratory Tests

For each participant, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

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

9.4.2 Vital Signs

For each participant, vital sign measurements should be conducted according to the Schedule of Activities (Section 2).

It is suggested that systolic and diastolic blood pressure and heart rate should be measured in supine position just after the ECG (if the ECG is recorded at the same time point) and before any other procedures according to the Schedule of Activities (Section 2).

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

9.4.3 Electrocardiograms

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

Participant must be supine for approximately 5 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

In the event that assessments are planned for the same time, the order of assessments should be arranged in such a way that PK blood samples will be taken after the ECG and vital sign recordings have been conducted, with PK blood sampling times adhered to as closely as possible.

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 to Lilly, or its designee, as an AE via EDC.

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 (e.g. palpitations, near syncope, syncope) to determine whether the participant can continue in the study. The investigator or qualified designee is responsible for determining if any change in participant management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

9.4.4 Physical Examination

A complete or directed physical examination will be conducted according to the Schedule of Activities (Section 2).

9.4.5 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered according to the Schedule of Activities (Section 2).

Columbia-Suicide Severity Rating Scale: A scale that captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience or some or all of the patients may have these data solicited through interactive web-response system or electronic patient-reported outcome technology. This tool was developed by the National Institute of Mental Health trial group (Treatment of Adolescent Suicide Attempters) for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events.

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, CRU should not change the AE form. If an event is serious or leads to

discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

Terms captured by the use of the C-SSRS can be mapped to Columbia Classification Algorithm for Suicide Assessment (Posner et al. 2007) to facilitate future pooling of data.

The first time the scale is administered in this study, the C-SSRS "Lifetime/Recent-Clinical" version will be used, and the findings will constitute the baseline assessment. The "Since Last Visit-Clinical" version will be used for all subsequent assessments. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then additional information will be collected to allow for a more complete assessment of these behaviors.

9.4.6 Safety Monitoring

The sponsor will monitor safety data throughout the course of the study and periodically will review evolving aggregate safety data within the study through appropriate methods.

9.4.6.1 Hepatic Safety

If a study participant experiences elevated ALT ≥3 × ULN, ALP ≥2 × ULN, or elevated TBL ≥2 × ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly medical monitor. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

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

9.5 Pharmacokinetic Assessments

9.5.1 Blood Sampling and Processing

For all participants, blood samples of up to 3 mL each for the determination of LY3526318 and metabolite(s) of interest concentrations will be collected at time points specified in the Schedule of Activities (Section 2). 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.

9.5.2 Urine Sampling and Processing

In Part A only, urine samples for LY3526318 and metabolite(s) of interest analyses will be collected at specified intervals, as specified in the Schedule of Activities (Section 2).

On Day 1 (Part A), participants will be asked to empty their bladders within approximately 60 minutes prior to the scheduled dosing time. This urine will not be collected. Participants will be instructed to collect all urine samples for 24 hours from the time of dosing, as indicated in the Schedule of Activities (Section 2). Urine will be refrigerated as soon as possible after the sample is provided by the participant. At the end of the collection time, the total urine volume will be measured, and aliquots will be prepared for the measurement of the concentration of LY3526318 and of metabolite(s) of interest.

Instructions for the collection and handling of urine samples will be provided by the sponsor.

9.5.3 Bioanalysis

Plasma and urine sample analyses of LY3526318 and possible metabolite(s) of interest will be performed using validated procedures and methods. Placebo samples are not planned to be analyzed.

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

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

9.6 Pharmacodynamics

Not applicable.

9.7 Genetics

Not applicable.

9.8 Biomarkers

Not applicable.

9.9 Health Economics

Not applicable.

10 Statistical Considerations and Data Analysis

10.1 Sample Size Determination

The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered based on statistical hypothesis testing.

10.2 Populations for Analyses

10.2.1 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.

10.2.2 Study Participant Characteristics

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

10.2.3 Concomitant Medications

Concomitant medications will be listed.

10.3 Statistical Analyses

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

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.

For continuous variables, summary statistics will include 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.

Any p-values to be calculated according to the statistical analysis plan will be interpreted in the perspective of the explorative character of this study.

10.3.1 Safety analysis

All study drug 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 AE and SAE will be provided by dose level 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.

