Protocol: J2U-MC-YBAA(c)

A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single-and Multiple-Ascending Doses of LY3522348 in Healthy Participants

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Title Page

Protocol Title: A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single- and Multiple-Ascending Doses of LY3522348 in Healthy Participants

Protocol Number: J2U-MC-YBAA

Amendment Number: (c)

Compound: LY3522348

Study Phase: 1

Short Title: Single- and Multiple-Ascending Doses of LY3522348 in Healthy Participants

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment (b)	04-Mar-2021
Protocol amendment (a)	09-Sep-2020
Original Protocol	14-Jul-2020

Amendment [c]

Overall Rationale for the Amendment:

Protocol was amended to remove sorbitol analysis from pharmacodynamic analysis section, as it is an indirect biomarker. The fructose level is a direct biomarker, and its analysis was confirmed to provide robust and sufficient pharmacodynamic information.

Section # and Name	Description of Change	Brief Rationale
Section 8.6 Pharmacodynamics	Removed sorbitol analysis	Fructose analysis was confirmed to provide robust information, as fructose level is a direct biomarker while sorbitol is indirect.
Section 9.4.3.1 Pharmacodynamic Parameter Estimation	Removed sorbitol analysis	Fructose analysis was confirmed to provide robust information, as fructose level is a direct biomarker while sorbitol is indirect.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore, not described

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single- and Multiple-Ascending Doses of LY3522348 in Healthy Participants

Short Title: Single- and Multiple-Ascending Doses of LY3522348 in Healthy Participants

Rationale

LY3522348, a novel KHK inhibitor, is being developed as a daily oral treatment for NASH.

Study J2U-MC-YBAA (YBAA) is a first-in-human study, which aims to assess the safety, tolerability, PK, and PD of single and multiple oral doses of LY3522348 in healthy participants. The PK, PD, safety, and tolerability data from this study in healthy participants will assist in identifying an appropriate dose range for subsequent clinical studies in participants with NASH. In addition, this study will assess the impact of LY3522348 on midazolam metabolism.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of LY3522348 following single and multiple oral doses	• Incidence of TEAEs and SAEs • Clinically significant changes in vital signs data, safety laboratory parameters, and electrocardiograms
Secondary	
• To determine the PK of LY3522348 following single and multiple oral doses	• AUC(0-24), AUC(0-inf), C_{max}, and t_{max}

Abbreviations: AUC = area under the concentration versus time curve; AUC(0-24) = AUC from time zero to 24 hours; AUC(0-inf) = AUC from time zero to infinity; C_{max} = maximum observed drug concentration; ECG = electrocardiogram; PK = pharmacokinetics; SAE = serious adverse event; t_{max} = time of C_{max}; TEAE = treatment-emergent adverse event.

Overall Design

Study YBAA is a Phase 1, single site, randomized, investigator- and participant-blind, placebo-controlled, 2-part study in healthy participants.

Disclosure Statement

This is a sequential single- and multiple-ascending dose study that is investigator- and participant-blind.

Number of Participants

A maximum of 100 participants will be randomly assigned to study intervention such that approximately

- 48 evaluable participants complete Part A, and
- 32 evaluable participants complete Part B of the study.

Intervention Groups and Duration

Intervention groups

Eligible participants will be randomly assigned to study intervention,

- 6 LY3522348 and 2 placebo per cohort in Part A, and
- 6 LY3522348 and 2 placebo per cohort in Part B.

Duration

Part A duration

Each participant's involvement in the study is expected to last up to 7 weeks, including

- a 4-week screening period
- a 1-week treatment period
- and a
- follow-up visit 2 weeks after the dose.

Part B duration

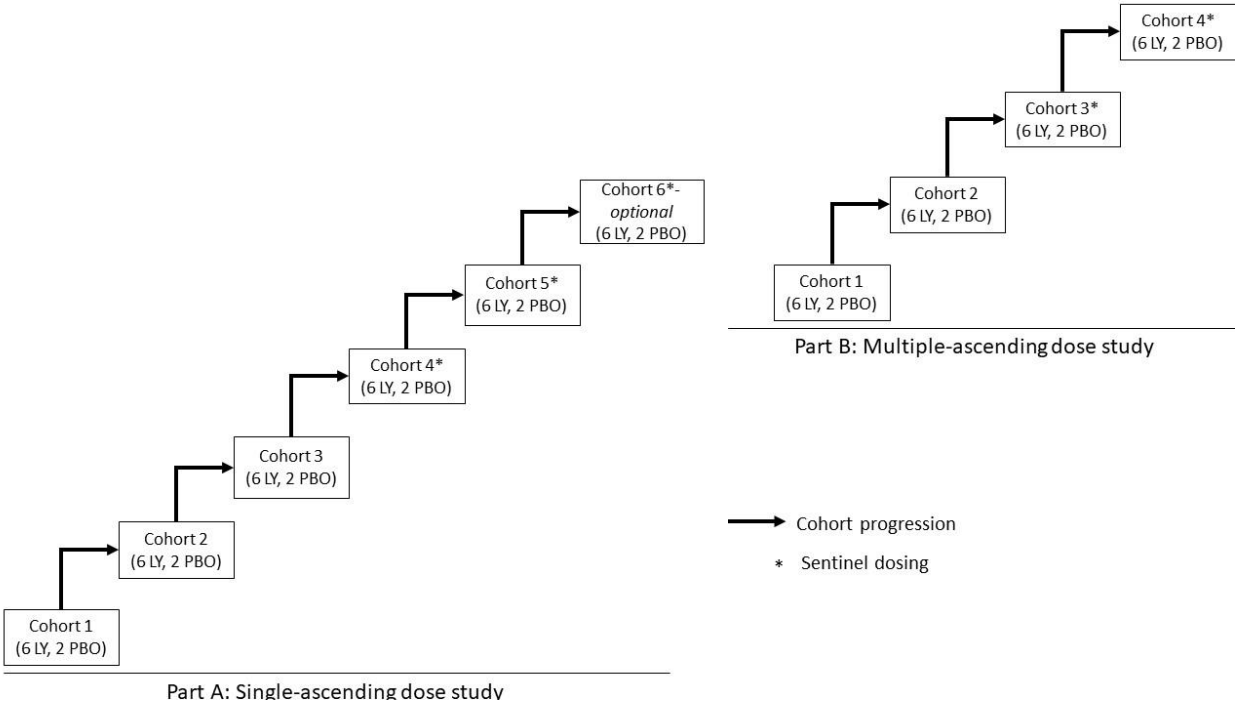
Each participant's involvement in the study is expected to last up to 8 weeks, including

- a 4-week screening period
- a 2-week treatment period, and a
- 2-week follow-up period after the last dose.

Data Monitoring Committee

No

1.2. Schema



Abbreviations: LY = LY3522348; PBO = placebo.

1.3. Schedule of Activities (SoA)

1.3.1. Schedule of Activities for Part A

	Screening	Days							FU	ED	Comments
Procedure	**≤28 days before Day -1**	**-1**	**1**	**2**	**3**	**4**	**5-6**	**7**	**Day 14±1**		
Informed Consent	X										
Admission		X									
Randomization			X								Occurs prior to study intervention administration.
Discharge								X			If clinically indicated, participants may remain inpatient longer.
Non-Residential Visit									X	X	
Medical History	X										
Complete Physical Examination	X	X				X		X	X	X	At the discretion of the investigator, targeted PE may be conducted at other visits.
Height	X										
Weight	X	X									
Pregnancy Test	X	X							X	X	Serum test at screening. Urine test at all other time points.
Blood Pressure and Pulse Rate	X	X	P, 0.75, 1.5, 3, 4, 6, 8, 10, 12 h	24, 36 h	48 h	72 h		X	X	X	If agreed upon between the sponsor and the investigator, more time points may be added.
Body Temperature	X	X							X	X	
Clinical Laboratory Tests	X	X	P	X	X			X	X		See Section 10.2 for complete list.
Serum Creatinine			P, 4, 12, 24 h								Sampling times are relative to the time of study intervention administration (0 min).
Triplicate 12-Lead ECG			-1.5, -1, -0.5, 0.75, 1.5, 3, 4, 6, 12 h	24 h							Sampling times are relative to the time of study intervention administration (0 min).
Single 12-Lead ECG	X				X	X		X	X	X	
Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	
LY3522348 Administration			X								

	Screening	Days							FU	ED	Comments
Procedure	**≤28 days before Day -1**	**-1**	**1**	**2**	**3**	**4**	**5-6**	**7**	**Day 14±1**		
Pharmacokinetic Sampling			P, 0.75, 1.5, 3, 4, 6, 8, 10, 12, 16 h	24 h	48 h	72 h	96 h	144 h			Sampling times are relative to the time of study intervention administration (0 min).
Low Fructose Meal			20 minutes, 6, 12 h								
Fructose Beverage (for FTT)			during meal: 20 minutes, 6, 12 h								
FTT Assay			0 (pre-meal), 1.5, 3, 4, 5, 6 (pre-meal), 8, 10, 12 (pre-meal), 14, 16 h	20, 24 h (pre-meal)							Sampling times are relative to the time of study intervention administration (0 min).
Genetic Sample			X								Only 1 sample is needed per participant.
Fasting Biomarker Samples - Nonpharmacogenetic			P	X							
24-hour Urine Collection for LY3522348 and Creatinine			0-24 h								Sampling times are relative to the time of study intervention administration (0 min).

Abbreviations: ECG = electrocardiogram; ED = early discontinuation; FTT = fructose tolerance test; FU = follow-up; h = hours; min = minutes; P = predose; PE = physical examination.

Notes: If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture. Samples collected for clinical laboratory tests including urine analysis may be analyzed at a local laboratory. All time points specified in the table are approximate and may be adjusted at the discretion of the investigator.

