Protocol: J4N-MC-YFAA (b)

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind Trial of LY3885125 to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Single Ascending Dose in Participants With Dyslipidemia and Repeat-Doses in Participants With NAFLD.

NCT06007651

Approval Date: 21-SEP-2023

Title Page

Protocol Title:

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind Trial of LY3885125 to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Single-Ascending Dose in Participants with Dyslipidemia and Repeat-Doses in Participants with NAFLD

Protocol Number: J4N-MC-YFAA

Amendment Number: (b)

Compound: LY3885125

Brief Title:

A study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of LY3885125 compared with placebo in participants aged 18 to 70 years with dyslipidemia or NAFLD

Study Phase: 1

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Lilly Research Labs, Indianapolis, IN 46285, United States

Regulatory Agency Identifier Number(s)

IND 165648

Approval Date: Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-128962

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment b	*21 September 2023*
Amendment a	*28 July 2023*
Original Protocol	*20 June 2023*

Amendment (b)

This amendment is substantial because it has a significant impact on study conduct.

Overall Rationale for the Amendment:

This amendment to the protocol implements a CCI [redacted] and other non-substantial updates, including

- excluding participants with an eGFR less than or equal to CCI mL/min/CCI m^2, and
- clarification of timing and assessments included in Extended Monitoring visits and completing participants' final visits.

Section # and Name	Description of Change	Brief Rationale
1.3.1 Part A Study Schedule (Single Dose Cohorts)	Footnote b clarifies timing of, and assessments included in, Extended Monitoring visits and completing participants' final visits	Changes were made to clarify Extension Monitoring visits and completing participants' final visits
1.3.2 Part B Study Schedule (Repeat Dose Cohort)		
5.2 Exclusion Criteria	Exclusion criteria #23 changed to exclude participants with eGFR ≤ [redacted] mL/min/[redacted] m^2	Changes were made in response to [redacted]
10.8.1 Blood Volumes to be Collected in Part A	Blood volume required for ADA assessment updated to [redacted]	Change was made to better inform total and ADA assessment blood volumes required

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind Trial of LY3885125 to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Single-Ascending Dose in Participants with Dyslipidemia and Repeat-Doses in Participants with NAFLD

Brief Title:

A study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of LY3885125 compared with placebo in participants aged 18 to 70 years with dyslipidemia or NAFLD.

Regulatory Agency Identifier Number(s):

IND 165648

Rationale:

LY3885125 is a N-acetylgalactosamine (GalNAc)-conjugated small interfering ribonucleic acid (siRNA) CCI [redacted]. SCAP regulates the activation of SREBPs, which are transcription factors that govern *de novo* lipogenesis, cholesterol biosynthesis, and metabolism pathways.

CCI [redacted]

This first-in-human (FIH) placebo-controlled study will evaluate the safety, tolerability, and pharmacokinetics (PK)/pharmacodynamics (PD) of single ascending subcutaneous (SC) doses of LY3885125 in participants with dyslipidemia (Part A of study), and of repeated SC doses of LY3885125 in participants with NAFLD and elevated alanine aminotransferase (ALT) (Part B of study). In Part A, the response to LY3885125 will be evaluated via changes in circulating levels of proprotein convertase substilisin/kexin type 9 (PCSK9), CCI [redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Part A: • To determine the safety and tolerability of LY3885125 after a single SC dose in participants with dyslipidemia.	• Adverse events (AEs). • Serious adverse events (SAEs).
Part B: • To determine the safety and tolerability of LY3885125 after 2 SC doses on Days [redacted] and [redacted] in participants with NAFLD and elevated ALT.	• AEs. • SAEs.
Secondary	
Part A: • To assess the PK and PD of LY3885125 after a single SC dose.	• LY3885125 area under the concentration-time curve (AUC), maximum observed concentration (C_{max}), time of C_{max} (T_{max}). • Changes in PCSK9 and apolipoprotein B (ApoB) from baseline relative to placebo.
Part B: • To assess the PK and PD of LY3885125 following 2 SC doses on Days [redacted] and [redacted].	• LY3885125 AUC, C_{max}, T_{max}. • Relative change of liver fat content from baseline to Weeks [redacted] and [redacted] by MRI-PDFF compared with placebo. • Changes in PCSK9 and ApoB from baseline relative to placebo.