10.3.2 Pharmacokinetic Analyses

10.3.2.1 Pharmacokinetic Population

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

10.3.2.1.1 Plasma Pharmacokinetic Parameter Estimation

Part A

Primary plasma LY3526318 PK parameters, including but not limited to the area under the concentration versus time curve (AUC) from time zero to the last measurable concentration (AUC_{0-t}), AUC from time zero to 24 hours (AUC_{0-24}), AUC from zero to infinity (AUC_{0-inf}), maximum observed drug concentration (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), and apparent volume of distribution (Vz/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 for the ratios will be reported.

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.

Part B

Plasma LY3526318 PK parameters will be calculated using noncompartmental methods as described for Part A, after single- and multiple-dose administration (on Days 1 and 14, respectively). Additional PK parameters may be calculated if deemed appropriate.

Pharmacokinetic parameters will be summarized by dose level using descriptive statistics. Mean and individual plasma concentration versus time curves will be graphically presented for LY3526318 and possibly metabolites.

Steady state will be graphically evaluated. Accumulation will be estimated.

Additional analyses will be performed as deemed necessary upon review of the data.

The relationship between LY3526318 PK and safety measures may be evaluated. Other analyses may be performed as needed.

10.3.2.1.2 Urine Pharmacokinetic Parameter Estimation

In Part A, urine LY3526318 PK parameters including Ae_{0-24}), F_e, and renal clearance will be calculated. Creatinine clearance will also be calculated for each participant.

10.3.2.2 Pharmacokinetic Statistical Inference

Dose proportionality may be assessed using the power model approach (Smith et al. 2000), as appropriate. Additional analyses will be performed as deemed necessary upon review of the data.

10.3.3 Data Review during the Study

Data will be reviewed following each cohort prior to dose escalation as described in Section 7.4.

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12 Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his 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
C_{max}	maximum observed drug concentration
CNS	central nervous system
CRF	case report form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DER	dose-escalation report
ECG	electrocardiogram
EDC	electronic data capture
ERB	ethical review board
FIH	first-in-human
GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
LDI	laser Doppler imaging
MAD	multiple-ascending dose
NOAEL	no-observed-adverse-event level
PK	pharmacokinetic(s)
SAD	single-ascending dose
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin level
TRPA1	transient receptor protein ankyrin 1
ULN	upper limit of normal
WOCBP	women of child-bearing potential

Appendix 2. Clinical Laboratory Tests

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	
	Urine drug screen[a,b]
Urinalysis Dipstick	Alcohol (ethanol)
Specific gravity	Nicotine metabolites
pH	Amphetamine (including XTC)
Protein	Barbiturates
Glucose	Benzodiazepine
Ketones	Cannabinoids
Bilirubin	Cocaine
Urobilinogen	Methadone
Blood	Opiates
Nitrite	
	Hepatitis B surface antigen[a]
	Hepatitis C antibody[a]
	HIV
	FSH[a]
	Beta-hCG

Abbreviations: FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; RBC = red blood cell; WBC = white blood cell.

[a] Performed at screening only.

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

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

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

Recruitment

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

Ethical Review

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

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

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

- study protocol and any amendments during the course of the study
- the current IB and updates during the course of the study
- ICF
- relevant site personnel curricula vitae

Regulatory Considerations

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

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

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

Protocol Signatures

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

Final Report Signature

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

Data Quality Assurance

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

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

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

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

Data Collection Tools/Source Data

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

Data Protection

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

The purpose and use of participant personal information collected will be provided in a written document to the participant by the sponsor.

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Appendix 5. Blood Sampling Summary

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

Protocol J2D-MC-CVAA Sampling Summary – Part A (Cohorts 1-6) (SAD)

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,b]	6.5	4	26
Pharmacokinetics[b]	3	9	27
Total for all cohorts, except for 100-mg cohort female participants and 400-mg participants			64.5
Total for 100-mg cohort female participants and 400-mg cohort participants[b]			111

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

[b] Female participants in the 100-mg cohort and all participants in the 400-mg cohort will receive study drug twice, once in fasted state and once in fed state. Hence, clinical laboratory and pharmacokinetic samples will be collected twice, except for the follow-up clinical laboratory sample that will be collected only after fed-state study drug administration.

Protocol J2D-MC-CVAA Sampling Summary – Part A (Cohort 10) (SAD)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Number of Periods Samples are Collected	Total Volume (mL)
Screening tests[a]	11.5	1	1	11.5
Clinical laboratory tests[a,b]	6.5	4	3	78
Pharmacokinetics[b]	3	11	3	99
Total				188.5

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

[b] Cohort 10 participants will receive study drug once in 3 different periods. Hence, clinical laboratory and pharmacokinetic samples will be collected three times, except for the follow-up clinical laboratory sample that will be collected only after the final period.

