J2M-MC-GZKA(c) Clinical Pharmacology Protocol

A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single- and Multiple-Ascending Doses of LY3478045 in Healthy Subjects

NCT04270370

Approval Date: 11-Aug-2021

Protocol J2M-MC-GZKA(c)
A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single- and Multiple-Ascending Doses of LY3478045 in Healthy Subjects

LY3478045

Eli Lilly and Company
Indianapolis, Indiana, USA 46285

Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 15 January 2020

Amendment (a) Electronically Signed and Approved by Lilly: 04 March 2020

Amendment (b) Electronically Signed and Approved by Lilly: 09 December 2020

Document ID: VV-CLIN-002394

Table of Contents

A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single- and Multiple-Ascending Doses of LY3478045 in Healthy Subjects

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

1. Protocol Synopsis

Title of Study:
A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single- and Multiple-Ascending Doses of LY3478045 in Healthy Subjects.

Rationale:
Lilly is developing LY3478045, a ketohexokinase inhibitor, that helps in attenuation of fructose metabolism thus, anticipated to result in

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

Study J2M-MC-GZKA (GZKA) is a first-in-human study, which aims to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple oral doses of LY3478045 in healthy subjects. The PK, PD, safety, and tolerability data from this study in healthy subjects will assist in identifying an appropriate dose range for subsequent clinical studies in patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To investigate the safety and tolerability of single and multiple oral doses of LY3478045 in healthy subjects.	Incidence of TEAE and SAE. Clinically significant changes in vital signs data, safety laboratory parameters, and electrocardiograms.
Secondary To determine the pharmacokinetics of LY3478045 following single and multiple doses in healthy subjects.	AUC(0-24), AUC(0-inf), C_{max}, and t_{max}.

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

Summary of Study Design:

Study GZKA is a Phase 1, single site, randomized, double-blind, placebo-controlled, 2-part study of LY3478045 in healthy subjects.

Part A: single-ascending dose.

Part B: multiple-ascending dose design that evaluates the potential for a drug-drug interaction.

In Part A, single-ascending oral doses of either LY3478045 or placebo will be administered in up to 5 cohorts. Each cohort will consist of at least 8 subjects, 6 subjects will receive LY3478045 and 2 subjects will receive placebo. Cohort 5 is an optional cohort that may be assessed based on the available safety and PK data from the previous 4 cohorts.

Part B will be initiated after assessing safety, tolerability, PK, and PD data through Cohort 3 in Part A. Multiple-ascending oral doses of LY3478045 will be administered once daily for 14 days in up to 4 cohorts. Each cohort will consist of at least 8 subjects. In Cohorts 1 and 3, six subjects will receive LY3478045 and 2 subjects will receive placebo. In Cohorts 2 and 4, six subjects will receive LY3478045 followed by single dose of CCI and 2 subjects will receive placebo followed by a single dose of atorvastatin CCI later.

Treatment Arms and Planned Duration for an Individual subject:

Treatment Name	LY3478045	Placebo	Atorvastatin
Dosage Formulation	CCI	Capsules	Tablets
Dose strength	CCI	-	40 mg
Route of Administration	Oral	Oral	Oral

The planned duration for each subject is approximately 43 days in Part A and 57 to 59 days in Part B of the study.

Number of Subjects:

Up to 50 subjects may be enrolled in Part A to ensure that at least 40 subjects complete the study (depending on whether subjects will be enrolled in optional Cohort 5). Up to 40 subjects may be enrolled in Part B to ensure that at least 32 subjects complete the study.

Statistical Analysis:

Pharmacokinetic/PD analyses will be conducted on data from all subjects who receive at least 1 dose of the investigational product and have evaluable PK and PD data. Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements. Additional exploratory analyses of the data may be conducted as deemed appropriate.

Safety parameters that will be assessed include clinical laboratory parameters, vital signs, and electrocardiogram parameters. Analyses may be performed to determine the effects of PK and PD parameters on QT interval corrected using Fridericia's formula.

The primary parameters for analysis will be maximum observed drug concentration (C_{max}), time of C_{max} (t_{max}), area under concentration versus time curve (AUC) from time zero to 24 hours (AUC0-24) and AUC from time zero to infinity (AUC0-inf) of LY3478045. The primary PK parameters for analysis of CCI will be AUC(0-inf) and C_{max}.

2. Schedule of Activities

Study schedules for Protocol J2M-MC-GZKA are presented for Part A (SAD; Section 2.1) and Part B (MAD; Section 2.2 [Cohorts 1 and 3]) and Section 2.3 [Cohorts 2 and 4 with atorvastatin]).

2.1. Part A (Single-Ascending Doses)

	Screening	Days							FU[a]	ED[b]	Comments
Procedure	**≤28 days before Day -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**7**	**14**		
Informed Consent	X										
Admission to CRU		X									
Discharge from CRU						X					Subjects may be discharged on Day 5 at the discretion of the investigator.
Non-Residential Visit							X	X	X	X	
LY3478045 Administration			X								
Medical History	X										Information regarding occasional use of vitamin/mineral supplements will be taken as a part of the medical history evaluation at the time of subject screening.
Complete Physical Examination	X								X	X	Targeted PE may be conducted at other visits at the discretion of the investigator.
Height	X										
Weight	X	X									
Pregnancy Test	X	X							X	X	Serum pregnancy test will be performed at screening and urine pregnancy test will be performed at all other specified timepoints.
Blood Pressure and Pulse Rate (Supine)[c]	X	X	P, every 1 h up to 12 h postdose	24, 36 h	48 h	72 h		X	X	X	
Body Temperature	X	X							X	X	
Clinical Laboratory Tests	X	X	P	X	X			X	X		See Appendix 2 for complete list.
Serum Creatinine[d]			P, 4, 12, 24 h								
Triplicate 12-Lead ECG			Predose: 1.5 h, 1 h, and 30 min. Postdose: 0.5, 1.5, 2.5, 4, 6, 8,	24 h							

	Screening	Days							FU[a]	ED[b]	Comments
Procedure	**≤28 days before Day -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**7**	**14**		
			10, 12, 16 h								
Single 12-Lead ECG	X				X				X	X	
Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic Sampling[d]			P, 0.75, 1.5, 3, 4, 6, 8, 10, 12 ,16 h	24 h	48 h	72 h	96 h				
Meal (Low Fructose)			20 min, 6, 12 h								
Fructose Beverage (for Fructose Tolerance Test)			during meal: 20 min, 6, 12 h								
Fructose Tolerance Test Assay[d]			CCI	CCI							
Genetic Sample			X								
Fasting Biomarker Samples (Nonpharmacogenetic)		X		X							
CCI			P, 0.75, 1.5, 3, 4, 8, 12, 16 h	24 h	48 h	72 h	96 h				
24-hour Urine Collection for LY3478045 and Creatinine[d]			0-12, 12-24 h	24-36, 36-48 h	48-60, 60-72 h						

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; h = hour(s); 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.

a Additional FU visits may occur depending upon emerging pharmacokinetic and/or safety data.

b At the discretion of the investigator, subjects may be requested to return to the CRU for safety monitoring at additional visits following completion of the ED procedures. At the discretion of the investigator, assessments may include, but will not be limited to, those presented for the FU visit with the addition of safety laboratory tests.

c Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.

d Sampling times are relative to the time of study treatment administration (0 min).

2.2. Part B (Cohorts 1 and 3; Multiple-Ascending Doses)

	Screening	Days									FU[a]	ED[b]	Comments
Procedure	**≤28 days before Day -1**	**-1**	**1**	**2**	**3 to 6**	**7**	**8**	**9 to 13**	**14**	**15 to 17**	**28**		
Informed Consent	X												
Admission to CRU[e]		X											
Discharge from CRU										Day 17			
LY3478045 Administration			X										
Medical History	X												Information regarding occasional use of vitamin/mineral supplements will be taken as a part of the medical history evaluation at the time of subject screening.
Complete Physical Examination	X										X	X	Targeted PE may be conducted at other visits at the discretion of the investigator.
Height	X												
Weight	X	X								Day 15	X	X	
Pregnancy Test	X	X									X	X	Serum pregnancy test will be performed at screening and urine pregnancy test will be performed at all other specified

	Screening	Days									FU[a]	ED[b]	Comments
Procedure	**≤28 days before Day -1**	**-1**	**1**	**2**	**3 to 6**	**7**	**8**	**9 to 13**	**14**	**15 to 17**	**28**		
													timepoints.
Blood Pressure and Pulse Rate (Supine)[c]	X	X	P, every 1 h up to 12 h postdose	24, 36 h	48, 72 h				X		X	X	
Body Temperature	X	X									X	X	
Clinical Laboratory Tests (See Appendix 2)	X	X	P		Day 4	X			X		X	X	
Serum Creatinine			X			X			X				
Total Testosterone, Follicle-Stimulating Hormone, and Luteinizing Hormone	X		P	P							X	X	Samples will be collected early in the morning on Days 1 and 2, at the same time for both days, before or immediately after breakfast.
Single 12-Lead ECG	X										X	X	
Triplicate 12-Lead ECG			Predose: 1.5 h, 1 h, and 30 min.						P, 0.5, 1.5, 2.5, 4, 6, 8, 12, 16 h	24 h			
Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic Sampling[d]			P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (predose)		P			P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h	24, 48, 72 h			Sampling times may be adjusted based upon review of interim PK
Fasting Insulin and Adiponectin			P						P				
Meal (Low Fructose)			20 min, 6 h, 12 h						20 min, 6 h, 12 h				