1.3.2. Schedule of Activities for Part B

Procedure	Screening	Days												Follow-up		Comments
	≤28 days before Day -2 or -1	-2	-1	1	2	3 to 6	7	8	9 to 13	14	15 to 17	18/19	20/21	28± 2	ED	
Informed Consent	X															
Admission		C3 C4	C1, C2													
Randomization			C3, C4	C1, C2												Occurs prior to study intervention administration.
Discharge													Day 20: C1, C2; Day 21: C3, C4			If clinically indicated, participants may remain inpatient longer.
Medical History	X															
Complete Physical Examination	X													X	X	At the investigator's discretion, targeted PE may be conducted at other visits.
Height	X															
Weight	X	C3 C4	C1, C2								Day 15			X	X	
Pregnancy Test	X	C3 C4	C1, C2											X	X	Serum test at screening. Urine test at all other time points.
Blood Pressure and Pulse Rate	X		X	P, 0.75, 1.5, 3, 4, 6, 12 h	24, 36 h	48, 72 h	P, 0.75, 1.5, 3, 4, 6, 12 h			P, 0.75, 1.5, 3, 4, 6, 12 h				X	X	If agreed upon between the sponsor and the investigator, more time points may be added.
Body Temperature	X		X											X	X	
Clinical Laboratory Tests	X	C3 C4	C1, C2	P		Day 4	X			X			Day 20: C1, C2 Day 21: C3, C4	X	X	See Section 10.2 for complete lists.
Single 12-Lead ECG	X												X (before	X	X	

Procedure	Screening	Days											Follow-up		Comments
	≤28 days before Day -2 or -1	-2	-1	1	2	3 to 6	7	8	9 to 13	14	15 to 17	18/19	20/21	28± 2	ED	
													144 h PK sampling)			
Triplicate 12-Lead ECG				-1.5, -1, -0.5, 0.75, 1.5, 3, 4, 6, 12 h			P, 0.75, 1.5, 3, 4, 6, 12 h			P, 0.75, 1.5, 3, 4, 6, 12 h	24 h (P)	96 h (before PK sampling)				Sampling times are relative to the time of study intervention administration. Day 18 for Cohorts 1 and 2 Day 19 for Cohorts 3 and 4
Adverse Event Recording	X	C3 C4	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study intervention administration				X							Day 15: C3, C4					
Pharmacokinetic Sampling for Cohorts 1 and 2				P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (P)		P			P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h	24, 48, 72 h	Day 18: 96 h	Day 20: 144 h			Sampling times are relative to the time of study intervention administration. After a review of preliminary PK data, sampling times may be adjusted.
Pharmacokinetic Sampling for Cohorts 3 and 4				P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (P)		P			P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h	P, 0.75, 1.5, 3, 4, 6, 8, 12, 16, 24, 48 h	72, 96 h	Day 21: 144 h			
Midazolam administration			X								Day 15					For Cohorts 3 and 4 only.
Midazolam PK sampling			P, 0.5, 1, 1.5, 3, 5, 8, 12 h	24 h (P)							Day 15: P, 0.5, 1, 1.5, 3, 5, 8, 12, 24 h					For Cohorts 3 and 4 only. Sampling times are based on midazolam administration.
Fasting Insulin and Adiponectin				P						P						

Procedure	Screening	Days												Follow-up		Comments
	≤28 days before Day -2 or -1	-2	-1	1	2	3 to 6	7	8	9 to 13	14	15 to 17	18/19	20/21	28± 2	ED	
Low Fructose Meal				20 minutes, 6, 12 h						20 minutes, 6, 12 h						
Fructose Beverage (for FTT)				during meal: 20 minutes, 6, 12 h						during meal: 20 minutes, 6, 12 h						
FTT Assay				0 (pre-meal), 1.5, 3, 4, 6 (pre-meal), 7, 8, 10, 12 (pre-meal), 13, 14, 16 h	24 h (predose and pre-meal)					0 (pre-meal), 1.5, 3, 4, 6 (pre-meal), 7, 8, 10, 12 (pre-meal), 13, 14, 16 h	24 h (pre-meal for C1 and C2 and predose and premeal for C3 and C4)					Sampling times are relative to the time of study intervention administration (0 min) on Day 1 or Day 14.
Genetic Sample				P												
Fasting Biomarker Samples - Nonpharmacogenetic				P	X						Day 15					
Coproporphyrin samples (stored)			P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h (C3, C4)	P						P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (P)					All cohorts should have a P sample collected on Day 1

Abbreviations: C1 = Cohort 1; C2 = Cohort 2; C3 = Cohort 3; C4 = Cohort 4; ECG = electrocardiogram; ED = early discontinuation; FTT = fructose tolerance test; FU = follow-up; h = hours; min = minutes; P = predose; PE = physical examination; PK = pharmacokinetics.

Notes: If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture. Samples collected for clinical laboratory tests including urine analysis may be analyzed at a local laboratory. All time points specified in the table are approximate and may be adjusted at the discretion of the investigator.

2. Introduction

LY3522348, a novel KHK inhibitor, is being developed as a daily oral treatment for NASH.

2.1. Study Rationale

Study J2U-MC-YBAA (YBAA) is a first-in-human study, which aims to assess the safety, tolerability, PK, and PD of single and multiple oral doses of LY3522348 in healthy participants. The PK, PD, safety, and tolerability data from this study in healthy participants will assist in identifying an appropriate dose range for subsequent clinical studies in patients with NASH. In addition, this study will assess the impact of LY3522348 on midazolam metabolism.

2.2. Background

Ketohexokinase

KHK, also known as fructokinase, is the enzyme responsible for the first step in fructose metabolism, which occurs through phosphorylation of fructose to fructose 1-phosphate. Fructose, per se, is biologically inactive and requires metabolism by KHK to elicit negative metabolic consequences. Excessive fructose causes pro-lipogenic and inflammatory profiles in the liver where KHK is abundantly expressed and is the primary site of fructose metabolism (Hannou et al. 2018).

Various epidemiological and human intervention studies revealed the association of fructose consumption with

- insulin resistance (Basciano et al. 2005)
- NAFLD and NASH (Vos and McClain 2009; Weber et al. 2018)
- CV disease (Fung et al. 2009; de Koning et al. 2012), and
- accompanying mortality (Collin et al. 2019).

Conversely, human intervention trials suggest significant metabolic benefits from isocaloric fructose restriction including

- reduced liver steatosis
- suppressed hepatic de novo lipogenesis
- decreased inflammation, and
- improved insulin sensitivity.

KHK inhibition is anticipated to mimic the isocaloric fructose restriction profiles.

Ketohexokinase as a therapeutic target

Human genetic validation of KHK as a therapeutic target exists based on loss-of-function mutations that result in essential fructosuria, an autosomal recessive disorder (Laron 1961; Froesch 1969; Bonthron et al. 1994). Individuals with this benign condition have inactive isoforms of KHK, which

- limits the liver's ability to metabolize and clear fructose
- increases fructose excursion into the serum, and
- results in excretion of fructose into urine.

Due to the low prevalence of condition (approximately 1/100,000) and/or its benign nature, individuals with essential fructosuria have not been characterized well enough to define potential metabolic phenotype improvements. However, characterization of these individuals supports the notion that a KHK inhibitor is anticipated to eliminate excess carbohydrates without a mechanism-based safety issue.

KHK inhibition (via mouse knockout, siRNA, small molecule) in nonclinical animal models support efficacy in NAFLD/NASH (Ishimoto et al. 2012; Ishimoto et al. 2013; Lanaspa et al. 2013; Lanaspa et al. 2018; Softic et al. 2017). KHK inhibition is expected to attenuate fructose metabolism resulting in

- reduction of liver fat, inflammation, and fibrosis
- improvement in glycemic control
- improvement in insulin sensitivity, and
- reduction in body weight, free fatty acids, and triglycerides.

A clinical trial in patients with NAFLD treated for 6 weeks with a KHK inhibitor demonstrated

- a statistically greater reduction from baseline in the whole liver fat
- a dose-dependent decrease in fasting insulin and insulin resistance
- a dose-dependent percentage changes in high-sensitivity C-reactive protein (reduction) and adiponectin (increase), and
- an acceptable safety and tolerability profile (Calle et al. 2019).

Nonclinical data

The nonclinical safety profile of LY3522348 was evaluated in a set of GLP in vitro and in vivo studies, including genetic toxicology assays, safety pharmacology studies, and repeat-dose toxicity studies in rats and dogs. In the 4-week GLP toxicology and toxicokinetic studies, a NOAEL was determined in both species. A no-observed-effect level was also determined in a single-dose CV safety pharmacology study in dogs. The key nonclinical safety characteristics of LY3522348 consist of

- morbidity and/or emesis/reflux resulting in early termination
- liver effects
- CV effects
- gastrointestinal effects, and
- lymphoid/hematopoietic effects.

It should be noted that the majority of the repeat-dose toxicity findings in both species occurred at the highest dose tested, which exceeded the maximum tolerated dose. At the mid-dose in each of the studies, effects were mild and not considered adverse. LY3522348 was not considered genotoxic based on the weight of evidence from a battery of genotoxicity tests and no notable findings in respiratory or neurologic safety pharmacology assessmentsLY3522348 IB.

2.3. Benefit/Risk Assessment

LY3522348 has not been administered to humans previously.

There is no anticipated therapeutic benefit for the healthy participants in this study.

Study YBAA will be conducted in accordance with principles outlined in the Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMA 2017). While this guidance recommends use of sentinel dosing in first-in-human studies, it also allows for flexibility in a proposed dosing approach based on the available scientific data and preclinical assessment of a given molecule. Based on the risk assessment of the available data, LY3522348 does not present a high-uncertainty profile, which would necessitate inclusion of sentinel dosing approach (DeGeorge et al. 2018). Nonetheless, sentinel dosing will be introduced in SAD and MAD cohorts anticipated to exceed 1/10th of the dog NOAEL exposure observed in the 1-month toxicity study that showed steep dose response.