Protocol J2D-MC-CVAA Sampling Summary – Part B, Cohort 7 (MAD)

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	5	32.5
Pharmacokinetics	3	19	57
Total			101

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

Protocol J2D-MC-CVAA Sampling Summary – Part B, Cohorts 8-9 (MAD)

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	5	32.5
Pharmacokinetics	3	22	66
Total			110

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

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.

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

Drug	Special status	Category
Aminoglutethimide	VL. Possibly available in Egypt, Lithuania	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
lenisurad		moderate
Lersivirine		moderate
lopinavir (alone)		moderate
Lorlatinib		moderate
Modafinil		moderate
nafcillin (intravenous)	VL; available in the US	moderate
Pentobarbital	VL	moderate
Primidone		moderate
telotristat ethyl		moderate
thioridizine	VL: available in the US; importable into the UK	moderate
tipranavir and ritonavir		moderate
tocilizumab (atlizumab)	NT	moderate
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		
FDA https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm		

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

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; Available in the US	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 ombitasvir and/or dasabuvir)		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
Fluvoxamine		moderate
fosnetupitant and palonosetron (see also netupitant)		moderate
Imatinib		moderate
indinavir (see indinavir and ritonavir)		moderate
Isavuconazole		moderate
ledipasvir/sofosbuvir		moderate
Letermovir		moderate
magnolia vine (*Schisandra*	SF	moderate

sphenanthera)		
Netupitant		moderate
Nilotinib		moderate
Tofisopam		moderate
Verapamil		moderate
SF: supplement or food/drink		
VL: very limited use		
University of Washington Drug Interaction Database https://www.druginteractioninfo.org/		
Hansten PD, Horn JR. *Top 100 Drug Interactions of 2018: A Guide to Patient Management*. Freeland, WA: H&H Publications; 2018.		

Moderate clinical inhibitors and inducers of CYP2C9

CYP2C9 Inhibitors	amiodarone, felbamate, fluconazole, miconazole, piperine
CYP2C9 Inducers	aprepitant, carbamazepine, enzalutamide, rifampin, ritonavir

Source: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm. Accessed 22 Apr 2019.

Appendix 7. Protocol Amendment: J2D-MC-CVAA(a)

Protocol J2D-MC-CVAA has been amended; the new will be indicated as amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

Section	Changes made	Rationale for the change
5.1 Overall Design	Footnotes added to Table 5.1 and Figure 5.1 to clarify that doses may be adjusted based on data obtained in previous cohorts (Part A only) and in previous cohorts and parts (Parts A and B)	Administrative updates
5.4 Scientific Rationale for Study Design	Text edited to clarify dosing in the food effect cohort.	Administrative updates
7.1 Treatment Administered	Text edited to clarify that the highest dose level to be tested is not intended to exceed the NOAEL	Administrative updates

Revised Protocol Sections

Note: Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of underscore.

5.1 Overall Design

Table 5.1 Part A Stratification Based on Sex

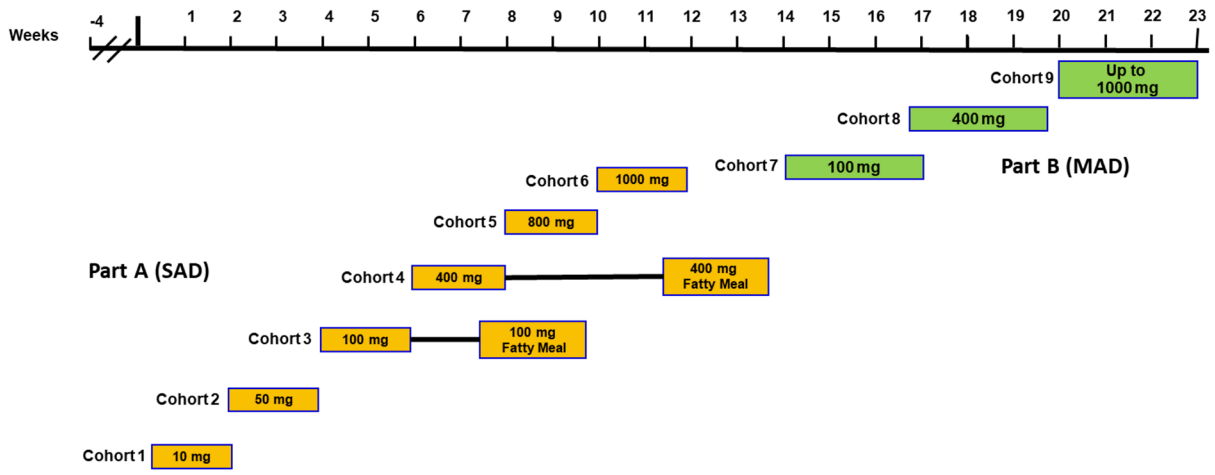
Cohort (Planned dose level [a])	Number of Females Randomized	Number of Males Randomized	Total Participants Randomized
Cohort 1 (10 mg)	Up to 8[ba]	Up to 8[ba]	8
Cohort 2 (50 mg)	4	4	8
Cohort 3 (100 mg)	8[cb]	4	12
Cohort 4 (400 mg)	8[cb]	NA	8
Cohort 5 (800 mg)	8	NA	8
Cohort 6 (1000 mg)	8	NA	8