	Screening	Days									FU[a]	ED[b]	Comments
Procedure	**≤28 days before Day -1**	**-1**	**1**	**2**	**3 to 6**	**7**	**8**	**9 to 13**	**14**	**15 to 17**	**28**		
Fructose Beverage (for Fructose Tolerance Test)			during meal: 20 min, 6, 12 h						during meal: 20 min, 6, 12 h				
Fructose Tolerance Test Assay[d]			CCI	CCI					CCI	CCI			
Genetic Sample		P											
Fasting Biomarker Samples (Nonpharmacogenetic)		X		X						Day 15			
CCI			P, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (predose)		P, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (predose)						Sampling times may be adjusted based upon review of preliminary data

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; h = hour(s); 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.

a Additional FU visits may occur depending upon emerging pharmacokinetic and/or safety data.

b At the discretion of the investigator, subjects may be requested to return to the CRU for safety monitoring at additional visits following completion of the ED procedures. At the discretion of the investigator, assessments may include, but will not be limited to, those presented for the FU visit with the addition of safety laboratory tests.

c Where possible, measurements of blood pressure and pulse rate should be performed at approximately the same time of day at each scheduled time point. Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.

d Sampling times are relative to the time of study treatment administration (0 min).

e If the predicted mean exposure for the dose at any cohort is estimated to be higher than 71.7 µg·hr/mL, only female subjects will be included in the cohort and mandated to stay in the CRU until 24 hours after the last dose.

2.3. Part B (Cohorts 2 and 4; Multiple-Ascending Doses)

	Screening	Days											FU[a]	ED[b]	Comments
Procedure	**≤28 days before Day -3**	**-3**	**-2**	**-1**	**1**	**2**	**3 to 6**	**7**	**8**	**9 to 13**	**14**	**15, 16, 17**	**28**		
Informed Consent	X														
Admission to CRU[e]		X													
Discharge from CRU												Day 17			
LY3478045 Administration					X										
Medical History	X														Information regarding occasional use of vitamin/mineral supplements will be taken as a part of the medical history evaluation at the time of subject screening.
Complete Physical Examination	X												X	X	Targeted PE may be conducted at other visits at the discretion of the investigator.
Height	X														
Weight	X	X										Day 15	X	X	
Pregnancy Test	X	X											X	X	Serum pregnancy test will be performed at screening and urine pregnancy test will be performed at all other specified timepoints.
Blood Pressure and Pulse Rate (Supine)[c]	X			X	P, every 1 h up to 12 h postdose	24, 36 h	48, 72 h				X		X	X	
Body Temperature	X			X									X	X	
Clinical Laboratory Tests (See Appendix 2)	X	X			P		Day 4	X			X		X	X	
Total Testosterone, Follicle-Stimulating Hormone, and Luteinizing Hormone	X				P	P							X	X	Samples will be collected early in the morning on Days 1 and 2, at the same time for both days, before or immediately

	Screening	Days											FU[a]	ED[b]	Comments
Procedure	**≤28 days before Day -3**	**-3**	**-2**	**-1**	**1**	**2**	**3 to 6**	**7**	**8**	**9 to 13**	**14**	**15, 16, 17**	**28**		
															after breakfast.
Serum Creatinine					X			X			X				
Single 12-Lead ECG	X												X	X	
Triplicate 12-Lead ECG					Predose: 1.5 h, 1 h, and 30 min.						P, 0.5, 1.5, 2.5, 4, 6, 8, 12, 16 h	24 h			
Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic Sampling[d]					P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (predose)		P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (predose)		P, 0.75, 1.5, 3, 4, 6, 8, 12, 16 h	24, 48, 72 h			Sampling times may be adjusted based upon review of interim PK
Fasting insulin and Adiponectin					P						P				
Meal (Low Fructose)			breakfast		20 min, 6, 12 h			20 min			20 min, 6, 12 h				
Fructose Beverage (for Fructose Tolerance Test)					during meal: 20 min, 6, 12 h						during meal: 20 min, 6, 12 h				
Fructose Tolerance Test Assay[d]					CCI	24 h (predose and premeal)					CCI	CCI			
CCI			X					X							Atorvastatin will be administered 4 hours after LY3478045 administration on Day 7 or 4 hours after breakfast on Day -2.
CCI Pharmacokinetics			P, 0.5, 1, 2, 3, 4, 6,	20, 32 h	48 h			P, 0.5, 1, 2, 3, 4,	20, 32 h	48 h					Sampling times are relative to the time of

	Screening	Days											FU[a]	ED[b]	Comments
Procedure	**≤28 days before Day -3**	**-3**	**-2**	**-1**	**1**	**2**	**3 to 6**	**7**	**8**	**9 to 13**	**14**	**15, 16, 17**	**28**		
			8, 12 h					6, 8, 12 h							atorvastatin administration
Genetic Sample				P											
Fasting Biomarker Samples (Nonpharmacogenetic)				X		X						Day 15			
CCI			P, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (predose)	P, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (predose)		P, 1.5, 3, 4, 6, 8, 12, 16 h	24 h (predose)						Sampling times may be adjusted based upon review of preliminary data

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; h = hour(s); 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.

[a] Additional FU visits may occur depending upon emerging pharmacokinetic and/or safety data.

[b] At the discretion of the investigator, subjects may be requested to return to the CRU for safety monitoring at additional visits following completion of the ED procedures. At the discretion of the investigator, assessments may include, but will not be limited to, those presented for the FU visit with the addition of safety laboratory tests.

[c] Where possible, measurements of blood pressure and pulse rate should be performed at approximately the same time of day at each scheduled time point. Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.

[d] Sampling times are relative to the time of study treatment administration (0 min). Time of breakfast represents 0 min on study Day -2.

e If the predicted mean exposure for the dose at any cohort is estimated to be higher than 71.7 µg·hr/mL, only female subjects will be included in the cohort and mandated to stay in the CRU until 24 hours after the last dose.

3. Introduction

3.1. Study Rationale

Lilly is developing LY3478045, a ketohexokinase (KHK) inhibitor, that helps in attenuation of fructose metabolism thus, anticipated to result in

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

Study J2M-MC-GZKA (GZKA) is a first-in-human study, which aims to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple oral doses of LY3478045 in healthy subjects. The PK, PD, safety, and tolerability data from this study in healthy subjects will assist in identifying an appropriate dose range for subsequent clinical studies in patients with nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).

3.2. Background

3.2.1. Nonalcoholic Steatohepatitis

Sugar consumption has significantly increased over the several decades; the per capita consumption of dietary fructose has increased 100-fold and fructose now accounts for approximately 10% of calorie intake in the United States (Bray et al. 2004; Tappy and Mittendorfer 2012). Furthermore, the polyol pathway, which converts glucose into fructose, is active in tissues including the liver, heart, and kidney. Activity of the polyol pathway is increased in metabolic disease conditions resulting in higher levels of endogenous fructose generated from glucose (Lanaspa et al. 2013; Andres-Hernando et al. 2019).

While modest amount of fructose found in fruits and vegetables is not of concern, the increased intake of sucrose (50% glucose/50% fructose) and high fructose corn syrup (55% to 90% fructose) is considered to be a cause for metabolic disease and complications including NAFLD/NASH.

Nonalcoholic steatohepatitis is the progressive stage of NAFLD, characterized histologically by the presence of steatosis, lobular inflammation, and hepatocyte injury (ballooning), with or without fibrosis (Chalasani et al. 2018).

Nonalcoholic steatohepatitis is currently the third most common cause of hepatocellular carcinoma (Chalasani et al. 2018) and NASH is expected to become the leading cause of liver transplantation in the future (Charlton et al. 2011).

Patients with NASH with fibrosis are at a higher risk of adverse outcomes, including liver cirrhosis, liver-related mortality, and cardiovascular (CV) mortality (Angulo et al. 2015). There is a high unmet medical need for safe and effective pharmacological treatments for NASH, as no approved therapies are currently available (Younossi et al. 2018).

3.2.2. Ketohexokinase

Ketohexokinase (also known as fructokinase) is the enzyme responsible for the first step in fructose metabolism (phosphorylation of fructose to fructose 1-phosphate).