The available nonclinical safety information for LY3522348 supports its evaluation in healthy participants. The overall nonclinical safety profile suggests that there is a low risk to human participants administered LY3522348 at the proposed dose range. The doses at the NOAELs in rat (30 mg/kg) and dog (20 mg/kg) produced exposures that are at least 3-fold greater and 4-fold greater than the predicted human exposures at the maximum planned doses in the SAD (400 mg) and MAD (300 mg) studies, respectively. The LY3522348-related adverse findings in the rat and dog repeat-dose toxicity studies were limited to dose levels that were not tolerated.

Any identified risks from nonclinical studies (gastrointestinal irritation, CV and vital signs changes, and liver function changes) are considered monitorable and manageable at the planned dose range of 5 to 400 mg of LY3522348 in healthy participants. To further minimize any potential risk, study participants will remain at the investigative site for at least 7 days in Part A and 20 or 21 days in Part B to monitor safety and tolerability during the treatment phase. During the inpatient stay, participants will be closely monitored with scheduled clinical safety laboratory tests, vital signs, and triplicate ECG measurements. The investigator will have the discretion to extend the participant inpatient stay if necessary, for further safety monitoring.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3522348 may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of LY3522348 following single and multiple oral doses	• Incidence of TEAEs and SAEs • Clinically significant changes in vital signs, safety laboratory parameters, and ECGs
Secondary	
• To determine the PK of LY3522348 following single and multiple doses	• AUC(0-24), AUC(0-inf), C_{max}, and t_{max}
Exploratory	
• To determine the PD of LY3522348 following single and multiple doses	• AUC(0-24) of fructose concentration over time following FTT
• To investigate the effect of multiple doses of LY3522348 on the PK of midazolam	• For midazolam and its metabolite, 1′-hydroxymidazolam o AUC o C_{max}, and o the ratio of 1′-hydroxymidazolam:midazolam

Abbreviations: AUC = area under the concentration versus time curve; AUC(0-24) = AUC from time zero to 24 hours; AUC(0-inf) = AUC from time zero to infinite hours; C_{max} = maximum observed drug concentration; FTT = fructose tolerance test; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; t_{max} = time of C_{max}; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study YBAA is a Phase 1, single site, randomized, investigator- and participant-blind, placebo-controlled, 2-part study in healthy participants. Part A is a SAD study and Part B is a MAD study with a DDI component.

All participants will enter a screening period prior to randomization to Part A or B of Study YBAA. Screening may occur up to 28 days prior to admission to the investigative site. Participants who are not enrolled within 28 days of screening may repeat screening assessments to confirm their eligibility.

Safety, PK, PD, and other assessments and activities will be performed as specified in Section 1.3. Section 6.6 describes the criteria for dose escalation.

At the end of the treatment period, all participants will attend a follow-up visit. Additional follow-up visits may occur depending upon emerging safety and PK data.

Study governance considerations are described in Section 10.1.

Refer to Section 1.2.

4.1.1. Part A

Single-ascending oral dose of LY3522348 or placebo will be administered in up to 6 cohorts. It is planned that each cohort will consist of 8 participants, 6 will receive LY3522348 and 2 will receive placebo. Cohort 6 is an optional cohort that may be assessed based on the available safety and PK data from the previous cohorts.

A sentinel dosing strategy will be utilized for Cohorts 4, 5, and 6 anticipated to have predicted mean exposure(s) between 8.1 µg hr/mL and 25.5 µg hr/mL. Two participants (1 LY3522348 and 1 placebo) in each cohort will receive the study drug (Sentinel dose) on the same day. After at least 48 hours of safety monitoring post-Sentinel dosing, the remaining participants in the cohort will be dosed based on the available safety data from the 2 Sentinel participants previously dosed.

A 7-day inpatient stay to allow intensive monitoring will be included for Cohorts 1 to 6.

A follow-up visit will occur approximately 14 days after the dose of study intervention as specified in Section 1.3.1.

The planned starting dose in Part A is 5 mg of LY3522348. Dose escalation will be based on safety and tolerability results from all previous cohorts and PK/PD information when available. Doses in the SAD study will escalate until the mean predicted AUC reaches approximately 25.5 µg·h/mL, which is 10-fold lower than the Day 1 exposure observed in the male rats at 250 mg/kg (this dose resulted in morbidity in rats) approximately 7.5-fold lower than the exposure observed at the rat NOAEL, see Section 4.3 for more details. Dose escalation in the SAD study will not proceed if the predicted mean exposure, $AUC_{(0\text{-inf})}$, in the next cohort is higher than 25.5 µg hr/mL. A dose of 400 mg is predicted to result in this exposure. Dose escalation to next cohort will be no more than 3.3-fold (approximately half-log). The current planned doses are 5, 15, 50, 150, and 400mg, but may be adjusted to reach the desired exposure.

4.1.2. Part B

Part B will be initiated after assessing safety and tolerability through Cohort 4 and PK and PD data through Cohort 3 in Part A.

Multiple-ascending oral doses of LY3522348 or placebo will be administered once daily for 14 days in Cohorts 1 and 2 and for 15 days in Cohorts 3 and 4. Each cohort will consist of 8 participants, 6 will receive LY3522348 and 2 will receive placebo.

In Cohorts 3 and 4, all participants will receive midazolam on Day -1 and study intervention co-administered with midazolam on Day 15.

A Sentinel dosing strategy will be utilized for Cohorts 3 and 4, which are anticipated to result in the exposure(s) between 8.1 µg hr/mL and 19.1 µg hr/mL. Two participants (1 LY3522348 and 1 placebo) in each cohort will receive the study drug (Sentinel dose) on the same day. After at least 48 hours of safety monitoring post Sentinel dosing, the remaining participants in the cohort will be dosed based on the available safety data.

Participants will be discharged on Day 20 for Cohorts 1 and 2 and on Day 21 for Cohorts 3 and 4.

A 21-day inpatient stay to allow intensive monitoring will be included for Cohorts 3 and 4.

A follow-up visit will occur approximately 28 days after the first dose of study intervention as specified in Section 1.3.2.

The current proposed starting dose in Part B is 25 mg of LY3522348, which is predicted to result in plasma concentrations less than the half maximal inhibitory concentration (IC50). This dose may be modified based on safety and tolerability results and available PK/PD information in the SAD study. Doses will be escalated until the mean predicted AUC reaches approximately 19.1 µg·hr/mL, which is $1/10^{th}$ of the NOAEL exposure in rats in the 1-month toxicity study, see Section 4.3 for more details. Dose escalation to next cohort will be based on safety and tolerability results from all previous cohorts and PK/PD information when available and the dose increase will be no more than 3.3-fold (approximately half-log). The current presumed doses are approximately 25, 75, 150, and 300mg but may be adjusted to reach the desired exposure.

4.2. Scientific Rationale for Study Design

Healthy participants

Conducting the study in healthy participants mitigates the potential confounding effects of the disease state and concomitant medications in patients, and therefore provides the most unbiased assessment of the safety and tolerability in this first-in-human study.

Safety, tolerability, PK, and PD data in healthy participants will assist in identifying an appropriate dose range for subsequent clinical studies.

Blinding

A participant- and investigator-blinded, randomized, placebo-controlled design has been chosen to minimize bias during the conduct of the study.

Seamless SAD and MAD studies

Participants will be inpatient during dose administration. If safety concerns arise, the investigator may delay discharge from the investigative site.

In Part A, participants will be admitted to the investigative site on Day -1 and discharged on Day 7 to monitor safety and tolerability of the study intervention.

Part B will be initiated after a review of the safety and tolerability data through Cohort 4 and PK and PD data through Cohort 3 in Part A. The starting dose for Part B will have a predicted mean steady-state AUC(0-24) and C_{max} that are no higher than the mean AUC(0-inf) and C_{max} at the dose completed in Cohort 4 of Part A.

In Part B, participants in Cohorts 1 and 2 will be admitted to the investigative site on Day -1 and discharged on Day 20 to monitor safety and tolerability of the study intervention. However, participants in Cohorts 3 and 4 will be admitted to the investigative site on Day -2 and discharge on Day 21. Participants in each of the 4 cohorts will receive a once-daily dose of study intervention starting on Day 1 and ending on Day 14. Participants in Cohorts 3 and 4 will receive an additional dose of study intervention on Day 15.

Sentinel dosing approach

Sentinel dosing will be included for the Cohorts 4, 5, and 6 in the SAD anticipated to result in the exposure(s) between 8.1 µg•hr/mL and 25.5 µg hr/mL and also for Cohorts 3 and 4 in the MAD, anticipated to result in the exposure(s) between 8.1 µg hr/mL and 19.1 µg hr/mL.

Midazolam

The impact of LY3522348 on in vivo CYP3A4 activity will be assessed in Cohorts 3 and 4 in Part B. The concentrations of LY3522348 in the intestinal lumen at doses to be evaluated in this study are likely to exceed concentrations that are able to be tested against enzyme activity in vitro. As such, plasma concentrations of CYP3A index substrate midazolam and its metabolite, 1′-hydroxymidazolam, will be collected in the absence and presence of LY3522348.

Periodic reviews

In case of any AE requiring such a decision, periodic trial-level safety data reviews will ensure that

- any participant can be discontinued early
- the dose escalation can be terminated, or
- the study can be terminated.

4.2.1. Participant Input into Study Design

Throughout this protocol, the term “participant” is used to indicate an individual who participates in a clinical trial, as a recipient of a study intervention. This usage reflects preferences indicated by patient advocates to more accurately reflect the role of people who take part in clinical trials.

4.3. Justification for Dose

Human apparent clearance of drug (CL/F) is predicted to be 10 to 22 L/h and half-life ($t_{1/2}$) of 15 to 28 hours, supporting once-daily dosing. The human efficacious dose was predicted as the dose

that results in unbound steady-state plasma concentrations of LY3522348 greater than the target (KHK) IC_{50} measured in vitro for 24 hours. This results in a predicted efficacious dose of 30 to 75 mg once daily. The human dose that results in unbound steady-state plasma concentrations of LY3522348 greater than the target (KHK) IC_{90} measured in vitro for 24 hours is predicted to be approximately 300 to 400 mg. Refer to the LY3522348 IB for more details on the initial human dose projections.