Abbreviation: NA = not applicable.

[a] Doses may be adjusted based on data obtained in previous study cohorts.

[ba] Cohort 1 will not have a defined stratification by sex scheme. Eight participants will be randomized including males and/or females.

[cb] Female participants in Cohorts 3 and 4 will receive study drug in fasted and fed conditions, separated by a washout period of at least 1 week.



Abbreviations: SAD = single-ascending dose (Orange); MAD = multiple-ascending dose (Green).

Note: Doses may be adjusted based on data obtained in previous study cohorts and parts. The timeline listed is an approximation intended to illustrate relative cohort timing within and between Parts A and B.

Figure 5.1 Illustration of study design for Protocol J2D-MC-CVAA.

5.4 Scientific Rationale for Study Design

The study will include a pilot assessment of food effect in female participants only. ~~Specifically, 8 female participants in the Part A 100- and 400-mg dose cohorts will receive 2 sequential 100- and 400-mg doses, respectively. In each of these~~ In the food effect cohorts, the first dose will be administered in the fasted state, and the second dose in fed state.

7.1 Treatment Administered

Part A:

The planned dose levels are 10, 50, 100, 400, 800, and up to 1000 mg. LY3526318 or matching placebo will be administered to participants as a single dose by trained CRU personnel. Dose levels may be modified based on safety and available PK, but which ~~will~~ are not intended to exceed the NOAEL.

Appendix 8. Protocol Amendment: J2D-MC-CVAA(b)

Protocol J2D-MC-CVAA has been amended; the new will be indicated as amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

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

Section	Changes made	Rationale for the change
2. Study Schedule Protocol J2D-MC-CVAA: Part B (MAD) and associated text throughout protocol	Two additional SOE tables for Cohorts 8 and 9 to clearly indicate differing in house stays for additional PK sample collection regimens between the MAD cohorts. For Cohorts 8 and 9, the revised PK sample collection schedule runs through 96 and 120 hours post Day 14 dose, respectively, with only 3 PK samples added in each cohort.	SAD PK data resulted in a longer half-life than was predicted, so additional collections required to characterize the terminal elimination of LY3526318
2. Study Schedule Protocol J2D-MC-CVAA: Part B (MAD)	Temperature timepoints revised to be consistent with Vital Sign timepoints	Administrative update
Appendix 5. Blood Sampling Summary	Revised blood volume based on additional PK samples	Same as above.
7.1 Treatment Administered	Revised the capsule strengths from “10 mg and 100 mg” to “10 mg to 100mg”	Capsules will be prepared at dosage strengths administered.

Revised Protocol Sections

Note: Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of underscore.