Objectives	Endpoints
Exploratory	
Parts A and B: • CCI [redacted]	• CCI [redacted] • CCI [redacted]
Part B: • CCI [redacted] • CCI [redacted]	• CCI [redacted] • CCI [redacted]

Overall Design

Study J4N-MC-YFAA is a Phase 1, multicenter, randomized, placebo-controlled, double-blind, 2-part study in participants with dyslipidemia, and participants with NAFLD and elevated ALT. The study design includes:

- **Part A (Cohorts 1 to 6)**: placebo-controlled, Investigator- and participant-blind, single SC dose of LY3885125 in participants with dyslipidemia:
  - To evaluate the safety, tolerability, PK, and PD of a single ascending dose (SAD) of LY3885125 in up to [redacted] cohorts (Cohorts CCI).
  - CCI
  - Data from Part A will inform the Part B dose.
- **Part B (Cohort 7)**: placebo-controlled, Investigator- and participant-blind, repeat SC doses of LY3885125 in participants with NAFLD and elevated ALT:
  - To evaluate the safety, tolerability, PK, PD, and change of liver fat content from baseline to Weeks CCI by MRI-PDFF of a repeated dose of LY3885125 at Days CCI
  - The Part B dose will be based on data from Part A and will not exceed what has been studied in Part A. The protocol will be amended prior to initiation of Part B to define the dose and dosing frequency.

The study will begin with Part A and proceed to Part B following reviews of safety, tolerability, and available PK and PD data.

Dose escalation decisions will be made by the Dose Escalation Committee (DEC). Recommendations to temporarily suspend study drug intervention or terminate the study early will be evaluated by a Safety Review Committee (SRC).

In both study parts, the identity of study intervention (LY3885125 or placebo) will be masked to participants, Investigators, and site-facing Sponsor personnel.

Brief Summary

The primary purpose of this study is to determine a safe and tolerable dose of LY3885125 in participants with dyslipidemia (Part A) and in participants with NAFLD and elevated ALT (Part B).

In Part A, the approximate total duration of study participation for each participant may be up to [redacted] days ([redacted] weeks), across the following study intervals:

- Screening, approximately 28 days.
- Participants will be admitted to the site on Day -1 for an inpatient treatment period of approximately [redacted] days, during which participants will receive a single dose of LY3885125 or placebo on Day 1. The single doses planned to be administered in Part A are as follows: [redacted]. If more than [redacted] mL of solution is required to deliver a dose, then it will be split into multiple injections, each with a maximum volume of [redacted] mL.
- Participants will then attend follow-up visits as outpatients for a minimum of 25 weeks as outlined in the schedule of activities.
- If discontinuation criteria are not met as outlined in the schedule of activities, participants will continue visits for up to a total of [redacted] weeks, as needed, including during the Monitoring Extension, unless discontinuation criteria are met.
- Each participant in Part A will be followed until the plasma concentration of [redacted] has returned to at least [redacted]% of the baseline level after administration of the single dose .

In Part B, the approximate total duration of study participation for each participant may be up to [redacted] days ([redacted] weeks), across the following study intervals:

- Screening, approximately 28 days.
- Participants will be admitted to the site on Day -1 for the first inpatient treatment period of approximately 2 days, during which they will receive the first dose of LY3885125 or placebo (Day 1).
- Participants will attend the first series of follow-up visits as outpatients every other week post first dose as outlined in the schedule of activities.
- Participants will be readmitted to the site on [redacted] for a second inpatient treatment period of approximately 2 days, during which they will receive the second dose of LY3885125 or placebo ([redacted]).
- Participants will then attend a second series of follow-up visits as outpatients for a minimum of [redacted] weeks post-second dose as outlined in the schedule of activities.
- If discontinuation criteria are not met as outlined in the schedule of activities, participants will continue visits for up to a total of [redacted] weeks post second dose, as needed, including during the Monitoring Extension, unless discontinuation criteria are met.