As fructose (exogenous or endogenous), per se, is biologically inactive, metabolism by KHK is required to elicit negative metabolic phenotype(s) associated with fructose intake, including NAFLD/NASH and insulin resistance. Excessive fructose flux through KHK 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/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, significant metabolic benefits from isocaloric fructose restriction in human intervention trials that may be anticipated by reducing fructose metabolism (via KHK inhibition) include

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

As KHK acts as the gatekeeper to fructose metabolism and associated adverse phenotypes, reducing fructose metabolism via KHK inhibition is anticipated to mimic the isocaloric fructose restriction profiles.

Ketohexokinase as a Therapeutic Target

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

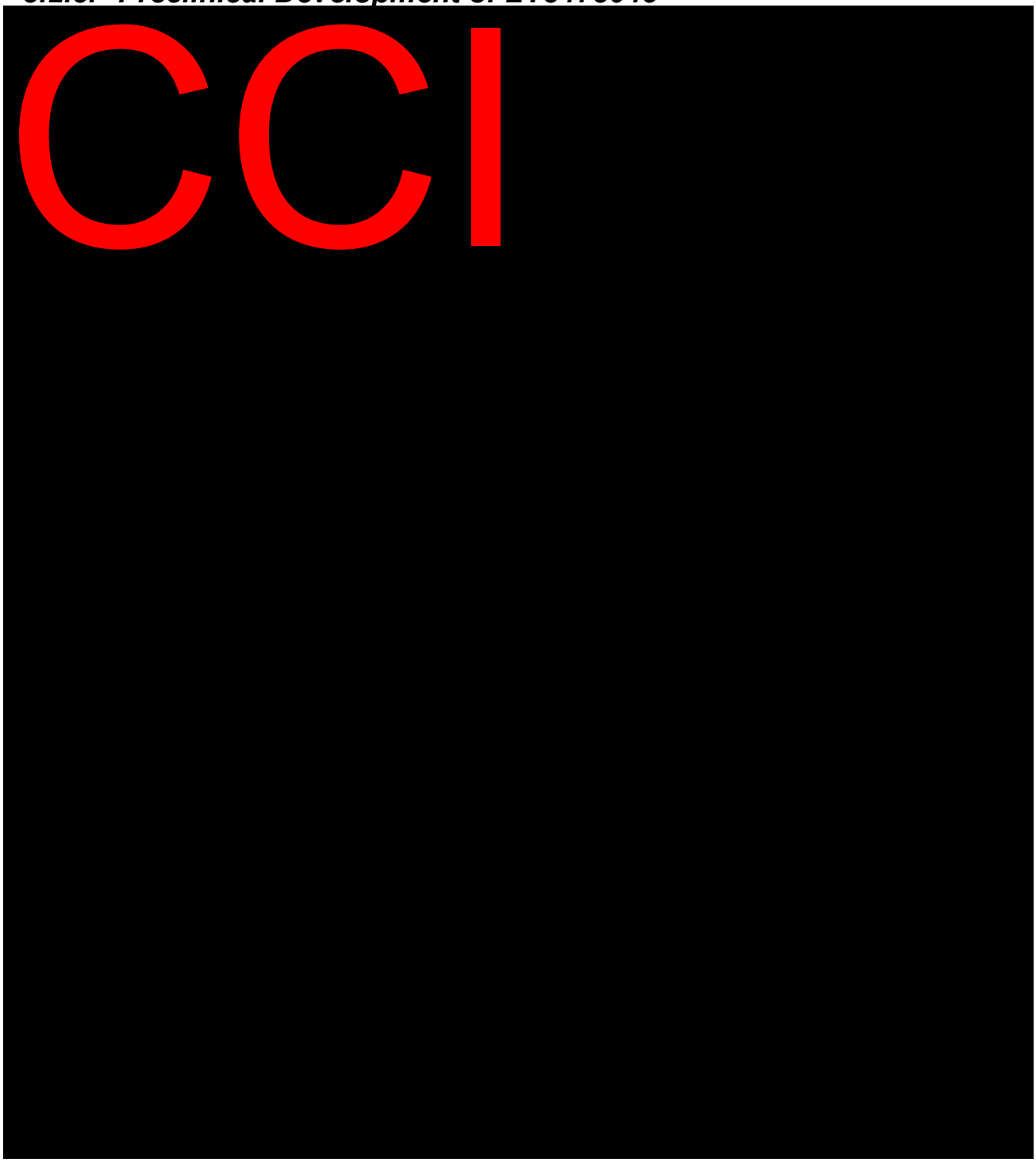
Human genetic validation of KHK as a therapeutic target exists based on loss of function mutations which results in essential fructosuria, an autosomal recessive disorder (Laron 1961; Froesch 1969; Bonthron et al. 1994). Individuals with this benign condition have inactive isoforms of KHK, limiting the liver's ability to metabolize and clear fructose upon fructose ingestion, increased fructose excursion into the serum, and ultimately 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.

A clinical trial (Calle et al. 2019) in patients with NAFLD treated for 6 weeks with a KHK inhibitor revealed

- statistically greater reduction from baseline in the whole liver fat

- dose-dependent decrease in fasting insulin and insulin resistance
- dose-dependent percent changes in high-sensitivity C-reactive protein (reduction) and adiponectin (increase), and
- six weeks of KHK inhibition was demonstrated to be safe and well tolerated.

3.2.3. Preclinical Development of LY3478045



3.3. Benefit/Risk Assessment

LY3478045 has not been administered to humans previously.

Given that there are no significant adverse events (AEs) in subjects who have a genetic deficiency for KHK (essential fructosuria), there are no anticipated risks based on target

inhibition. Further, the nonclinical pharmacology does not predict mechanism of action-based risk for this compound.

Study GZKA will be conducted in accordance with principles outlined in the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (EMA 2017). Based on the nonclinical data, LY3478045 is not considered to be a high uncertainty compound.

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

The available nonclinical safety information for LY3478045 supports its evaluation in healthy subjects.

CCI

In recognition of the apparent steep dose-response curve in rats between the repeat-dose NOAEL in the 1-month GLP study and a nontolerated dose in a 14-day non-GLP study that was associated with mortality, sentinel dosing will be performed in Cohorts 3, 4, and 5 of Part A, as drug exposures in these dose cohorts are projected to approach 10-fold below the exposure observed at the NOAEL (CCI in dogs).

Overall, the nonclinical safety assessment risks identified for the planned doses in the current study are considered low.

More details about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of LY3478045 is available in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table GZKA.1 shows the objectives and endpoints of the study.

Table GZKA.1. Objectives and Endpoints

Objectives	Endpoints
Primary To investigate the safety and tolerability of single and multiple oral doses of LY3478045 in healthy subjects.	Incidence of TEAE and SAE. Clinically significant changes in vital signs data, safety laboratory parameters, and electrocardiograms.
Secondary To determine the pharmacokinetics of LY3478045 following single and multiple doses in healthy subjects.	AUC(0-24), AUC(0-inf), C_{max}, and t_{max}.
Exploratory To determine the pharmacodynamic effects of LY3478045 following single and multiple doses in healthy subjects. CCI [redacted] CCI [redacted]	AUC(0-24) of fructose concentration over time following fructose tolerance test. CCI [redacted] CCI [redacted]

Abbreviations: AUC(0-24) = area under concentration curve from time zero to 24 hours; AUC(0-inf) = area under concentration curve from time zero to infinite hours; C_{max} = maximum observed drug concentration; OATP = organic-anion-transporting polypeptide; SAE = serious adverse event; t_{max} = time of C_{max}; TEAE = treatment-emergent adverse event.

5. Study Design

5.1. Overall Design

Study GZKA is a Phase 1, single site, randomized, double-blind, placebo-controlled, 2-part study of LY3478045 in healthy subjects.

Part A: single-ascending doses (SAD) (Section 5.1.1).
Part B: multiple-ascending dose (MAD) design that evaluates the potential for a drug-drug interaction (Section 5.1.2).

During the study, replacement of subjects who do not have any safety concerns due to the study drug administration may be allowed at the discretion of investigator. Replaced subject will assume the randomization schedule of the discontinued subject for treatment assignment.

Safety, PD, PK, and other assessments and activities will be performed as specified in Section 2. Section 7.4.1 describes the criteria for dose escalation.

Study governance considerations are described in Appendix 3.