2 Schedule of Activities

Study Schedule Protocol J2D-MC-CVAA: Part B (MAD)-Cohort 7

	S	Treatment/In CRU								Post treatment	ED[a]
Study Day	**≤28**	**-1**	**1**	**2**	**3**	**5**	**8**	**14**	**15**	**23**	
Visit Window (days)										**±2**	
Visits	**1[b]**	**2**								**3**	
CRU admission		X									
CRU discharge									X		
Participant information (including I/E criteria)	X	X									
Informed consent	X										
Medical history	X										
Height	X										
Weight	X		X							X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	D	D		C	C
Urine drug screen and ethanol test	X	X									
Vital signs including temperature[c]	X	X	X	X	X	X	X	X		X	X
Hematology and clinical chemistry[d]	X	X		X			X	X		X	X
Urinalysis[e]	X	X									
Pregnancy test (serum beta-hCG)[f]	X	X								X	X
HIV, HCV, HBsAg	X										
ECG[g]	X		X					X		X	X
C-SSRS	X	X							X	X	X
Randomization			X								
Study drug administration[h]			← X →								
PK blood sample[i]			X	X	X	X	X	X	X		X
Adverse event	← X →										
Concomitant medications	← X →										

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hours; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; MAD = multiple-ascending dose; PK = pharmacokinetic; S = screening.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of first dose administration.

[c] Vital signs and temperature should be measured at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose; predose on all other indicated dosing days. ~~Temperature should be measured predose on all indicated days.~~

[d] Hematology and chemistry sample should be collected predose on stipulated visits.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose.

[h] Study drug will be administered once daily in the CRU through Day 14, and the exact time of administration will be recorded. All doses are planned to be administered in a fasting state; however, following a review of the food effect data from Part A, all doses may be administered with food. Fasting on PK sampling days is defined as at

least 8 hours predose and 4 hours postdose. Fasting on non-PK and predose only PK sampling days is defined as at least 8 hours predose and 2 hours postdose on all other indicated days.

[i] On Days 1 and Day 14, PK samples will be collected at time zero (predose) and at approximately at 1, 2, 4, 6, 8, and 12 hours after dosing. On Day 2 (at predose) and on Day 15 (prior to discharge), 1 PK sample will be taken at 24 hours postdose. Predose PK samples will also be obtained on Days 3, 5, and 8. If applicable, a sample will be collected at the ED visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. Post-assay remaining PK plasma samples may be stored for metabolite identification.

Study Schedule Protocol J2D-MC-CVAA: Part B (MAD)-Cohort 8

	S	Treatment/In CRU							Post treatment	ED[a]
Study Day	≤28	-1	1	2	3	5	8	14	15	16	17	18	23	
Visit Window (days)														±2	
Visits		1[b]								2				3	
CRU admission			X												
CRU discharge													X		
Participant information (including I/E criteria)	X	X													
Informed consent	X														
Medical history	X														
Height	X														
Weight	X		X											X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	D	D	D	D	D			C	C
Urine drug screen and ethanol test	X	X													
Vital signs including temperature[c]	X	X	X	X	X	X	X	X						X	X
Hematology and clinical chemistry[d]	X	X		X			X	X						X	X
Urinalysis[e]	X	X													
Pregnancy test (serum beta-hCG)[f]	X	X												X	X
HIV, HCV, HBsAg	X														
ECG[g]	X		X					X						X	X
C-SSRS	X	X											X	X	X
Randomization			X												
Study drug administration[h]			← X →												
PK blood sample[i]			X	X	X	X	X	X	X	X	X	X	X		X
Adverse event	← X →														
Concomitant medications	← X →														

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hours; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; MAD = multiple-ascending dose; PK = pharmacokinetic; S = screening.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of first dose administration.

[c] Vital signs and temperature should be measured at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose; predose on all other indicated dosing days.

[d] Hematology and chemistry sample should be collected predose on stipulated visits and approximately 24 hours post Day 14 dose on Day 15.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose.

[h] Study drug will be administered once daily in the CRU through Day 14, and the exact time of administration will be recorded. All doses are planned to be administered in a fasting state; however, following a review of the food effect data from Part A, all doses may be administered with food. Fasting on PK sampling days is defined as at least 8 hours predose and 4 hours postdose. Fasting on non-PK and predose only PK sampling days is defined as at least 8 hours predose and 2 hours postdose on all other indicated days.

[i] On Day 1 and Day 14, PK samples will be collected at time zero (predose) and at approximately at 1, 2, 4, 6, 8, and 12 hours after dosing. Predose PK samples will also be obtained on Days 2, 3, 5, and 8. One PK sample will be taken at approximately 24, 48, 72, and 96 hours post Day 14 dose on Days 15, 16, 17, and 18, respectively. If applicable, a sample will be collected at the ED visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. Post-assay remaining PK plasma samples may be stored for metabolite identification.