Study Population:

Males, and females of nonchildbearing potential, aged 18 to 70 years, with dyslipidemia or NAFLD and [redacted].

Number of Participants:

Enrollment for Part A will enable completion of up to CCI participants in up to 6 cohorts.

Enrollment for Part B will enable completion of approximately CCI participants in a single cohort (Cohort 7) that consists of 3 treatment arms with 2 doses administered per arm.

Intervention Groups:

Intervention Groups

Participants will be sequentially enrolled into the study. After the screening period, eligible participants will be randomized to receive either LY3885125 or placebo.

Part A:

Part A Cohort	n	Randomization (LY3885125:placebo)
1-2	CCI	6:2
3-5	CCI	9:2
6 (optional)	CCI	10:9

Part B:

- Cohort 7: This is a repeat dose cohort evaluating a single dose level administered on CCI as shown in the table below. A total of CCI participants will be randomized at the start of Cohort 7 to 1 of 3 treatment arms:
  - Arm 1: Participants will receive the same dose of LY3885125 CCI .
  - Arm 2: Participants will receive a dose of LY3885125 (same as in Arm 1) on CCI .
  - Arm 3: Participants will receive placebo on CCI .

Part B (Cohort 7) Treatment Arm	CCI	First Dose (CCI)[a]	Second Dose (CCI)[a]
1	CCI	LY3885125	LY3885125
2	CCI	LY3885125	Placebo
3	CCI	Placebo	Placebo

[a] The dose administered on CCI (first dose) and CCI (second dose) will be the same dose level