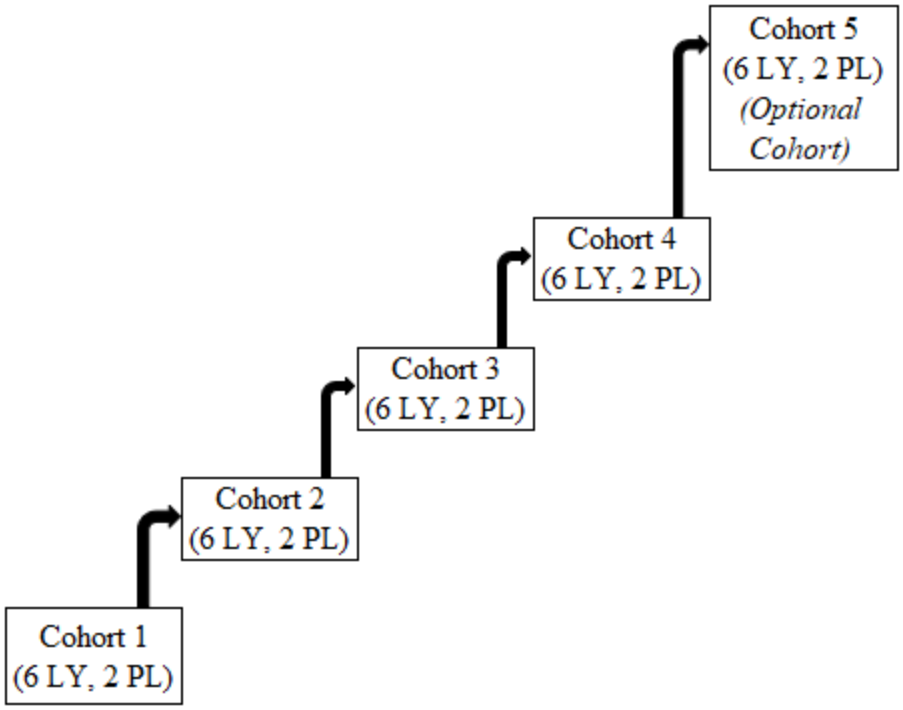
5.1.1. Part A

Single-ascending oral doses of either LY3478045 or placebo will be administered in up to 5 cohorts. Each cohort will consist of 8 subjects. Cohort 5 is an optional cohort that may be assessed based on the available safety and PK data from the previous cohorts. CCI

CCI

A sentinel dosing strategy will be utilized for Cohorts 3, 4, and 5. Two subjects (1 LY3478045 and 1 placebo) in each cohort will receive a sentinel dose on the same day. After at least 48 hours after dose, the remaining subjects in each cohort may be dosed based on the available safety data.

Figure GZKA.1 illustrates the study design.



Abbreviations: LY = LY3478045; PL = placebo.

Figure GZKA.1. Illustration of study design for Part A.

5.1.2. Part B

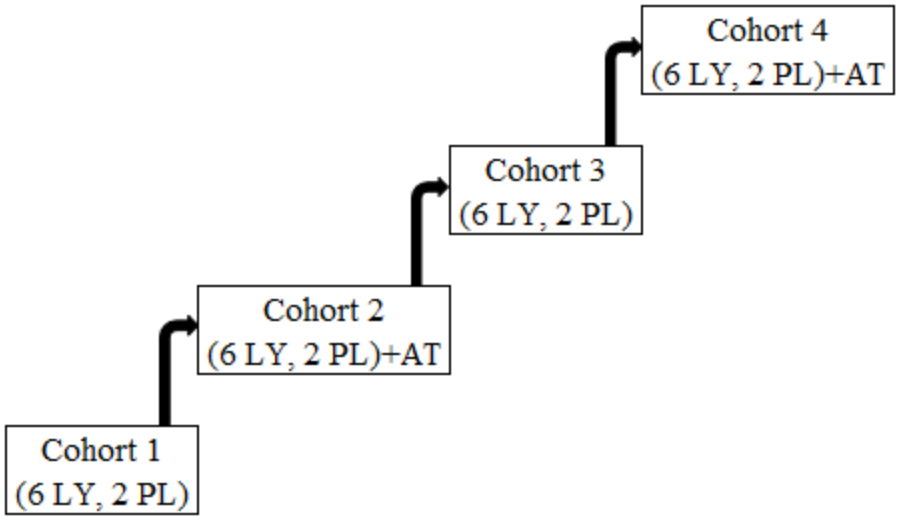
Part B will be initiated after assessing safety, tolerability, PK, and PD data through Cohort 3 in Part A.

Multiple-ascending oral doses of LY3478045 will be administered once daily for 14 days in up to 4 cohorts. Each cohort will consist of 8 subjects. In Cohorts 1 and 3, six subjects will receive LY3478045 and 2 subjects will receive placebo. In Cohorts 2 and 4, six subjects will receive LY3478045 followed by a single dose of atorvastatin 4 hours later and 2 subjects will receive placebo followed by a single dose of atorvastatin 4 hours later.

The maximum dose in males and females in the MAD will be determined based on the PK analyses from previous cohorts, to ensure that the predicted mean exposure at steady state (AUC0-24) at the maximum dose in males does not exceed CCI [redacted] CCI [redacted]

A sentinel dosing strategy will be utilized in the cohorts for which the mean AUC0-24 is predicted to exceed CCI [redacted] Two subjects (1 LY3478045 and 1 placebo) in the cohorts for which the mean AUC0-24 is predicted to exceed CCI [redacted] will receive a sentinel dose on the same day. At least 48 hours after dose, the remaining subjects in each cohort may be dosed based on the available safety data.

Figure GZKA.2 illustrates the study design.



Abbreviations: AT = atorvastatin; LY = LY3478045; PL = placebo.

Figure GZKA.2. Illustration of study design for Part B.

5.2. Number of Participants

Up to 50 subjects may be enrolled in Part A to ensure that at least 40 subjects complete the study (depending on whether subjects will be enrolled in optional Cohort 5). Up to 40 subjects may be enrolled in Part B to ensure that at least 32 subjects complete the study. For purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been completed.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

Healthy Subjects

Conducting the study in healthy subjects 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.

Sentinel Dosing

Consistent with the concept of sentinel dosing (EMA 2017), sentinel dosing will be performed in:

Part A: Cohorts 3, 4, and 5 as the exposures of LY3478045 in these cohorts may approach 1/10th the exposure at the NOAEL (CCI [redacted]). Sentinel dosing will not be performed in Cohorts 1 and 2 as LY3478045 exposures in these cohorts are anticipated to be substantially below 1/10th the exposure at the NOAEL.

Part B: Sentinel dosing will be included for the cohort(s) of female subjects tested at dose(s) predicted to result in mean exposure(s) between CCI

Blinding

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

Clinical Data

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

Periodic Reviews

Periodic trial-level safety data reviews will ensure that any subject can be discontinued early, or the dose escalation can be terminated, or the study can be terminated, in case of any AE requiring such a decision.

5.5. Justification for Dose

A planned dose range of 20 to 320 mg was selected to assess safety, tolerability, PK, and PD of LY3478045 following SAD and MAD in healthy subjects:

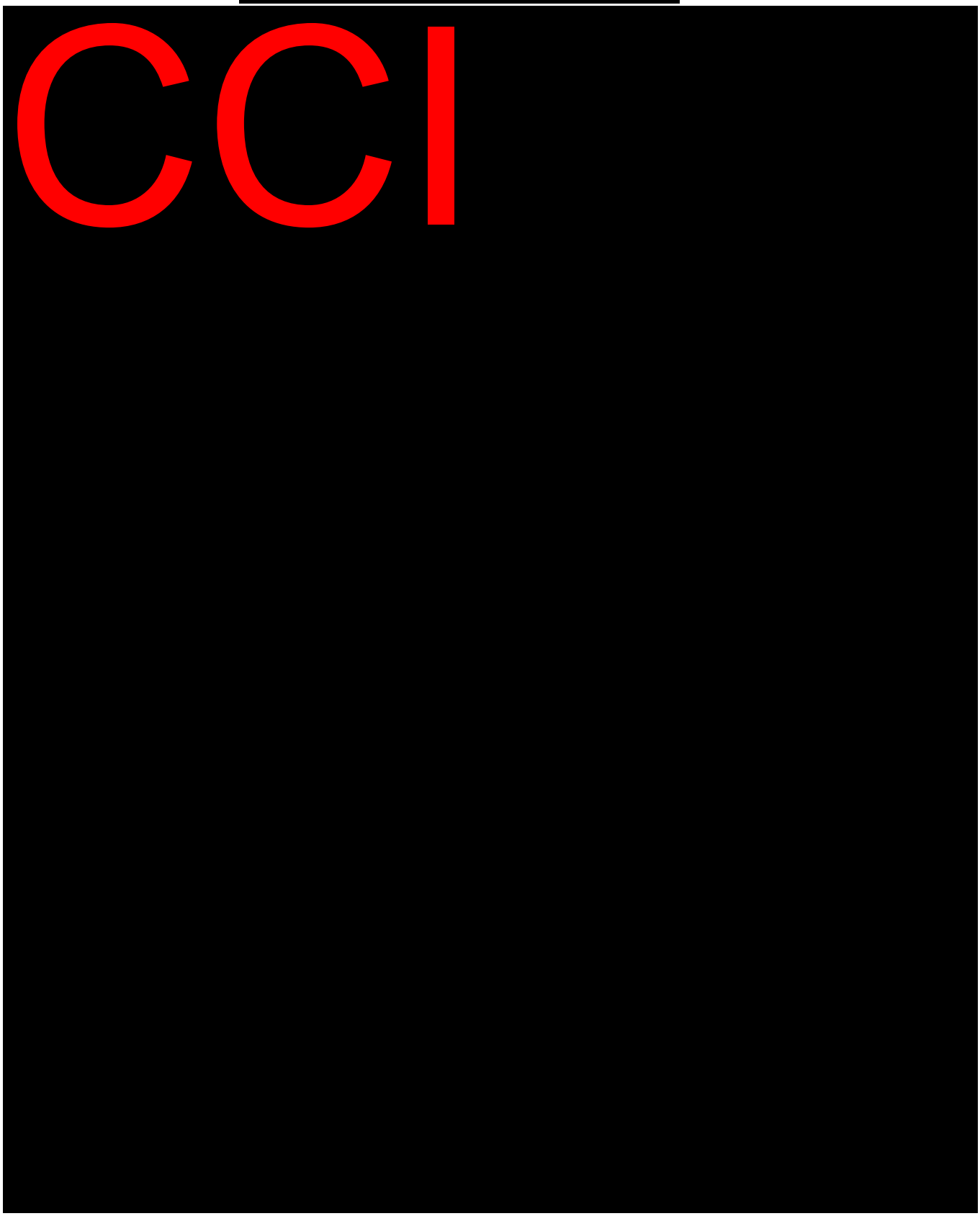
The planned starting dose in Part A (SAD) is 20 mg in both male and female subjects. The planned top dose in Part A (SAD) is a dose that is predicted to not exceed the mean exposure CCI (it is currently anticipated that this dose is 320 mg; however, the exact dose will be determined once PK data are analyzed from the previous cohorts in Part A).