Study Schedule Protocol J2D-MC-CVAA: Part B (MAD)-Cohort 9

	S	Treatment/In CRU						Post treatment	ED[a]							
Study Day	≤28	-1	1	2	3	5	8	14	15	16	17	18	19	23		
Visit Window (days)															±2	
Visits									1[b]	2					3	
CRU admission										X						
CRU discharge														X		
Participant information (including I/E criteria)									X	X						
Informed consent									X							
Medical history									X							
Height									X							
Weight									X		X				X	X
Physical examination (complete [C] or directed [D])									C	D	D	D	D	D	C	C
Urine drug screen and ethanol test									X	X						
Vital signs including temperature[c]									X	X	X	X	X	X	X	X
Hematology and clinical chemistry[d]									X	X		X		X	X	X
Urinalysis[e]									X	X						
Pregnancy test (serum beta-hCG)[f]									X	X					X	X
HIV, HCV, HBsAg									X							
ECG[g]									X		X			X	X	X
C-SSRS									X	X				X	X	X
Randomization											X					
Study drug administration[h]											← X →					
PK blood sample[i]											X	X	X	X		X
Adverse event										← X →						
Concomitant medications										← X →						

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hours; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; MAD = multiple-ascending dose; PK = pharmacokinetic; S = screening.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of first dose administration.

[c] Vital signs and temperature should be measured at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose; predose on all other indicated dosing days.

[d] Hematology and chemistry sample should be collected predose on stipulated visits and approximately 24 hours post Day 14 dose on Day 15.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest at following time points: Days 1 and 14 – predose and 2 hours, 4 hours, and 8 hours postdose.

[h] Study drug will be administered once daily in the CRU through Day 14, and the exact time of administration will be recorded. All doses are planned to be administered in a fasting state; however, following a review of the food effect data from Part A, all doses may be administered with food. Fasting on PK sampling days is defined as at

least 8 hours predose and 4 hours postdose. Fasting on non-PK and predose only PK sampling days is defined as at least 8 hours predose and 2 hours postdose on all other indicated days.

[i] On Day 1 and Day 14, PK samples will be collected at time zero (predose) and at approximately at 1, 2, 4, 6, 8, and 12 hours after dosing. Predose PK samples will also be obtained on Days 2, 3, 5, and 8. One PK sample will be taken at approximately 24, 48, 72, and 120 hours post Day 14 dose on Days 15, 16, 17, and 19, respectively. If applicable, a sample will be collected at the ED visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. Post-assay remaining PK plasma samples may be stored for metabolite identification.

Section 5.1 Overall Design

Following a screening period of up to 28 days, eligible participants will receive once-daily treatment with study drug for 14 days. Participants will be confined to the CRU from Day -1 until all study assessments are completed on Day 15 (Cohort 7), Day 18 (Cohort 8) or Day 19 (Cohort 9). Within each cohort, eligible participants will be randomly assigned to receive LY3526318 or placebo in a 6:2 ratio. The first cohort will be administered LY3526318 following a review of safety and PK data through Part A 400-mg cohort and fed period of the 100-mg cohort.

Section 7.1 Treatment Administered

Part B

The LY3526318 drug product is supplied as a hard gelatin capsule in dosage strengths of 10 ~~and~~ to 100 mg. Placebo capsules will be identical in size and shape.

Appendix 5 Blood Sampling Summary

Protocol J2D-MC-CVAA Sampling Summary – Part B, Cohort 7 (MAD)

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	5	32.5
Pharmacokinetics	3	19	57
Total			101

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

Protocol J2D-MC-CVAA Sampling Summary – Part B, Cohorts 8-9 (MAD)

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	5	32.5
Pharmacokinetics	3	22	66
Total			110

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

Appendix 9. Protocol Amendment: J2D-MC-CVAA(c)

Protocol J2D-MC-CVAA has been amended; the new will be indicated as amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

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

Section	Changes made	Rationale for the change
2 Schedule of Activities Part B Tables Cohorts 8 and 9	Deleted erroneous text regarding collection of Day 15 clinical lab samples	Administrative (error correction)
Throughout document-Added additional SAD Cohort-(Cohort 10)	Added an additional cohort of 8 female participants Revised food effect language throughout too	To further assess food effect on a single dose of LY in 3 period crossover design
Throughout document	Indicated that men would only continue to be dosed in the study if the exposure data from previous cohorts supported it	To further clarify dosing in men based on exposure data

Revised Protocol Sections

Note: Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of underscore.