The planned starting dose in Part A is 5 mg of LY3522348. When adjusted for body surface area, this dose is at least 60-fold lower than the rat NOAEL dose and 150-fold lower than the dog NOAEL dose. The human exposure at the starting dose is predicted to cover the IC_{10} for approximately 24 hours and is greater than 200-fold lower than the observed exposure at the dog NOAEL. Doses in the SAD study will be escalated until the mean predicted AUC reaches approximately 10-fold lower than the Day 1 exposure AUC observed in the male rat in the 1-month GLP toxicology study(25.5 µg·h/mL), which is approximately 7.5-fold lower than the exposure observed at the rat NOAEL. A dose of 400 mg is predicted to result in this exposure, at which the plasma concentrations are predicted to approach the target IC_{90}, and will provide the opportunity to fully explore the efficacious dose range in human.

The starting dose in the MAD study will be no higher than a tolerated dose at which the predicted exposure has been assessed in the SAD study. Because the cause of the morbidity and early termination in the animal studies was not fully established, the proposed high dose in the MAD study was selected to maintain adequate projected exposure multiples to both the NOAEL as well as the effect levels that caused early termination. Doses in the MAD study will be escalated until the mean predicted AUC reaches 19.1 µg·h/mL, which is $1/10^{th}$ of the exposure at the NOAEL in rats (30 mg/kg) in the 1-month toxicity study. This exposure is 15.4-fold lower than the exposure associated with clinical observations in the rat that resulted in early termination and 10-fold lower and 4.2-fold lower than the exposure observed at the rat and dog NOAELs, respectively. A dose of 300 mg once daily is predicted to result in this exposure. The accumulation ratio is predicted to be approximately 2-fold.

Table 1 shows the dose multiples and exposure multiples between the planned clinical dose levels and relevant endpoints in toxicity studies with LY3522348.

For the DDI assessment, a 200-µg dose of midazolam was chosen to determine a CYP3A-mediated interaction. This subtherapeutic dose is sufficiently measurable in plasma, but should avoid the sedative effect of midazolam (Cannady et al. 2015).

Table 1. Margin of Safety for Oral Administration of LY3522348 Based on Administered Dose and Predicted Human Exposure

	Dose (mg/kg)	Dose (mg/m^2)	Dose Multiple[a]	AUC (ng·hr/mL)	Exposure Multiple[b]
Human Start Dose (5 mg)[c]	0.0714	2.64	-	312	-
Rat NOAEL[e]	30	180	68	191000	612
Dog NOAEL[f]	20	400	152	80800	259
Human Maximum Dose in the SAD (400 mg)[d]	5.71	211	-	25500[g]	-
Rat NOAEL[e]	30	180	0.9	191000	7.5
Dog NOAEL[f]	20	400	1.9	80800	3.2
Rat Dose > MTD[e]	250	1500	7.1	294000	11.5
Dog Dose > MTD[f]	60	1200	5.7	222000	8.7
Human Maximum Dose in the MAD (300 mg)[d]	4.3	159	-	19100[h]	-
Rat NOAEL[e]	30	180	1.1	191000	10
Dog NOAEL[f]	20	400	2.5	80800	4.2
Rat Dose > MTD[e]	250	1500	9.4	294000	15.4
Dog Dose > MTD[f]	60	1200	7.5	222000	11.6

Abbreviations: AUC = area under the concentration versus time curve; MAD = multiple-ascending dose; MTD = maximum tolerated dose; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; QD = daily dosing; SAD = single-ascending dose.

a Dose multiple is the dose in animals/dose in humans based on mg/m2. Doses were converted from mg/kg to mg/m2 using a km conversion factor of 6 for the rat, 20 for the dog, and 37 for a 70-kg human.

b Exposure multiple is the calculated AUC in animals/predicted AUC in humans.

c Clinical starting dose is based on IC10 (5 mg QD).

d Maximum clinical dose proposed in SAD and MAD.

e NOAEL and Dose > MTD in rat 4-week repeat-dose toxicity study (Study 8415214). Average of male and female rat AUC on Day 29 (NOAEL) or Day 1 (Dose > MTD).

f NOAEL and Dose > MTD in dog 4-week repeat-dose toxicity study (Study 8415213). Average of male and female dog AUC on Day 29 for NOAEL and average of male and female dog AUC on Day 15 for Dose > MTD.

g AUC(0-inf).

h AUC(0-24).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study including the last scheduled procedure shown in the SoA. As such, it is planned that each cohort will achieve

- 8 completers per cohort in Part A, and
- 8 completers per cohort in Part B.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

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

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

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

Participants enrolled in Part A will not be allowed to participate in Part B of the study.

5.1. Inclusion Criteria

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

Informed Consent

1. Capable of giving signed informed consent as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
2. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures including dietary requirements

Participant Characteristics

3. Are overtly healthy as determined through medical evaluation including medical history and physical examination
4. Are male, regardless of fertility status, or female, not of childbearing potential, aged from 18 to 65 years inclusive, at the time of signing the informed consent

   Note: Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For contraception requirements of this protocol, see Section 10.4
5. Have a body mass index of ≥18.5 and ≤40 kg/m^2
6. Have had a stable weight for the 1 month prior to screening and enrollment (<5% body weight change) and have not received dietary intervention in the 1 month prior to screening and enrollment
7. Have safety laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator
8. Have venous access enough to allow for blood sampling as per the protocol

5.2. Exclusion Criteria

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

Medical Conditions

9. Have an abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study or may confound ECG data analysis
10. Have blood pressure of >160/90 mmHg and pulse rate <50 or >100 bpm, supine (at screening), or with minor deviations judged to be acceptable by the investigator
11. Have a significant history of or current CV (e.g., myocardial infarction, congestive heart failure, cerebrovascular accident, venous thromboembolism), respiratory, hepatic, renal, gastrointestinal, endocrine, hematological (including platelet count ≤150,000/mcL), or neurological disorders capable of
    - significantly altering the absorption, metabolism, or elimination of the study intervention including bariatric surgery
    - constituting a risk while taking the study intervention, or
    - interfering with the interpretation of data
12. Have a history of fructosuria.
13. Have obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis.
14. Have AST or ALT, ALP, or TBL ≥1.5x ULN. Participants with Gilbert's syndrome can be enrolled with TBL of <2x ULN.
15. Have estimated glomerular filtration rate <60 mL/min/1.73 m^2.

Prior/Concomitant Therapy

16. Intend to use over-the-counter or prescription medication including herbal medications such as St. John's wort and vitamin/mineral supplements within 14 days prior to dosing.
17. Use of any drugs or substances that are known strong inducers or inhibitors of CYP3A is specifically excluded within 14 days prior to the first administration of study intervention and during the study.

Prior/Concurrent Clinical Study Experience

18. 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.
19. Have completed or withdrawn from this study or any other study investigating LY3522348 and have previously received the study intervention.
20. Are currently enrolled in or past participation, within the 30 days prior to screening, in a clinical study involving a study intervention for which at least 5 half-lives or 30 days (whichever is longer) have not passed.

Diagnostic Assessments

21. Regularly use known drugs of abuse and/or positive urine drug screen at screening or check-in.
22. Show evidence of HIV infection and/or positive human HIV antibodies.
23. Show evidence of hepatitis B and positive hepatitis B surface antigen.
24. Show evidence of hepatitis C and/or positive hepatitis C antibody.

Other Exclusions

25. Smoke >10 cigarettes per day or the equivalent or are unable or unwilling to refrain from nicotine during investigative site admission.
26. Have either moderate or severe alcohol consumption. Moderate alcohol consumption is defined as 1 drink per day for women and 2 standard drinks per day for men, whereby, 1 standard drink is equivalent to 12 ounces of beer (5% alcohol) or 5 ounces of wine (12% alcohol), or 1.5 ounces of distilled spirits (40% alcohol).
27. Have known allergies to LY3522348, related compounds, or any components of the formulation, or a history of significant atopy.
28. For participants in Cohorts 3 and 4 of Part B, have known allergies to midazolam or its metabolites.
29. Are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
30. Are Lilly or investigative site employees.
31. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

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

5.3.1. Meals and Dietary Restrictions

Participants should be fasted for 8 hours prior to predose blood sampling and performing ECGs. As such, participants in Part B do not need to fast on Days 3, 5, 6, and Days 8 to 13. On days of midazolam drug-drug interaction assessment (Part B Cohorts 3 and 4), participants should fast overnight prior to midazolam administration and abstain from food for 2 hours and fluid for 1 hour after midazolam administration.

Within 14 days prior to the first dose of any study intervention until discharge from the study, participants should not consume

- herbal supplements
- grapefruits or grapefruit-containing products
- Seville oranges or Seville orange-containing products

- star fruits or star fruit-containing products, pomelo, or
- commercial apple juice or orange juice.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants will be encouraged to maintain their regular caffeine consumption.

Nicotine use is not permitted at the investigative site.

Alcohol consumption is not permitted from 48 hours prior to admission and while resident at the investigative site.

5.3.3. Activity

Participants should avoid strenuous exercise immediately prior to the screening visit and should avoid strenuous exercise 3 days prior to each admission and while at the investigative site. Participants should maintain their normal levels of activity at other times.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened. Repeating of vital signs and laboratory tests during the screening period or repeating screening assessments to comply with the protocol-designated screening period does not constitute rescreening. However, participants who are eligible for inclusion in previous cohorts, but who are not randomized for nonmedical reasons, may be re-assessed for inclusion in subsequent cohorts.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

LY3522348 or placebo will be administered orally with approximately 240 mL of room temperature water in the morning on Day 1 in Part A and Days 1 to 14 in Part B. Participants in Cohorts 3 and 4 of Part B will receive an additional dose of either LY3522348 or placebo on Day 15.