The human PK in healthy subjects was projected with physiologically based pharmacokinetic (PBPK) modeling using data from in vitro studies in human systems. CCI The predicted efficacious dose is 100 to 200 mg once daily based on maintaining plasma exposure over the total cell-based KHK half maximal inhibitory concentration for 24 hours. The PD measurement of serum fructose in Part A (SAD) will define the level of target engagement at each dose, which will further allow refinement of predicted efficacious dose.

The starting dose of CCI

The dose levels in MAD (Part B) will be selected based on available PK/PD data from Part A. The maximum dose in males in the MAD will be determined based on the PK analyses from previous cohorts to ensure that the predicted mean exposure AUC0-24 at the maximum dose in males does not CCI This is 1/10th of the mean exposure level observed at 75 mg/kg in dogs, which is the lowest dose tested in dogs with no testicular findings. The maximum dose in females in the MAD will be determined based on the PK analyses from previous cohorts to ensure that the predicted mean exposure AUC0-24 at the maximum dose in females does not exceed CCI This is 1/12th of NOAEL exposure at CCI dose in dogs.

Table GZKA.2. CCI




CCI

6. Study Population

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

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

Screening may occur up to 28 days prior to day of clinical research unit (CRU) admission. Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Subjects will continue the study procedures despite clinical laboratory abnormalities on Day -1 of Part A and Part B (Cohorts 1 and 3) and on Day -3 of Part B (Cohorts 2 and 4) unless otherwise specified by the investigator or sponsor.

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

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

6.1. Inclusion Criteria

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

[1] are overtly healthy subjects as determined through medical history and physical examination.

[1a] male subjects agree to use a highly effective method of contraception for the duration of the study and for 90 days thereafter, which corresponds to 4 months after the last investigational product dose. See Sections 6.3.4 and 7.4.1.

[1b] female subjects not of child-bearing potential may participate and include those who are

i. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or

ii. postmenopausal – defined as either

a. a woman at least 40 years of age with an intact uterus, not on hormone therapy, who has

i. cessation of menses for at least 1 year without an alternative medical cause, AND

ii. a follicle-stimulating hormone >40 mIU/mL; or

b. A woman 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or

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

[2] are aged between 18 and 60 years, inclusive.

[3] have a body mass index of ≥18.5 and ≤40 kg/m^2.

[4] have had a stable weight for the 3 months prior to screening and enrollment (<5% body weight change) and have not received dietary intervention in the 3 months prior to screening and enrollment.

[5] 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.

[6] have venous access enough to allow for blood sampling as per the protocol.

[7] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures including dietary requirements.

[8] are able and willing to give signed informed consent.

6.2. Exclusion Criteria

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

[9] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.

[10] are Lilly employees.

[11] are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[12] have participated, within 30 days of screening, in a clinical study involving an investigational product. At least 5 half-lives or 30 days (whichever is longer) should have passed.

[13] have known allergies to LY3478045, related compounds, or any components of the formulation, or history of significant atopy.

[14] 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 (QT) data analysis.

[15] 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 (see Section 6.4).

[16] 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, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk while taking the investigational product; or of interfering with the interpretation of data.

[17] have a history of fructosuria.

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

[19] show evidence of hepatitis B and positive hepatitis B surface antigen.

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

[21] have obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis.

[22] have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatine phosphokinase >1.5x upper limit of normal (ULN), or total bilirubin level (TBL) ≥1.5x ULN. Participants with Gilbert's syndrome can be enrolled with TBL of <2x ULN.

[23] intend to use over-the-counter or prescription medication including herbal medications such as St. John's wort and/or vitamin/mineral supplements within 14 days prior to dosing.

[24] CCI

[25] CCI

[26] have consumed or intend to 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 within 14 days prior to the first dose of any study drug until discharge from the study

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

[28] regularly use known drugs of abuse and/or positive urine drug screen at screening or check-in.

[29] smoke >10 cigarettes per day or the equivalent or are unable or unwilling to refrain from nicotine during CRU admission.

[30] have either moderate or severe alcohol consumption. Moderate alcohol consumption is defined as 1 standard 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).

[31] have estimated glomerular filtration rate <60 mL/min/1.73 m^2.

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

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Subjects should be fasted for 8 hours prior to predose blood sampling, performing ECGs, and LY3478045 dose administration. On days of CCI assessment (Cohorts 2 and 4), subjects should fast overnight, eat breakfast, and be given CCI after breakfast (Day -2) or 4 hours after LY3478045 (Day 7). Subjects should not eat again until 2 hours after CCI administration on Days -2 and Day 7.

6.3.2. Caffeine, Alcohol, and Tobacco

Subjects will be encouraged to maintain their regular caffeine consumption.

Nicotine use is not permitted at the CRU.

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

6.3.3. Activity

Subjects 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 CRU. Subjects should maintain their normal levels of activity at other times.

6.3.4. Contraception for Males

Male subjects (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), or to use condoms as well as 1 additional highly effective (<1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or 2 effective methods of contraception (such as diaphragms with spermicide or cervical sponges) from the entirety of the study, plus 90 days thereafter, which corresponds to 4 months after the last investigational product dose.

Men and their partners may choose to use a double-barrier method of contraception; however, barrier protection methods without concomitant use of a spermicide are not considered an effective or acceptable method of contraception (each barrier method must include use of a spermicide). The use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

Male subjects 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 subjects 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.

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

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened with the exception of vital signs and laboratory values slightly outside the normal range, in the opinion of the investigator. These participants may be re-screened. However, participants who were eligible for inclusion in previous cohorts, but who were not randomized for nonmedical reasons, may be re-assessed for inclusion in subsequent cohorts.

7. Treatment

7.1. Treatment Administered

LY3478045 or placebo will be administered orally with approximately 240 mL of room temperature water in the morning of each dosing day (Day 1 in SAD; Days 1 to 14 in MAD) in a sitting position. Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Table GZKA.3. Treatments Administered

Treatment Name	LY3478045	Placebo	Atorvastatin
Dosage Formulation	CCI	Capsules	Tablets
Dose strength		-	40 mg
Route of Administration	Oral	Oral	Oral

The investigator or designee is responsible for

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

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

7.1.1. Packaging and Labeling

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

Each capsule of LY3478045 will contain CCI active ingredient. Placebo capsules will match LY3478045 capsules in appearance.

LY3478045 and matching placebo capsules will be supplied to the investigator by Lilly for dispensing by unblinded pharmacy staff.

Atorvastatin will be sourced locally by the site.

7.2. Method of Treatment Assignment

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

7.2.1. Selection and Timing of Doses

The doses will be administered at the visits and times specified in Section 2 of this protocol. The actual time of all dose administrations will be recorded in the subject's case report form (CRF).

7.3. Blinding

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

The unblinded pharmacist or designee will prepare the study drug.

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

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

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

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

7.4. Dose Modification

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the highest planned dose has been administered, or the maximum tolerated dose (MTD) is determined. If the highest planned dose is not reached, the highest dose level that is tolerated will be designated as the MTD.

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 Lilly CP/CRP/study team.

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).

7.4.1. Dose Decision/Escalation

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

- All planned subjects in current cohort must have been dosed.

- Clinical assessment through Day 7 for at least 6 of 8 subjects.
- Safety laboratory tests are obtained from Day 7 for at least 6 of 8 subjects.