2 Schedule of Activities

Table 2-1 title updated as: Study Schedule Protocol J2D-MC-CVAA: Part A Cohorts 1-6 (SAD)

Table 2-2 Study Schedule Protocol J2D-MC-CVAA: Part A-Cohort 10-(3 Period Food Effect Cohort)

	S	Treatment/ In CRU					Posttreatment	ED[a]
Study Day (visit window)	**≤28**	**-1**	**1**	**2**	**3**	**4**	**10 (± 2)**	
Period		**1-3**					**3**	**1-3**
Visits	**1[b]**	**2[c]**					**3**	
CRU admission		X						
CRU discharge						X		
Participant information (including I/E criteria)	X	X						
Informed consent	X							
Medical history	X							
Height	X							
Weight	X		X				X	X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	C	C
Urine drug screen and ethanol test	X	X						
Vital signs including temperature	X	X	X (predose, 2 h, 4 h, 8 h)	X	X		X	X
Hematology and clinical chemistry	X	X		X[d]	X[d]		X	X
Urinalysis[e]	X	X						
Pregnancy test (serum beta-hCG)[f]	X	X					X	X
HIV, HCV, HBsAg	X							
ECG[g]	X		X (predose, 2 h, 4 h, 8 h)				X	X
C-SSRS	X	X					X	X
Randomization			X[h]					
Study drug administration[i]			X					
PK blood sample[j]			X	X	X	X		X
PK 24-hour urine collection[k]			← X →					
Adverse event	← X →							
Concomitant medications	← X →							

Abbreviations: C = complete physical examination; CRU = clinical research unit; C-SSRS= Columbia-Suicide Severity Rating Scale; D = directed physical examination; ECG = electrocardiogram; ED = early discontinuation; h = hour; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; PK = pharmacokinetics; S = screening; SAD = single-ascending dose.

[a] Participants who discontinue from the study prior to study completion should complete the ED visit procedures.

[b] Screening will be performed within 28 days of the first dose being administered.

[c] All participants will remain in the CRU until completion of Day 4 procedures.

[d] Hematology and clinical chemistry sample to be taken in the morning.

[e] A standard urine test strip/dipstick may be used.

[f] A serum beta-hCG test will be performed in all female participants, except in female participants with confirmed hysterectomy.

[g] A single 12-lead ECG will be recorded in the supine position after 5 minutes of rest.

[h] Randomization will occur during first period only.

[i] Doses are planned to be administered as follows in each period:

- Period 1-Fed standardized high fat meal to start 30 minutes prior to dose administration
- Period 2-Fasted at least 8 hours predose with a standardized high fat meal administered 30 minutes post dose
- Period 3-Fasted at least 8 hours predose with a standardized high fat meal administered 1 hour post dose

Periods will be separated by a washout of at least 1 week. The meals administered in all treatment periods should be consumed within 30 minutes. The exact time study drug is administered will be recorded.

[j] In each treatment period, on Day 1, PK samples will be collected at time zero (predose) and at approximately 1, 2, 4, 6, 8, and 12 hours after dosing. One PK sample will be taken at 24, 48, and 72 hours postdose (Days 2, 3, and 4), and if applicable, at the ED Visit. PK sample collection times are provided as a guidance and may be modified based on clinical needs. Actual dates and times of sample collection must be recorded. The following time collection intervals are proposed: predose samples may be obtained between waking up and dosing. Postdose samples may be obtained within ±5% of the scheduled collection time. The ±5% time window also applies to the start and end times of urine collection intervals. Post-assay remainder PK plasma samples may be stored for metabolite identification.

[k] Urine collection interval is 0 to 24 hours postdose. The total urine volume of the 0- to 24-hour collection will be recorded.

Tables 2-4 and 2-5, Footnote d: Hematology and chemistry sample should be collected predose on stipulated visits~~. and approximately 24 hours post Day 14 dose on Day 15~~.

3.3 Benefit/Risk Assessment

CCI [redacted]

5.1 Overall Design

Table 5-1 Part A Stratification Based on Sex

Cohort (Planned dose level [a])	Number of Females Randomized	Number of Males Randomized	Total Participants Randomized
Cohort 1 (10 mg)	Up to 8[b]	Up to 8[b]	8
Cohort 2 (50 mg)	4	4	8
Cohort 3 (100 mg)	8[c]	4	12
Cohort 4 (400 mg)	8[c]	NA	8
Cohort 5 (800 mg)	8	NA	8
Cohort 6 (1000 mg)	8	NA	8
Cohort 10 (100 mg)	8[d]	NA	8

Abbreviation: NA = not applicable.