Doses should be administered while the participant is in sitting position. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Participants in Cohorts 3 and 4 will be administered midazolam orally on Days -1 and 15. On Day -1, participants will receive midazolam alone. On Day 15, participants will receive midazolam co-administered with either LY3522348 or placebo. Midazolam administration should occur within 15 minutes of LY3522348 administration.

Study Intervention Name	**LY3522348**	**Placebo**	**Midazolam**
Dosage Formulation	Capsules	Capsules	Oral solution
Dose Strength	5 and 50 mg	-	200 μg
Route of Administration	Oral	Oral	Oral

The investigator or designee is responsible for

- explaining the correct use of the study interventions to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of study intervention dispensing and collection, and
- returning all unused medications to the sponsor or its designee at the end of the study.

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

6.1.1. Packaging and Labeling

Clinical trial materials will be labeled according to the country's regulatory requirements.

Each capsule of LY3522348 will contain 5 or 50 mg of active ingredient. Placebo capsules will resemble LY3522348 capsules in appearance.

LY3522348 and placebo capsules will be supplied to the investigator by the sponsor for dispensing by unblinded pharmacy staff.

Midazolam will be sourced locally by the investigative site.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Instructions.

6.3. Measures to Minimize Bias: Randomization and Blinding

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

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

Method of treatment assignment

Participants will be randomized to a treatment using a computer-generated randomization schedule.

Unblinded site pharmacist

The unblinded pharmacist or designee will prepare the study intervention.

Participants will be randomly assigned in the ratio determined at randomization to receive study intervention. Investigators will remain blinded to each participant’s assigned study intervention throughout the course of the study.

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

Blind break

Emergency codes will be available to the investigator. A code, 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 the sponsor as soon as possible.

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

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the site personnel other than the person administering the study intervention. Site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

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

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

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

Vitamin/mineral supplements are not allowed during the study.

Acetaminophen, at doses of ≤3 g/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the sponsor's medical monitor.

Drugs that are known strong inducers or inhibitors of CYP3A are specifically excluded. For more information, refer to Section 10.7.

6.6. Dose Modification

By nature of being a dose-escalation study, cumulative safety data will be evaluated on an ongoing basis until the highest tolerated dose has been administered.

Safety and tolerability data will be the primary criteria for the dose escalation. No dose decision can occur without prior discussion and agreement between the investigator and the sponsor.

Any available PK data may be used to guide dose selection or to determine if the number of doses to be studied may be reduced.

After review of these data, an agreement on the appropriate dose will be made by the investigator and sponsor for the next cohort/dose level. A lower dose may be administered; dose levels may be repeated provided that it is not the result of a safety finding; or the magnitude of dose escalations may be reduced following data review, provided that subsequent escalations do not increase by more than approximately 3-fold (a half-log increment).

6.6.1. Dose Decision/Escalation

Dose Decision

Pharmacokinetics (PK) data will be reviewed for each cohort to inform the next dose level prior to dose escalation and to ensure the predicted mean exposure $AUC_{(0\text{-}inf)}$ will not exceed 25.5 µg·h/mL in Part A and the predicted mean steady-state exposure ($AUC_{0\text{-}24}$) will not exceed 19.1 µg·h/mL in Part B.

Dose escalation

For dose-escalation decisions in Part A, the following must occur:

- All planned participants in current cohort must have been dosed.
- Clinical assessment is done through Day 3 for at least 6 participants.
- Safety laboratory tests, including ECG measurements, are obtained through Day 3 for at least 6 participants.
- Pharmacokinetics (PK) data will be reviewed for each cohort prior to dose escalation

For dose-escalation decisions in Part B, the following must occur:

- All planned participants in current cohort must have been dosed.
- Clinical assessment is done through Day 7 for at least 6 participants.
- Safety laboratory tests, including ECG measurements, are obtained through Day 7 for at least 6 participants.

Pharmacokinetics (PK) data will be reviewed for each cohort prior to dose escalation. If any of the following scenarios occur, dosing at the current level and further dose escalation will be interrupted until further sponsor's decision:

1. One or more participants on active drug experience an SAE considered to be related to LY3522348.
2. One or more participants on active drug experience 2 clinically significant events related to LY3522348 defined as moderate to severe symptoms, clinical signs, and clinical laboratory findings that could cause harm to health. The clinically significant events will be determined by the investigator or the sponsor
3. CP and may include findings that do not fulfill the criteria for SAEs.

6.6.2. Data Review during the Study

Trial level safety reviews of safety and tolerability data are scheduled to occur after every dosing session. PK data will be included in these reviews. The purpose of these reviews are to guide dose selection for the next dosing session, and/or to inform the design of subsequent studies. The investigator and the sponsor will make the determination regarding dose escalation, based upon their review of the data. The investigator will remain blinded, and the sponsor will be unblinded during these reviews.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for early discontinuation procedures. At the discretion of the investigator, participants may be requested to return to the investigative site for safety monitoring at additional visits following completion of the early discontinuation procedures. Assessments may include, but will not be limited to, those presented for the follow-up visit with the addition of safety laboratory tests.

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

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

Discontinuation of a participant from a study intervention should be considered if there is a marked prolongation of the QT/QTc interval during the study. Prolongation is defined as an increase in QT/QTc of greater than 500 ms in more than 1 ECG.

7.1.1. Hepatic Criteria for Discontinuation

In Part B, discontinuation of the investigational product for abnormal liver test results **should be considered** by the investigator when a participant meets 1 of the following conditions, after consultation with the Lilly-designated medical monitor:

- ALT or AST >8X ULN
- ALT or AST >5X ULN sustained for more than 2 weeks or
- ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio >1.5 or
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- creatine kinase >5X ULN.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

- at any time at his/her own request

- at the request of his/her designee (e.g., parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP. As such, a participant may withdraw from the study if he or she experiences

- any TEAE or SAE considered possibly or probably related to study intervention that is severe or medically significant but not immediately life threatening; or where hospitalization or prolongation of hospitalization is indicated; or is disabling; or limits self-care activities of daily living, or
- any TEAE or SAE regardless of attribution to study intervention that has life-threatening consequences or urgent intervention is indicated.

Discontinuation is expected to be uncommon.

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

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment and safety follow-up should be performed as outlined in Section 1.3, Section 8.2, and Section 8.3 of the protocol.

7.2.2. Discontinuation of the Study

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

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

- Three study participants develop the same TEAE or SAE considered possibly or probably related to study intervention that
  - is severe or medically significant, but not immediately life threatening
  - requires hospitalization or prolongation of hospitalization
  - is disabling, or
  - limits self-care activities of daily living; OR
- Two study participants develop any TEAE or SAE regardless of attribution to study intervention that has life-threatening consequences or requires urgent intervention; OR
- Death of any study participant at any time related to AE.

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The specifications in this protocol for the timings of safety, PK, and PD sampling are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon the safety and PK information obtained. The scheduled time points may be participant to minor alterations; however, the actual time must be correctly recorded in the eCRF. Failure or being late (i.e. outside stipulated time allowances) to perform procedures or obtain samples within the stipulated time allowances due to legitimate clinical issues will not be considered protocol deviations. Legitimate clinical issues include

- equipment technical problems
- venous access difficulty, or
- participant defaulting or turning up late on an agreed scheduled procedure.

However, the investigative site will still be required to notify the sponsor in writing to account for missing samples to facilitate data reconciliation.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

Physical examinations and routine medical assessments including body temperature will be conducted as specified in Section 1.3 and as clinically indicated.

From Day 1 until 4 days after the last dose of study intervention, participants will be advised to wear sunglasses, hats, and sunscreen during sun exposure. During physical examination, treatment-emergent ocular and dermal photosensitivity events will also be assessed by asking the participant for any abnormal eye or skin irritation, redness, itching, burning sensation in daylight or on exposure to sunlight. The participant will be examined for abnormal skin erythema and hyperemia in exposed areas, hyperemia, scleritis, and conjunctivitis.

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to Section 1.3. If warranted, additional vital signs may be measured.

Blood pressure and pulse rate should be measured after at least 5 minutes supine. When possible, measurements of blood pressure and pulse rate should be performed at approximately the same time of day at each scheduled time point.

If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 2 minutes.

If the participant feels unable to stand, supine vital signs only will be recorded.

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

8.2.3. Electrocardiograms

For each participant, single and triplicate ECGs should be collected according to Section 1.3.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of study intervention should be reported to the sponsor, or its designee, as an AE via eCRF.

ECGs must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

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

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

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

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

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Body Temperature

Body temperature will be measured as specified in the Section 1.3 and as clinically indicated.

8.2.6. Safety Monitoring

The sponsor’s CP or CRP/scientist will monitor safety data throughout the course of the study.

The sponsor will review SAEs within time frames mandated by company procedures. The sponsor’s CP or CRP will periodically review

- trends in safety data
- laboratory analytes, and
- AEs.

When appropriate, the sponsor’s CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

If the safety monitoring procedure uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the site personnel included in the unblinding/blinding plan.

8.2.6.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Section 10.6), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

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

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

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

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

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

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

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined earlier, as well as tests for prothrombin time-international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (e.g., ultrasound or computed tomography scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and
- plasma phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a

- hepatologist or gastroenterologist consultation
- magnetic resonance cholangiopancreatography
- endoscopic retrograde cholangiopancreatography
- cardiac echocardiogram, or a
- liver biopsy.

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

Additional hepatic safety data collection in hepatic safety CRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    a. In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive test***s***
2. Elevation of TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
    a. In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    a. In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study intervention due to a hepatic event

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

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

All SAEs will be collected from the signing the ICF the follow-up visit at the time points specified in Section 1.3.

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

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

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

intervention, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

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

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

8.3.5. Pregnancy

Pregnancy (maternal or paternal exposure to study intervention) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Section 10.4.3 to collect data on the outcome for both mother and fetus.

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 90 days after the last dose of study intervention.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Complaint Handling

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

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

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

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

8.3.6.1. Time Period for Detecting Product Complaints

Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug is used.