For Cohorts 3, 4, and 5 in Part A, the PK results (C_{max}, AUC0-inf, AUC0-tlast, and apparent clearance of drug [CL/F]) estimated from the previous cohorts will also be used as supporting data for dose escalation. For Cohort 2 in Part A, PK results may be used if available at the time of dose escalation decision.

In Part A, male and female subjects will only be dosed up to the dose with predicted mean exposure not exceeding CCI For Part B, the PK results (C_{max}, AUC0-24, and apparent clearance of drug [CL/F]) estimated from the previous cohorts will also be used as supporting data for dose escalation.

Male subjects are allowed in Part B in the cohorts for which the predicted mean exposure AUC0-24 levels for the dose will not exceed CCI 1/10th exposure level observed at CCI in dogs, which is the lowest dose tested in dogs with no testicular findings, as determined from PK data in Parts A and B.

Female subjects are allowed in Part B in every cohort. The predicted mean exposure AUC0-24 levels for the doses investigated in Part B will not exceed CCI, 1/12th exposure level observed at CCI in dogs, as determined from PK data in Parts A and B.

More details about the planned dose levels in Parts A and B are available in Section 5.5.

If any of the following scenarios occur, dosing at the current level and further dose escalation will be interrupted until a further sponsor decision:

1) One or more subjects on active drug experience an SAE considered to be related to LY3478045.
2) One or more subjects on active drug experience 2 clinically significant events 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 Lilly CP and may include findings that do not fulfill the criteria for SAEs.

7.5. 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 investigational products received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive investigational product 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).

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

Subjects on stable concomitant medications at the time of study entry should continue their regular, unchanged dose throughout the study.

In general, concomitants medication should be avoided; however, acetaminophen (1 g, maximum 4 g/24 hours) may be administered at the discretion of the investigator for treatment of headache, etc. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly CP or CRP. Any medication used during the study must be documented.

Vitamin/mineral supplements are not allowed during the study.

Drugs that are known strong inducers or inhibitors of CYP3A or OATPs and known substrates of OATPs or BCRP are specifically excluded. For more information, refer to Appendix 6.

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

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

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

8.1. Discontinuation from Study Treatment

In Part B, discontinuation of the investigational product for abnormal liver test results **should be considered** by the investigator when a subject 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.

8.2. Discontinuation from the Study

Subjects will be discontinued under the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
    - Any TEAE or SAE considered possibly or probably related to study drug 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.
    - Any TEAE or SAE regardless of attribution to study drug that has life-threatening consequences or urgent intervention is indicated.
- Investigator Decision

- the investigator decides that the subject should be discontinued from the study
- if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

- Subject Decision
  - the subject, or legal representative, requests to be withdrawn from the study.

The replacement strategy for discontinued participants is described in Section 10.1. If deemed appropriate by the investigator, early discontinuation procedures will be performed as shown in the Schedule of Activities (Section 2).

8.3. Subjects Lost to Follow-up

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

8.4. Discontinuation of the Study

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

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 drug 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
- Two study participants develop any TEAE or SAE regardless of attribution to study drug that has life-threatening consequences or requires urgent intervention OR
- Death of any study participant at any time related to AE.

9. Study Assessments and Procedures

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

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

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

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

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 subject to minor alterations; however, the actual time must be correctly recorded in the electronic case report form (eCRF). Failure to obtain samples due to clinical issues, such as problems with venous access, technical difficulty with obtaining samples, or if the subject does not show up for planned procedural visits will not be considered a protocol deviation. However, the CRU will still be required to notify the sponsor in writing to account for missing samples to facilitate data reconciliation.

If the predicted mean exposure for the dose at any cohort is estimated to be higher than 71.7 µg·hr/mL, only female subjects will be included in the cohort and mandated to stay in the CRU until 24 hours after the last dose.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

The investigator will record all relevant AE and SAE information in the eCRF. After the informed consent form (ICF) is signed, study site personnel will record, via eCRF, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether an AE has a reasonable possibility of being related to study treatment, or a study procedure, considering the disease, concomitant treatment or pathologies.

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

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

If a subject's investigational product is discontinued because of an AE, study site personnel must report this to Lilly or its designee via eCRF.

9.2.1. Serious Adverse Events

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

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

Study site personnel must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible.

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

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving

investigational product, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study (the subject summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

9.2.2. Complaint Handling

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

Subjects should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product [or drug delivery system] so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3478045 is considered any dose higher than the dose assigned through randomization.

Refer to the LY3478045 IB for more details.

9.4. Safety

9.4.1. Laboratory Tests

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

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

9.4.2. Physical Examination

Physical examinations and routine medical assessments including body temperature will be conducted as specified in the Schedule of Activities (Section 2) and as clinically indicated.

Subjects 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 subject for any abnormal eye or skin irritation, redness, itching, burning sensation in daylight or on exposure to sunlight. The subject will be examined for abnormal skin erythema and hyperemia in exposed areas, hyperemia, scleritis, and conjunctivitis.

9.4.2.1. Vital Signs

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

Blood pressure and pulse rate should be measured after at least 5 minutes supine.

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

If the subject 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.

9.4.3. Electrocardiograms

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

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

Electrocardiograms must be recorded before collecting any blood samples. Subjects 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.

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

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subject for symptoms (e.g., palpitations, near syncope, syncope) to determine whether the subject can continue in the study. The investigator

or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

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

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

9.4.4. Body Temperature

Body temperature will be measured as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.5. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes, and
- adverse events.

When appropriate, the Lilly 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 personnel included in the unblinding/blinding plan.

9.4.5.1. Hepatic Safety

If a study participant experiences elevated ALT ≥3x ULN, AST ≥3x ULN, ALP ≥2x ULN, or TBL ≥2x, tests specified in Appendix 4 should be repeated within 48 to 72 hours to confirm the abnormality and to determine if the abnormality is increasing or decreasing.

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 consumption 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.

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

- Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests
- Elevated TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests
- Hepatic event considered to be an SAE
- Discontinuation of study drug due to a hepatic event

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

9.4.5.2. Testicular safety

Male subjects will be enrolled in this trial only if they agree to comply with the contraception requirements specified in this protocol.

In Part B (MAD), blood samples for evaluating hormonal biomarkers of testicular injury (serum concentrations of total testosterone, follicle-stimulating hormone, and luteinizing hormone) will be collected at the visits and times specified in the Schedule of Activities (Section 2).

To mitigate risks of testicular injury, in Part B of the study (MAD), male participants' dose will be restricted to the dose with predicted mean exposure not exceeding CCI [redacted] CCI [redacted] which is the lowest dose tested in dogs with no testicular findings.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of LY3478045. 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. The actual date and time (24-hour clock time) of each sampling will be recorded.

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

Urine samples will be collected for the characterization of renal clearance. Total urine output for the appropriate period after investigational product administration will be collected, pooled, and refrigerated. The final urine sample will be collected at a time that coincides with a PK sample. At the end of the collection period, the total urine volume will be recorded. Urine samples will be used to determine creatinine, quantification of LY3478045, and exploratory metabolite identification.

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine serum creatinine measurements.

Atorvastatin will be administered in Part B as indicated in the Schedule of Activities (Section 2). Blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of atorvastatin and metabolites.

9.5.1. Bioanalysis

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

Concentrations of LY3478045 will be assayed using a validated liquid chromatography-tandem mass spectrometry method. Analyses of samples collected from placebo-treated subjects are not planned.

Plasma concentrations of CCI [redacted] will be analyzed using validated liquid chromatography/tandem mass assay. Analyses of samples collected from LY- and placebo-treated subjects are planned.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 2 years following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses.

9.6. 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 containing mixture of fructose and glucose CCI [redacted] in approximately 300 to 500 mL of non-caloric solution) 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 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) 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 the Schedule of Activities (Section 2). Sample handling and shipment to the central laboratory will occur per instructions given to the study site.

The samples will be stored for up to a maximum of 1 year after the last subject visit for the study at a facility selected by the sponsor.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to LY3478045 and to investigate genetic variants thought to play a role in NASH. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or institutional review boards (IRBs) impose shorter time limits, for the study at a facility selected by Lilly or its designee. 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 LY3478045 or after LY3478045 is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

9.8.1. CCI

CCI

9.8.1.1. Bioanalysis

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

CCI will be assayed using a validated liquid chromatography tandem mass spectrometry method. It is planned that samples collected from both LY3478045- and placebo-treated subjects will be analyzed.

9.8.2. Fasting Insulin and Adiponectin

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the plasma concentrations of fasting insulin and adiponectin.