[a] Doses may be adjusted based on data obtained in previous study cohorts.

[b] Cohort 1 will not have a defined stratification by sex scheme. Eight participants will be randomized including males and/or females.

[c] Female participants in Cohorts 3 and 4 will receive study drug in fasted and fed conditions, separated by a washout period of at least 1 week.

[d] All 8 female participants in Cohort 10 will receive LY3526318 in a 3-period crossover with standardized high fat meals administered prior to dose, and at 30 min and 1 hour post dose. Participants receiving meals post dose administration will receive their dose in the fasted state. Periods are separated by a washout period of at least 1 week.

Cohorts administered above LY3526318 100 mg are anticipated to exceed the approximate 10x margin to the projected no-observed-adverse-event-level (NOAEL)-equivalent exposure for males; for this reason, only female participants will be enrolled at dose levels higher than 100 mg. Additionally, if exposure data from previous cohorts does not support dose escalation in males through 100 mg, males will be discontinued from further dosing in the study.

An additional cohort (Cohort 10) will assess the effect of food on LY3526318 PK in 8 female participants. All participants in this cohort will received 100 mg LY3526318 with standardized high fat meal in an open-label, 3-way crossover manner (meal administered prior to dose, at 30 minutes and at 1 hour post dose; Table 2-2). Participants receiving meals post dose administration will receive their dose after an approximately 8-hour fast. Periods will be separated by a washout period of at least 1 week.

5.2 Number of Participants

Part A: Approximately 52 participants will be randomized to achieve 8 evaluable participants per cohort, except the 100-mg cohort that will include 8 evaluable females and 4 evaluable males and 100 mg food assessment cohort (Cohort 10) that will include 8 evaluable females.

5.4 Scientific Rationale for Study Design

This study will include a pilot assessment of food effect in female participants only. In the food effect cohorts, the first doses will be administered in fed and ~~the~~ fasted states, as indicated ~~and the second dose in the fed state~~. Residual exposure will be minimized with a washout period of at least 1 week between doses. The 100 and 400-mg doses and the high-fat meal were chosen because preclinical data suggest that study drug administration with a high-fat meal may increase exposures of LY3526318 by approximately 5 fold, compared to administration in the fasted state. Having a food assessment at 2 different dose levels will help inform the mode of study drug administration in the MAD and subsequent studies. In addition, because LY3526318 preclinical PK was subproportional to dose, and the effect of food may also be nonlinear, assessing the food effect at 2 different dose levels will provide a better understanding of LY3526318 PK.

7.1 Treatment Administered

Part A:

All doses are planned to be administered in a fasting state (at least 8 hours predose and 4 hours postdose), with the exception of the indicated doses in the food effect cohorts ~~second dose in the food effect assessment cohorts~~ (100 and 400 mg), where the study drug will be administered in both the fasted and fed states, as specified ~~with a high-fat meal~~. Approximately 50% of the total caloric content of the meal should be from fat. Study participants should eat this meal in 30 minutes or less; and the study drug should be administered 30 minutes after the start of the meal. In all cases, study drug should be taken with 1 glass (approximately 240 mL) of water and no food should be allowed for at least 4 hours postdose. Water can be allowed as desired except for 1 hour before and after drug administration.

7.2 Method of Treatment Assignment

Randomization in the first cohort (10 mg, Cohort 1) will not be stratified by sex and participants will receive either LY3526318 or placebo in a 6:2 ratio, unless otherwise indicated.

Participants in Cohorts 4 and onwards will receive either LY3526318 or placebo in a 6:2 ratio, except for Cohort 10 where all participants will receive LY3526318.

Appendix 5. Blood Sampling Summary

Protocol J2D-MC-CVAA Sampling Summary – Part A (Cohort 10) (SAD)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Number of Periods Samples are Collected	Total Volume (mL)
Screening tests[a]	11.5	1	1	11.5
Clinical laboratory tests[a,b]	6.5	4	3	78
Pharmacokinetics[b]	3	11	3	99
Total				188.5

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

[b] Cohort 10 participants will receive study drug once in 3 different periods. Hence, clinical laboratory and pharmacokinetic samples will be collected three times, except for the follow-up clinical laboratory sample that will be collected only after the final period.

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