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug provided for the study, the investigator will promptly notify the sponsor.

8.3.6.2. Prompt Reporting of Product Complaints to Sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.

The Product Complaint Form will be sent to the sponsor by the method provided in the form. If the primary method is unavailable, then an alternative method provided in the form should be utilized.

8.3.6.3. Follow-up of Product Complaints

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

For the purposes of this study, an overdose of LY3522348 is considered any dose higher than the dose assigned through randomization.

Refer to the LY3522348 IB for more details.

In the event of an overdose, the investigator or treating physician should

1. contact the medical monitor immediately.
2. closely monitor the participant for any AE/SAE and laboratory abnormalities until LY3522348 can no longer be detected systemically.

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

8.5. Pharmacokinetics

Samples will be collected at the visits and times specified in Section 1.3. The actual date and time (24-hour clock time) of each sampling will be recorded.

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

8.5.1. Bioanalysis

Plasma and urine samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

The retention period for bioanalytical samples collected to measure LY3522348 concentrations is provided in Section 10.1.10. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism and/or protein-binding work.

8.5.2. LY3522348 Measurement

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor.

Plasma and urine concentrations of LY3522348 will be assayed using a validated liquid chromatography tandem mass spectrometry method. Analyses of samples collected from placebo-treated participants are not planned.

8.5.3. Drug-Drug Interaction with Midazolam

Midazolam will be administered to Cohorts 3 and 4 in Part B as indicated in Section 1.3 on Days -1 and 15. Blood samples will be collected to determine the plasma concentrations of midazolam and its metabolite, 1′-hydroxymidazolam.

Plasma concentrations of midazolam and its metabolite, 1′-hydroxymidazolam, will be analyzed using validated liquid chromatography tandem mass assay. Analyses of samples collected from LY3522348- and placebo-treated participants are planned.

8.5.4. Renal Clearance

Urine samples will be collected for the characterization of renal clearance. Total urine output for the appropriate period after study intervention administration will be collected, pooled, and refrigerated. At the end of the collection period, the total urine volume will be recorded. Urine samples will be used to determine creatinine, quantification of LY3522348, and exploratory metabolite identification.

Assessment of renal clearance will be an exploratory assessment; therefore, failure to collect samples or analyze all collected samples will not be a deviation. Samples will be analyzed using a validated fit-for-purpose liquid chromatography tandem mass assay.

At the visits and times specified in Section 1.3, venous blood samples will be collected to determine serum creatinine measurements.

8.6. Pharmacodynamics

Fructose tolerance test

Three meals (breakfast, lunch, and dinner) will be served at approximately 20 minutes, 6 hours, and 12 hours after dose with low fructose content. A beverage will be served with each of the 3 meals on Day 1 in Part A (SAD) and Days 1 and 14 in Part B (MAD). The beverage contains a mixture of approximately 30.25 g of fructose and 24.75 g of glucose in approximately 300 to 500 mL of non-caloric solution. The beverage should be served after a portion of the meal has been consumed. The meals should start at the defined time (20 minutes, 6 hours, and 12 hours post dose).

Blood samples for the analysis of fructose will be collected into appropriately labeled tubes containing ethylene diamine tetra acetic acid at the time points specified in Section 1.3. Sample handling and shipment to the central laboratory will occur per instructions given to the investigative site.

The retention period for PD samples is provided in Section 10.1.10.

8.7. Genetics

A blood sample will be collected and stored from participants.

See Section 10.5 for information regarding genetic research and Section 10.1.10 for details about sample retention and custody.

8.8. Biomarkers

8.8.1. Fasting Insulin and Adiponectin

At the visits and times specified in Section 1.3, venous blood samples will be collected to determine the blood concentrations of fasting insulin and adiponectin.

8.8.2. Coproporphyrins

At the visits and times specified in the SoA (Section 1.3.2), venous blood samples will be collected and stored to determine the plasma concentrations of coproporphyrins 1 and 3.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded.

Clinical study data indicate that the endogenous coproporphyrins can be used to detect in vivo inhibition of hepatic OATPs; therefore, coproporphyrins 1 and 3 are being explored in this study as potential biomarkers of OATP function (Lai et al. 2016). If in vitro transporter inhibition data indicate potential in vivo OATP inhibition by LY3522348, the coproporphyrin samples may be analyzed.

8.8.2.1. Bioanalysis

Samples may be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of coproporphyrins may be assayed using a validated liquid chromatography tandem mass spectrometry method. Samples collected from both LY3522348- and placebo-treated participants may be analyzed.

8.8.3. Nonpharmacogenetic Biomarkers

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

Blood samples for nonpharmacogenetic biomarker research will be collected at the times specified in Section 1.3, where local regulations allow.

Samples will be used for research on the

- drug target
- disease process
- variable response to LY3522348
- effect of LY3522348 on enzymes/transporters
- pathways associated with targeted indication and/or comorbidities
- potential mechanism of action of LY3522348 and/or research method
- for validating diagnostic tools or assays related to indication and/or comorbidities, or the
- potential mechanism of action of LY3522348.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the site personnel.

The retention period for biomarker samples is provided in Section 10.1.10. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3522348 or after LY3522348 is commercially available.

8.9. Immunogenicity Assessments

Not applicable.

8.10. Health Economics

Not applicable

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary objectives of this study are to evaluate the safety and tolerability of LY3522348 in healthy participants. No statistical hypotheses will be tested for this objective.

9.2. Sample Size Determination

The sample size for Parts A and B of the study was chosen to provide sufficient data for evaluating safety, tolerability, and PK parameters, as well as PD and other exploratory objectives of this study.

A maximum of 100 participants will be randomly assigned to study intervention such that approximately

- 48 evaluable participants complete Part A, and
- 32 evaluable participants complete Part B the study.

Participant replacement

To ensure that enough participants complete the study, participants who discontinue from the study, for reasons other than an AE suspected to be related to study intervention, may be replaced as agreed between the sponsor and investigator. The replacement participant will assume the randomization schedule of the discontinued participant.

9.3. Populations for Analyses

9.3.1. Study Participant Disposition

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

9.3.2. Study Participant Characteristics

The participant's age, sex, race, weight, height, and other demographic characteristics will be summarized.

9.4. Statistical Analyses

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

PK/PD analyses will be conducted on data from all participants who receive at least 1 dose of the study intervention and have evaluable PK and PD data.

Safety analyses will be conducted for all enrolled participants, irrespective of the completion of all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Additional exploratory analyses of the data, other than the ones outlined in these subsections, may be conducted as deemed appropriate.

9.4.1. Safety Analyses

9.4.1.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each study intervention will be presented by severity and by association with the study intervention as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

The number of study intervention-related SAEs will be reported.

9.4.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include clinical laboratory parameters, vital signs, and ECG parameters. All laboratory values will be reported in both absolute values and changes from baseline. The parameters will be listed and summarized using standard descriptive statistics.

Analyses may be performed to determine the effects of LY3522348 concentrations on QTc. A concentration-response analysis will be performed according to the ICH-E14 (the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs) guidelines.

Additional analysis will be performed if warranted upon review of the data.

9.4.2. Pharmacokinetic Analyses

9.4.2.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3522348 will be calculated using standard noncompartmental methods of analysis in Parts A and B.

Pharmacokinetic parameter estimation in Parts A and B

The primary parameters for LY3522348 analysis will be

- C_{max}
- t_{max}
- AUC

Other noncompartmental parameters, such as $t_{1/2}$, apparent clearance, and apparent volume of distribution may be reported.

Pharmacokinetic parameter estimation in Part A only

Renal clearance of LY3522348 will be calculated as the ratio of total amount excreted/plasma AUC(0-inf) in Part A only. The amount excreted is calculated as AUC(0-t), where t is the time interval over which urine is collected. This will be compared to the unbound glomerular filtration rate, which is estimated using creatinine.

Pharmacokinetic parameter estimation in Part B only

Accumulation ratio for LY3522348 based on AUC(0-24) and C_{max} may be reported.

The primary parameters for analysis for midazolam and its metabolite, 1′-hydroxymidazolam, will be AUC(0-tlast) and C_{max}. Other parameters, including t_{max}, $t_{1/2}$, CL/F, apparent volume of distribution during the terminal elimination phase (V_z/F), metabolite ratios based on AUC(0-tlast) will be calculated as appropriate.

9.4.2.2. Pharmacokinetic Statistical Inference

The descriptive statistics for the PK parameters will be provided for each dose level. Where appropriate, geometric mean and coefficient of variation will be reported. The dose proportionality for LY3522348 will be assessed for AUC and C_{max} using a power model. The power parameter will be evaluated to determine the dose proportionality.

Comparisons of PK parameters between different treatments on the PK sampling days will be performed with appropriate statistical models. Test significance (unadjusted p-values) and 90% confidence intervals will be reported. The analyses will be detailed in a separate statistical analysis plan.

9.4.3. Pharmacodynamic Analyses

9.4.3.1. Pharmacodynamic Parameter Estimation

The primary PD effect will be evaluated using FTT for fructose. Area under the curve over times sampled for FTT will be calculated using trapezoid methods. Other biomarkers including low- and high-density lipoproteins, cholesterol, and triglycerides will be determined if appropriate.

9.4.3.2. Pharmacodynamic Statistical Inference

PD data will be summarized using descriptive statistics. Where appropriate, geometric mean and coefficient of variation will be reported. Comparison of FTT and biomarker measurements between different treatments over time will be performed with appropriate statistical models. Test significance (unadjusted p-values) and 90% confidence intervals will be reported. The analyses will be detailed in a separate statistical analysis plan.

9.4.4. Pharmacokinetic/Pharmacodynamic Analyses

PK/PD modeling may be employed to characterize the exposure-response relationships between LY3522348 concentrations and various PD endpoints, provided enough data are available.

9.5. Interim Analyses

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

The ongoing safety reviews planned for this study are described in Section 6.6.2.