9.8.3. Nonpharmacogenetic Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of subject 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 the Schedule of Activities (Section 2), where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3478045, pathways associated with type 2 diabetes mellitus (T2DM), diabetic complications, obesity, or the potential mechanism of action of LY3478045 and/or research method, or for validating diagnostic tools or assay related to T2DM, diabetic complications, obesity, or the potential mechanism of action of LY3478045.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or IRBs impose shorter time limits, at a facility selected by Lilly or its designee. 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 LY3478045 or after LY3478045 is commercially available.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The sample size for Parts A and B of the study was chosen to provide sufficient data for evaluating safety, PK, and/or PD parameters, as well as primary objectives of this study. For details regarding the number of subjects planned for each part, refer to Section 5.2.

Subjects who are randomized but not administered treatment, and who are discontinued from the study (providing that discontinuation was not as a result of a safety finding) may be replaced to ensure that enough subjects may complete the study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

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

10.3. Statistical Analyses

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

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

Safety analyses will be conducted for all enrolled subjects, whether they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to 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 investigational product-related SAEs will be reported.

10.3.1.2. 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 in units acceptable to the FDA. The parameters will be listed and summarized using standard descriptive statistics.

Analyses may be performed to determine the effects of PK parameters on QT interval corrected. A concentration-response analysis will be performed according to International Council for Harmonisation (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.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3478045 will be calculated using standard noncompartmental methods of analysis in Parts A and B.

Parts A and B:

The primary parameters for analysis will be C_{max}, time of C_{max} (t_{max}), AUC from time zero to 24 hours (AUC0-24), and AUC from time zero to infinity (AUC0-inf) of LY3478045. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

Part A only:

Renal clearance of LY3478045 will be calculated as the ratio of amount excreted/AUC in Part A only. This will be compared to the unbound glomerular filtration rate, which is estimated using creatinine.

Part B only:

Accumulation ratio for LY3478045 based on AUC0-24 and C_{max} may be reported.

The primary parameters for analysis for CCI [redacted] will be AUC(0-inf) and C_{max}. Other parameters, including t_{max}, $t_{1/2}$, CL/F, apparent volume of distribution during the terminal elimination phase (Vz/F), metabolite ratios based on AUC0-inf, and AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC0-tlast) CCI [redacted] will be calculated as appropriate.

10.3.2.2. 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 LY3478045 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.

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

The primary PD effect will be evaluated using fructose tolerance test (FTT). 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.

10.3.3.2. Pharmacodynamic Statistical Inference

Pharmacodynamic 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.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/PD modeling may be employed to characterize the exposure-response relationships between LY3478045 concentrations and various PD endpoints, provided enough data are available.

10.3.5. Data Review During the Study

Interim access to safety and tolerability data is scheduled to occur after every dosing session. Pharmacokinetic/PD data may be included in these reviews, when available. The purpose of these reviews is to guide dose selection for the next dosing session, and/or to inform the design of subsequent studies. The investigator and the Lilly sponsor team will make the determination regarding dose escalation, based upon their review of the data. The investigator will remain blinded, and the Lilly sponsor team will be unblinded during these reviews.

10.3.6. Interim Analyses

No interim analyses are planned for this study except the interim access to safety, tolerability, and other PK/PD data to guide dose selection for the next dosing session as described in Section 10.3.5.

If an unplanned interim analysis is deemed necessary, the Lilly CP, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

11. References

Andres-Hernando A, Johnson RJ, Lanaspa MA. Endogenous fructose production: what do we know and how relevant is it? *Curr Opin Clin Nutr Metab Care.* 2019;22(4):289-294.

Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Keach JC, Lafferty HD, Stahler A, Haflidadottir S, Bendtsen F. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2015;149(2):389-397.

Basciano H, Federico L, Adeli K. Fructose, insulin resistance, and metabolic dyslipidemia. *Nutr Metab (Lond)*. 2005;2(1):5.

Bonthron DT, Brady N, Donaldson IA, Steinmann B. Molecular basis of essential fructosuria: molecular cloning and mutational analysis of human ketohexokinase (fructokinase). *Hum Mol Genet.* 1994;3(9):1627-1631.

Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr.* 2004;79:537-543.

Calle R, Bergman A, Somayaji V, Chidsey K, Kazierad D. PS-110-ketohexokinase inhibitor PF-06835919 administered for 6 weeks reduces whole liver fat as measured by magnetic resonance imaging-proton density fat fraction in subjects with non-alcoholic fatty liver disease. *J Hepatol.* 70(1)(Suppl);2019:e69-e70.

Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-357.

Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology*. 2011;141(4):1249-1253.

Collin LJ, Judd S, Safford M, Vaccarino V, Welsh JA. Association of sugary beverage consumption with mortality risk in us adults: a secondary analysis of data from the REGARDS study. *JAMA Netw Open*. 2019;2(5):e193121.

de Koning L, Malik VS, Kellogg MD, Rimm EB, Willett WC, Hu FB. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. *Circulation*. 2012;125(14):1735-1741.

[EMA] European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. 20 July 2017. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf. Accessed on 14 November 2019.

[FDA] Food and Drug Administration. Guidance for industry on estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. July 2005. Available at: https://www.fda.gov/media/72309/download. Accessed 23 December 2019.

Froesch ER. Disorders of fructose metabolism. J Clin Pathol Suppl (Assoc Clin Pathol). 1969;2:7–12.

Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. *Am J Clin Nutr.* 2009;89(4):1037-1042.

Hannou SA, Haslam DE, McKeown NM, Herman MA. Fructose metabolism and metabolic disease. *J Clin Invest*. 2018;128(2):545-555.

Ishimoto T, Lanaspa MA, Le MT, Garcia GE, Diggle CP, Maclean PS, Jackman MR, Asipu A, Roncal-Jimenez CA, Kosugi T, Rivard CJ, Maruyama S, Rodriguez-Iturbe B, Sánchez-Lozada LG, Bonthron DT, Sautin YY, Johnson RJ. Opposing effects of fructokinase C and A isoforms on fructose-induced metabolic syndrome in mice. *Proc Natl Acad Sci U S A.* 2012;109(11):4320-4325.

Ishimoto T, Lanaspa MA, Rivard CJ, Roncal-Jimenez CA, Orlicky DJ, Cicerchi C, McMahan RH, Abdelmalek MF, Rosen HR, Jackman MR, MacLean PS, Diggle CP, Asipu A, Inaba S, Kosugi T, Sato W, Maruyama S, Sánchez-Lozada LG, Sautin YY, Hill JO, Bonthron DT, Johnson RJ. High-fat and high-sucrose (western) diet induces steatohepatitis that is dependent on fructokinase. *Hepatology.* 2013;58(5):1632-1643.

Lai Y, Mandlekar S, Shen H, Holenarsipur VK, Langish R, Rajanna P, Murugesan S, Gaud N, Selvam S, Date O, Cheng Y, Shipkova P, Dai J, Humphreys WG, Marathe P. Coproporphyrins in Plasma and Urine Can Be Appropriate Clinical Biomarkers to Recapitulate Drug-Drug Interactions Mediated by Organic Anion Transporting Polypeptide Inhibition. *J Pharmacol Exp Ther.* 2016;358(3):397-404.

Lanaspa MA, Ishimoto T, Li N, Cicerchi C, Orlicky DJ, Ruzycki P, Rivard C, Inaba S, Roncal-Jimenez CA, Bales ES, Diggle CP, Asipu A, Petrash JM, Kosugi T, Maruyama S, Sanchez-Lozada LG, McManaman JL, Bonthron DT, Sautin YY, Johnson RJ. Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome. *Nat Commun.* 2013;4:2434.

Lanaspa MA, Andres-Hernando A, Orlicky DJ, Cicerchi C, Jang C, Li N, Milagres T, Kuwabara M, Wempe MF, Rabinowitz JD, Johnson RJ, Tolan DR. Ketohexokinase C blockade ameliorates fructose-induced metabolic dysfunction in fructose-sensitive mice. *J Clin Invest.* 2018;128(6):2226-2238.

Laron Z. Essential benign fructosuria. *Arch Dis Child*. 1961;36:273-277.

Lau YY, Huang Y, Frassetto L, Benet LZ. Effect of OATP1B transporter inhibition on the pharmacokinetics of atorvastatin in healthy volunteers. *Clin Pharmacol Ther.* 2007;81(2):194-204.

Softic S, Gupta MK, Wang GX, Fujisaka S, O'Neill BT, Rao TN, Willoughby J, Harbison C, Fitzgerald K, Ilkayeva O, Newgard CB, Cohen DE, Kahn CR. Divergent effects of glucose and fructose on hepatic lipogenesis and insulin signaling. *J Clin Invest.* 2017;127(11):4059-4074.

Tappy L, Mittendorfer B. Fructose toxicity: is the science ready for public health actions? *Curr Opin Clin Nutr Metab Care*. 2012;15(4):357–361.

Vos MB, McClain CJ. Fructose takes a toll. *Hepatology.* 2009;50(4):1004-1006.

Weber KS, Simon MC, Strassburger K, Markgraf DF, Buyken AE, Szendroedi J, Müssig K, Roden M; GDS Group. Habitual fructose intake relates to insulin sensitivity and fatty liver index in recent-onset type 2 diabetes patients and individuals without diabetes. *Nutrients*. 2018;10(6).pii:E774.

Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol.* 2018;15(1):11-20.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	serum aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC0-inf	AUC from time zero to infinity
BCRP	breast cancer resistance protein
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
CL/F	apparent clearance of drug
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.
CRU	clinical research unit
CV	cardiovascular
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
Enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
Enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FTT	fructose tolerance test
GCP	good clinical practice
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
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.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.

KHK	ketohexokinase
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
MTD	maximum tolerated dose
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NOAEL	no-observed-adverse-effect level
non-investigational product	A product that is not being tested or used as a reference in the clinical study, but is provided to subjects 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.
CCI	
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PBPK	physiologically based pharmacokinetics
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
QTc	corrected QT
Randomize	the process of assigning subjects to an experimental group on a random basis
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.
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
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
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests (Fasting)

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
	Creatinine
Differential WBC (absolute counts of):	Blood urea nitrogen (BUN)
Neutrophils	Uric acid
Lymphocytes	Total cholesterol
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin[d]
	Alkaline phosphatase (ALP)
Urinalysis[e]	Aspartate aminotransferase (AST)
Specific gravity	Alanine aminotransferase (ALT)
pH	Creatine Phosphokinase
Protein	Gamma-glutamyl transferase (GGT)
Glucose	
Ketones	Ethanol testing[a,b]
Bilirubin	Urine drug screen[a,b]
Urobilinogen	Hepatitis B surface antigen[a]
Blood	Hepatitis C antibody[a]
Nitrite	HIV[a]
	Pregnancy test
	FSH[a,c]
	Thyroid-stimulating hormone[a]

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] Performed in 40- to 55-year old females to confirm their post-menopausal status. In males, FSH will be collected at screening and at other times indicated in the Schedule of Activities, as part of testicular hormonal function assessment.

[d] Reflex test will be done if abnormalities are noted.

[e] Reflex microscopy will be done if abnormalities are noted.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for

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

Recruitment

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

Ethical Review

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

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

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

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

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

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

Protocol Signatures

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

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

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

Data Quality Assurance

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

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

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor,

applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; TBL = total bilirubin level; WBC = white blood cell.

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

Appendix 5. Blood Sampling Summary

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

Protocol J2M-MC-GZKA 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	3	7.5
Pharmacokinetics	2	14	28
Pharmacodynamics, including fructose tolerance test	2	13	26
Pharmacogenetics	10	1	10
Fasting biomarker samples (nonpharmacogenetic)	11.5 (4 mL plasma; 7.5 mL serum)	2	23
CCI	3	12	36
Total			251
Total for clinical purposes (rounded up to the nearest 10 mL)			260

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

Protocol J2M-MC-GZKA Sampling Summary for Part B (Cohorts 1 and 3)

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
Serum creatinine	2.5	3	7.5
Testosterone, follicle-stimulating hormone, and luteinizing hormone	3.5	4	14
LY3478045 pharmacokinetics	2	23	46
Fasting insulin and adiponectin	2.5	2	5
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
CCI [redacted]	3	18	54
Total			355.5
Total for clinical purposes (rounded up to the nearest 10 mL)			360

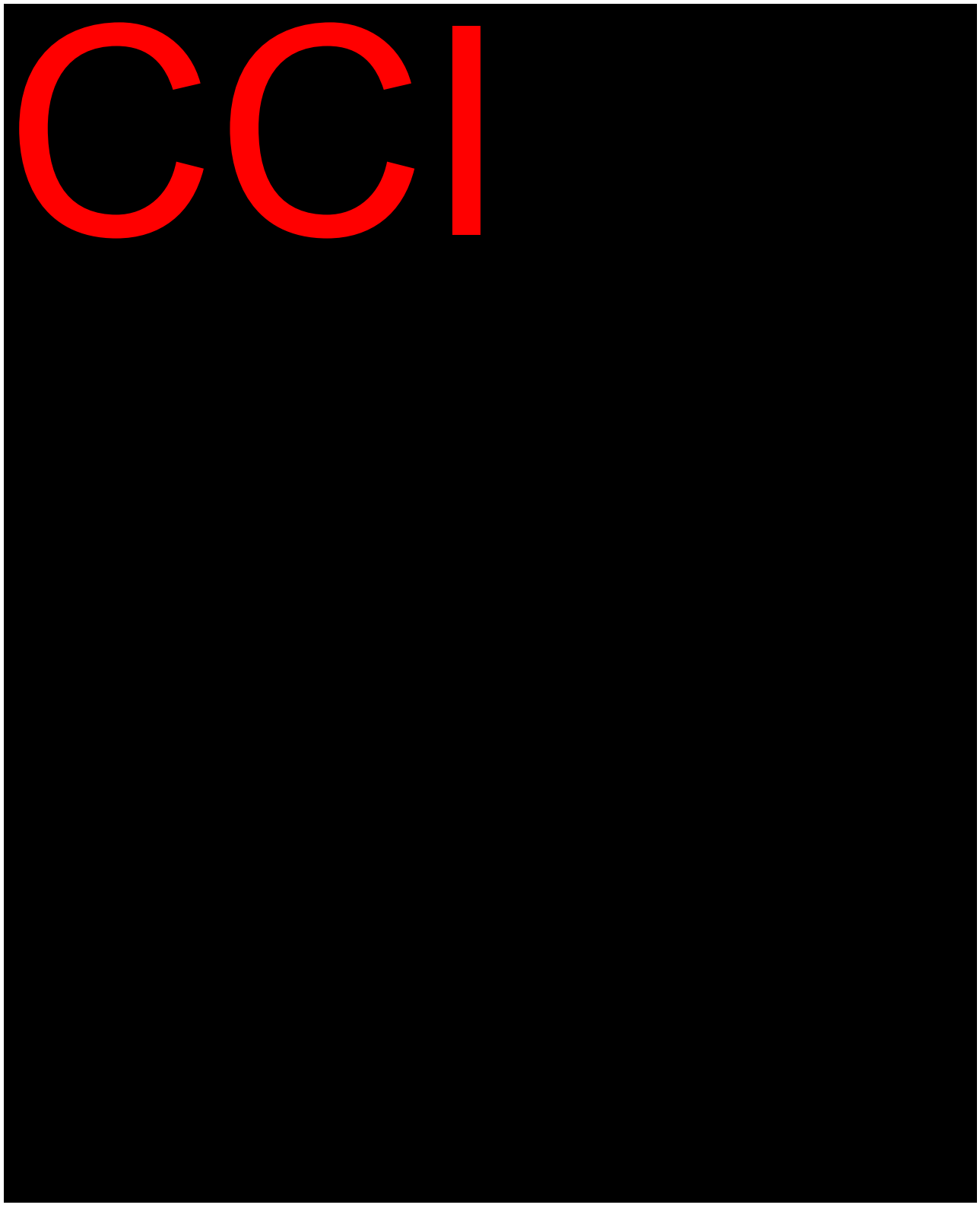
[a] Additional samples may be drawn if needed for safety purposes.

Protocol J2M-MC-GZKA Sampling Summary for Part B (Cohorts 2 and 4)

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
Serum creatinine	2.5	3	7.5
Testosterone, follicle-stimulating hormone, and luteinizing hormone	3.5	4	14
LY3478045 pharmacokinetics	2	32	64
Fasting insulin and adiponectin	2.5	2	5
Pharmacodynamics, including fructose tolerance test	2	26	52
CCI [redacted]	2	24	48
Pharmacogenetics	10	1	10
Fasting biomarker samples (nonpharmacogenetic)	11.5 (4 mL plasma; 7.5 mL serum)	3	34.5
CCI [redacted]	3	27	81
Total			448.5
Total for clinical purposes (rounded up to the nearest 10 mL)			450

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

Appendix 6. Excluded Concomitant Medications




CCI

Appendix 7. Protocol Amendment J2M-MC-GZKA(c) Summary - A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single- and Multiple-Ascending Doses of LY3478045 in Healthy Subjects

Overview

Protocol J2M-MC-GZKA, A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single- and Multiple-Ascending Doses of LY3478045 in Healthy Subjects, has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

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

- 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.

Revised Protocol Sections

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

9.6 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 containing mixture of fructose and glucose (CCI [redacted] in approximately 300 to 500 mL of non-caloric solution) 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 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). Blood samples for the analysis of fructose ~~and sorbitol~~ will be collected into appropriately labeled tubes containing ethylene diamine tetra acetic acid at the time points specified in the Schedule of Activities (Section 2). Sample handling and shipment to the central laboratory will occur per instructions given to the study site.

Signature Page for VV-CLIN-002394 v1.0

Approval	PPD 10-Aug-2021 20:27:10 GMT+0000

Approval	PPD 11-Aug-2021 05:07:33 GMT+0000

Signature Page for VV-CLIN-002394 v1.0