9.6. Data Monitoring Committee (DMC)

Not applicable.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant and is kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

Communication of suspended for terminated dosing

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

Reports

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

Data

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

10.1.6. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Data monitoring and management

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

Data Capture System

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

An electronic data capture 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 collected via the sponsor-provided data capture system(s) will be stored by third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

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

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

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Study and Site Start and Closure

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

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

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

Reasons for the early closure of an investigative site by the sponsor or investigator may include but are not limited to

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment of participants by the investigator
- discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

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

10.1.10. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3522348 or after LY3522348 becomes commercially available.

The following table lists the maximum retention period for sample types. The retention period begins after the last participant visit for the study.

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

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

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

Sample Type	Custodian	Retention Period after Last Patient Visit[a]
Biomarkers	Sponsor or designee	15 years
PK	Sponsor or designee	2 years
PD	Sponsor or designee	1 year
Genetics	Sponsor or designee	15 years

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the central laboratory or by the local laboratory.
- Local laboratory results are required only in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing will occur as indicated in Section 1.3.

Investigators must document their review of each laboratory safety report.

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

Table 2. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Magnesium
Platelets	Glucose
Differential WBC (absolute counts of):	Creatinine
• Neutrophils	Blood urea nitrogen (BUN)
• Lymphocytes	Lipid panel
• Monocytes	Total protein
• Eosinophils	Albumin
• Basophils	Total bilirubin level
	Alkaline phosphatase (ALP)

Urinalysis	Aspartate aminotransferase (AST)
Specific gravity	Alanine aminotransferase (ALT)
pH	Gamma-glutamyl transferase (GGT)
Protein	
Glucose	Ethanol testing[a,b]
Ketones	Urine drug screen[a,b]
Bilirubin	Hepatitis B surface antigen[a]
Urobilinogen	Hepatitis C antibody[a]
Blood	HIV
Nitrite	
	Pregnancy test[c]
Thyroid-stimulating hormone[a]	FSH[a,d]

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

[a] Performed at screening only.

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

[c] Serum pregnancy test will be performed at screening and urine pregnancy test will be performed at all other specified time points.

[d] Performed in 40- to 55-year-old females to confirm their postmenopausal status.

10.2.1. Blood Sampling Summary

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

Protocol J2U-MC-YBAA Sampling Summary for Part A

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Serum pregnancy test	3.5	1	3.5
Clinical laboratory tests[a]	12	6	72
Serum creatinine	2.5	4	10
Pharmacokinetics	2	15	30
Pharmacodynamics, including fructose tolerance test	2	13	26
Pharmacogenetics[b]	10	1	10
Fasting biomarker samples (nonpharmacogenetic)	11.5 (4 mL plasma; 7.5 mL serum)	2	23
Total			219.5
Total for clinical purposes (rounded up to the nearest 10 mL)			220

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

[b] Only 1 pharmacogenetic sample is needed for each participant.

Protocol J2U-MC-YBAA Sampling Summary for Part B – Cohorts 1 and 2

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Serum pregnancy test	3.5	1	3.5
Clinical laboratory tests[a]	12	7	84
LY3522348 pharmacokinetics	2	25	50
Adiponectin	2.5	2	5
Fasting insulin ~~and adiponectin~~	2	2	4
Pharmacodynamics, including fructose tolerance test	2	26	52
Pharmacogenetics	10	1	10
Fasting biomarker samples (nonpharmacogenetic)	11.5 (4 mL plasma; 7.5 mL serum)	3	34.5
Coproporphyrin (stored)	3	11	33
Total			348
Total for clinical purposes (rounded up to the nearest 10 mL)			350

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

Protocol J2U-MC-YBAA Sampling Summary for Part B – Cohorts 3 and 4

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening testsa	45	1	45
Serum pregnancy test	3.5	1	3.5
Clinical laboratory testsa	12	7	84
LY3522348 pharmacokinetics	2	34	68
Adiponectin	2.5	2	5
Fasting insulin	2	2	4
Pharmacodynamics, including fructose tolerance test	2	26	52
Midazolam pharmacokinetics	2	18	36
Pharmacogenetics	10	1	10
Fasting biomarker samples (nonpharmacogenetic)	11.5 (4 mL plasma; 7.5 mL serum)	3	34.5
Coproporphyrin (stored)	3	20	60
Total			402
Total for clinical purposes (rounded up to the nearest 10 mL)			410

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

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

Events Not Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

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

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

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The investigator will consider any AEs, SAEs, and clinically important laboratory abnormalities as related to the study intervention unless there is clear evidence that the event is not related.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting via SAE Report

- Facsimile transmission of the SAE Report is the preferred method to transmit this information to the sponsor or designee.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Report within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SAE Report.

10.3.5. Sponsor Surveillance Process for Dose Escalation or Cohort Expansion

The sponsor has systematic and robust internal processes in place that ensure safety surveillance of development compounds in line with the Food and Drug Administration's expectations for safety assessment committees (FDA 2012, 2015, 2018a, 2018b). This includes processes with clearly described roles and responsibilities that are owned by the sponsor's Global Patient Safety organization. These processes are designed to monitor the evolving safety profile (i.e., review of cumulative SAEs, other important safety information) by designated cross-functional teams in a timely manner at predefined intervals or on an ad hoc basis. In addition, a dedicated process may be used to perform unblinded comparisons of event rates for SAEs as necessary.

This system ensures that the accumulating safety data derived from individual and multiple trials across a development program is reviewed on a regular basis and that important new safety information such as the need for protocol modification or other relevant safety related material is identified and communicated to regulators and investigators appropriately and in a timely manner. An internal review of aggregate safety data occurs on at least a quarterly basis or more frequently, as appropriate. Any serious adverse reactions are reported within the required timeline for expedited reporting.

In addition to annual periodic safety updates and to further inform investigators, a line listing report of suspected unexpected serious adverse reactions is created and distributed to investigators on a biannual (twice yearly) basis. Any significant potential risk-safety concerns that are being monitored as well as any results being reported in other periodic reports for the compound; safety assessment committee decisions; and other significant safety data (e.g., nonclinical, clinical findings, removal of serious adverse reactions) are included in the report.

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

10.4.1. Definitions

Female of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

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

Female NOT of Childbearing Potential

Females in the following categories are not considered females of childbearing potential:

1. Premenarchal

2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- Tubal ligation

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

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

3. Postmenopausal female is defined as, females who are

- at least aged 40 years with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL; or
- aged 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
- at least aged 55 years with a diagnosis of menopause prior to starting hormone replacement therapy.

10.4.2. Contraception Guidance

Female participants

Female participants of childbearing potential are excluded from this study.

Female participants who are not of childbearing potential may participate in this study.

Male participants

Male participants (regardless of their fertility status) with nonpregnant female partners of childbearing potential must agree to either

- remain abstinent (if this is their preferred and usual lifestyle),
- use condoms as well as 1 additional highly effective method of contraception, or
- use condoms as well as 1 additional effective contraception method (such as diaphragms with spermicide or cervical sponge).

Male participants with pregnant partners should use condoms during intercourse from the entirety of the study, plus 90 days thereafter, which corresponds to 4 months after the last investigational product dose.

Male participants who chose to remain abstinent (if this is their preferred and usual lifestyle) must adhere to the contraception requirements indicated above should their circumstances change.

Male participants should refrain from sperm donation from the entirety of the study, plus 90 days thereafter, which corresponds to 4 months after the last investigational product dose.

Contraception methods

Abstinence

Participants who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) must agree to either remain abstinent without sexual relationships with the opposite sex.

Same-sex relationships

Participants who are in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to stay in a same-sex relationship without sexual relationships with the opposite sex.

Participants who are in exclusively same-sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

Highly effective and effective contraception methods

Highly effective methods of contraception (less than 1% failure rate)	
Combined oral contraceptive pill and mini-pill	Intrauterine device (such as Mirena® and ParaGard®)
NuvaRing®	Contraceptive patch – ONLY women less than 198 pounds (90 kg)
Implantable contraceptives	Vasectomy – for men in clinical trials
Injectable contraceptives (such as Depo-Provera®)	Fallopian tube implants (Essure®) if confirmed by hysterosalpingogram
Total abstinence	
Effective methods of contraception (use 2 forms combined except where noted)	
Male condom with spermicide[a]	Diaphragm with spermicide
Female condom with spermicide[a]	Cervical sponge
	Cervical cap with spermicide

[a] Due to a high failure rate, male and female condoms should not be used in combination.

Unacceptable contraception methods

Unacceptable methods of contraception include

- periodic abstinence, such as
  - calendar
  - ovulation
  - symptothermal, or
  - post-ovulation methods
- declaration of abstinence just for the duration of the trial, and
- withdrawal.

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LY3522348.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated

delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to LY3522348 or NAFLD, NASH, and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3522348 and interventions of this drug class, NAFLD, and NASH. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome, as appropriate.

Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3522348 or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the CSR or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on LY3522348, similar study interventions of this class, or NAFLD and NASH continue but no longer than 15 years or other period as per local requirements.

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

See Section 8.2.6.1 for guidance on appropriate test selection.

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

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

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

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin level
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
Prothrombin time, international normalized ratio (PT-INR)	Ethyl alcohol (EtOH)
Serology	Haptoglobin
Hepatitis A virus (HAV) testing:	Immunoglobulin (Ig)A (quantitative)
HAV total antibody	IgG (quantitative)
HAV IgM antibody	IgM (quantitative)
Hepatis B virus (HBV) testing:	Phosphatidylethanol (PEth)
Hepatitis B surface antigen (HBsAg)	**Urine Chemistry**
Hepatitis B surface antibody (anti-HBs)	Drug screen
Hepatitis B core total antibody (anti-HBc)	Ethyl glucuronide (EtG)
Hepatitis B core IgM antibody	**Other Serology**
Hepatitis B core IgG antibody	Anti-nuclear antibody (ANA)

HBV DNA[a]	Anti-smooth muscle antibody (ASMA)[b]
Hepatis C virus (HCV) testing:	Anti-actin antibody[c]
HCV antibody	Epstein-Barr virus (EBV) testing:
HCV RNA[a]	EBV antibody
Hepatitis D virus (HDV) testing:	EBV DNA[a]
HDV antibody	Cytomegalovirus (CMV) testing:
Hepatitis E virus (HEV) testing:	CMV antibody
HEV IgG antibody	CMV DNA[a]
HEV IgM antibody	Herpes simplex virus (HSV) testing:
HEV RNA[a]	HSV (Type 1 and 2) antibody
Microbiology[d]	HSV (Type 1 and 2) DNA[a]
Culture:	Liver kidney microsomal type 1 (LKM-1) antibody
Blood	
Urine	

[a] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.
[b] Not required if anti-actin antibody is tested.
[c] Not required if anti-smooth muscle antibody (ASMA) is tested.
[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

10.7. Appendix 7: Excluded Concomitant Medications

Strong CYP3A inhibitors	**Strong CYP3A inducers**
Boceprevir	apalutamide
Clarithromycin	avasimibe
Cobicistat	carbamazepine
Conivaptan	enzalutamide
danoprevir and ritonavir	fosphenytoin (see also phenytoin)
Diltiazem	ivosidenib
elvitegravir and ritonavir	lumacaftor
grapefruit juice	mitotane
Idelalisib	phenobarbital
indinavir and ritonavir	phenytoin
Itraconazole	rifabutin
Ketoconazole	rifampicin (rifampin)
lopinavir and ritonavir	rifapentine
Nefazodone	St. John's wort
Nelfinavir	
Posaconazole	
Ribociclib	
Ritonavir	
saquinavir and ritonavir	
Telithromycin	
tipranavir and ritonavir	
Viekira Pak® (paritaprevir and ritonavir and ombitasvir and/or dasabuvir)	
Voriconazole	

Abbreviation: CYP = cytochrome P450.

Note: This list may be updated at the investigator's discretion.

10.8. Appendix 8: Abbreviations

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation participant 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
AUC(0-24)	AUC from time zero to 24 hours
AUC(0-tlast)	AUC from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-inf)	AUC from time zero to infinity
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 personnel 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 personnel and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor personnel who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received
CL/F	apparent clearance of drug
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be re-tested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.

CV	Cardiovascular
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	Electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FTT	fructose tolerance test
GCP	good clinical practice
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
IC_{90}	90% maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigator	A person responsible for the conduct of the clinical study at an investigative site. If a study is conducted by a team of individuals at an investigative site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB	institutional review board
KHK	Ketohexokinase
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study.
MAD	multiple-ascending dose
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NOAEL	no-observed-adverse-effect level

noninvestigational product	A product that is not being tested or used as a reference in the clinical study, but is provided to participants and used in accordance with the protocol, such as concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
QTc	corrected QT
randomize	The process of assigning participants to an experimental group on a random basis.
SAD	single-ascending dose
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
study intervention	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time of C_{max}
ULN	upper limit of normal

10.9. Appendix 9: Protocol Amendment History

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

Amendment [a]: (09-Sep-2020)

Overall Rationale for the Amendment:

The protocol was amended to

- address FDA comments received during the review of the Initial Investigational New Drug Application for LY3522348 and
- correct minor typo errors which are not reflected in the table below.

The following table describes the changes made for Amendment (a).

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema	Changes to this section were made to reflect the changes made in Section 4.1.1-Part A and Section 4.1.2-Part B.	Adjustments to the study design for the single-ascending dose (SAD) part of the study (PART A) were made to account for timeline and design element changes following implementation of specific design elements that were agreed upon with FDA during the initial IND review, such as sentinel dosing and mandatory PK after each cohort. Sentinel dosing requires 1 placebo and 1 LY to be dosed prior to dosing of the other participants. With only 1 placebo per cohort as proposed in the original SAD design, this would have led to unblinding of the investigator. Therefore, Lilly changed the design to include 2 placebo participants per cohort in the SAD. Mandatory PK analysis after each SAD cohort prior to dose escalation imposes additional time between cohorts. With the re-randomization design, this would have required participants to stay in the study for a significantly longer time. Therefore, the SAD design has been changed to a sequential parallel design without re-randomization from the originally proposed sequential cross-over design with re-randomization. Consequently, 40-48 participants (instead of 21) will complete part A of the study.
Section 1.3. 2 Schedule of Activities for Part B	In the multiple-ascending dose (MAD) part of the study, Part B, triplicate ECG monitoring was added on Day 18 for Cohorts 1 and 2 and on Day 19 for Cohorts 3 and 4.	Response to FDA comment
Section 4.1.1 Part A	Changes in Part A are: • Removed study intervention sequence progression	Response to FDA comment

Section # and Name	Description of Change	Brief Rationale
	• Added sentinel dosing for Cohorts 4, 5, and 6 anticipated to result in the exposure(s) between 8.1 µg hr/mL and 25.5 µg hr/mL. • Added 7-day in-patient stay to allow intensive monitoring for Cohorts 1 to 6. • Added dose escalation will not proceed if the predicted mean exposure, $AUC_{(0\text{-}inf)}$, in the next cohort is higher than 25.5 µg hr/mL. • Cohort 6 was changed into an optional cohort.	
Section 4.1.2 Part B	Changes in Part B are: • Added sentinel dosing for Cohorts 3 and 4, anticipated to result in the exposure(s) between 8.1 µg hr/mL and 19.1 µg hr/mL. • Added 20-day in-patient stay for Cohorts 1 and 2. • Added 21-day in patient stay to allow intensive monitoring for Cohorts 3 and 4. • Added dose escalation will not proceed if the predicted mean exposure, $AUC_{(0\text{-}24)}$, in the next cohort is higher than 19.1 µg hr/mL, which is $1/10^{th}$ of the AUC at the NOAEL (30 mg/kg) in the 4-week rat study.	Response to FDA comment
Section 4.3 Justification for Dose	Added dose escalation in the SAD study will not proceed if the predicted mean exposure, $AUC_{(0\text{-}inf)}$, in the next cohort is higher than 25.5 µg hr/mL. Updated mean predicted AUC criteria (Part B) to 19.1 µg·hr/mL, which is $1/10^{th}$ of the AUC at the NOAEL (30 mg/kg) in the 4-week rat study.	Response to FDA comment
Section 5.2 Exclusion Criteria	Changes in Exclusion Criteria are to: • Exclude participants with a platelet count ≤150,000/mcL. • Exclude all participants who have undergone bariatric surgery.	Response to FDA comment

Section # and Name	Description of Change	Brief Rationale
Section 6.6.1 Dose Decision/Escalation	Changes to this section are: • dose escalation in the SAD study will not proceed if the predicted mean exposure, AUC(0-inf), in the next cohort is higher than 25.5 µg hr/mL. • Updated mean predicted $AUC_{(0-24)}$ criteria (Part B) to 19.1 µg·hr/mL. • pharmacokinetics (PK) data will be reviewed after completion of each cohort prior to dose escalation in both Parts A and B.	Response to FDA comment
Section 10.4.2 Contraception Guidance	Added use of condoms as well as 1 additional effective contraception method (such as diaphragms with spermicide or cervical sponge).	Added this information as it was inadvertently missed previously.

Amendment [b]: (04-Mar-2021)

Overall Rationale for the Amendment:

The protocol was amended to

- revise the Schedule of Activities for MAD part of the study "Fructose Tolerance Test Assay" by removing time points 5 and 20 hours and adding time points 7 and 13 hours on Days 1 and 14 to better capture the pharmacokinetic profile of fructose following oral administration and
- revise additional language for clarification as follows:

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.1. Schedule of Activities for Part A	• Meal for Fructose Tolerance Test is changed to Low Fructose Meal. • 0.3 hour is changed to 20 minutes for Low Fructose Meal. • 0.3 hour is changed to 20 minutes for Fructose Beverage (for FTT).	To provide more clarity
Section 1.3.2. Schedule of Activities for Part B	• Additional language is added in Midazolam PK sampling "Sampling times are based on midazolam administration". • Meal for Fructose Tolerance Test is changed to Low Fructose Meal. • 0.3 hour is changed to 20 minutes for Low Fructose Meal on Days 1 and 14. • 0.3 hour is changed to 20 minutes for Fructose Beverage (for FTT) on Days 1 and 14.	To provide more clarity

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.2. Schedule of Activities for Part B	Timepoints are revised for "Fructose Tolerance Test Assay" by removing time points 5 and 20 hours and adding time points 7 and 13 hours on Days 1 and 14.	To better capture the pharmacokinetic profile of fructose following oral administration
Section 1.3.2. Schedule of Activities for Part B	Added additional text on Day 2 and Days 15 to 17 FTT Assay "predose sample on Day 2 and pre-meal for C1 and C2 and predose and premeal for C3 and C4 on Days 15 - 17".	To provide more clarity
Section 5.2. Exclusion Criteria	Revised exclusion criteria 23 to remove hepatitis B core antibody.	To provide more clarity, (hepatitis B antigen is tested but hepatitis B core antibody is not tested at screening)
Section 5.3.1. Meals and Dietary Restrictions	Added additional text about midazolam administration "On days of midazolam drug-drug interaction assessment (Part B Cohorts 3 and 4), participants should fast overnight prior to midazolam administration and abstain from food for 2 hours and fluid for 1 hour after midazolam administration".	To provide more clarity
Section 8.2.6.1. Hepatic Safety	serum phosphatidylethanol is changed to plasma phosphatidylethanol	Lab prefers to analyze in plasma.
Section 8.6. Pharmacodynamics – Fructose tolerance test	Additional language has been added about beverage timing "The beverage should be served after a portion of the meal has been consumed. The meals should start at the defined time (20 minutes, 6 hours, and 12 hours postdose)."	To provide more clarity
Section 10.2. Appendix 2: Clinical Laboratory Tests	Superscript "a" is added to Thyroid-stimulating hormone.	To provide more clarity

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