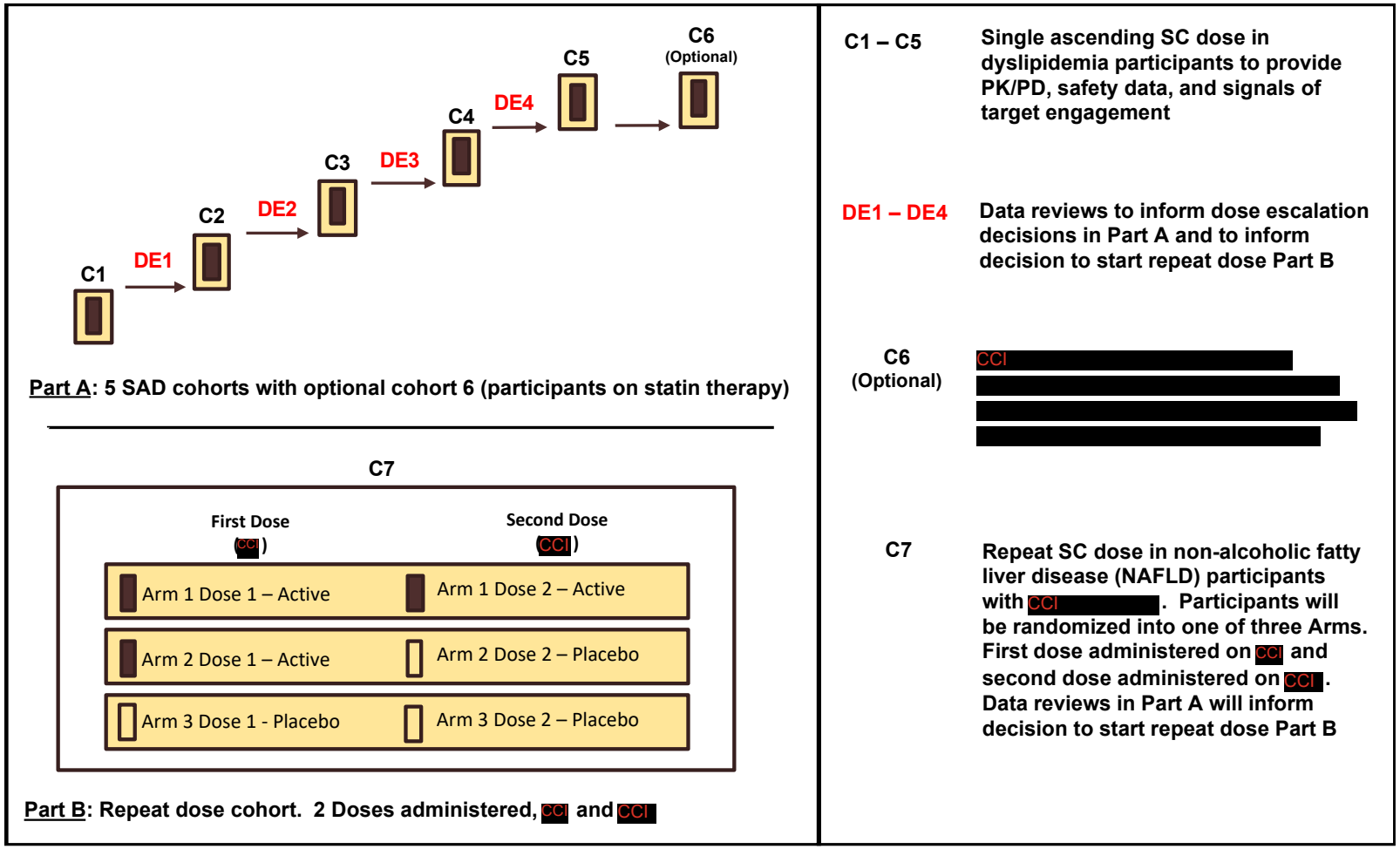
Dose Modification

Increases or decreases in dose levels or additional dose levels may be warranted as determined by the DEC, based on a review of all safety data and available PK and PD data from prior dose levels.

No dosing decision can occur without prior discussion and agreement of the DEC. If the dose escalation stopping criteria (Section 4.5.1) are met, the dose level will not be repeated or exceeded. If the temporary stopping criteria are met (Section 4.5.2), dosing in the study will be paused. The SRC will be convened in either scenario to review available data and provide recommendations regarding the continued conduct of the study.

Safety Review Committee: A Safety Review Committee (SRC) will be employed to review the benefit-risk profile of the LY3885125 throughout the conduct of the study. The SRC will meet CCI and may be convened in response to any emerging safety signal (see Safety Review Committee Charter for additional details).

1.2. Schema



Abbreviations: ALT = alanine aminotransferase; SAD = single ascending dose; SC = subcutaneous.

1.3. Schedule of Activities (SoA)

1.3.1. Part A Study Schedule (Single Dose Cohorts)

Procedure	Screening	Inpatient Visit					Outpatient Follow-up Visits[a]						ET
							Post-Dose					Monitoring Extension[b]	
Week													
CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	
Informed Consent	X												
Demographics	X												
Medical history	X	X											
Review/confirm I/E criteria	X	X[d]											
Randomization		X											
Admit to CRU		X											
Discharge from CRU						X[e]							
Administer study intervention[f]			X										
Physical examination (PE)[g]	X	X											X
Symptom directed PE				X	X	X	X	X	X	X	CCI	X	
Height	X												
Weight[h]	X	X								X	CCI	X	X
COVID-19 PCR test[i]	X	X											
Pregnancy test[j]	X	X									CCI	X	X
FSH[k]	X												
Hepatic serologies[l]	X												
Urine drug screen and ethanol	X	X											
Urinalysis	X	X					X		X				
Safety laboratory tests	X		P	X	X	X	X	X	X	X	CCI		X
Body Temperature	X		P						X				X
Vital signs - PR/BP/RR	X		CCI	CCI	CCI	CCI	X	X	X	X	CCI	X	X
12-lead ECG[m]	X		CCI	CCI	CCI	CCI	X			X		X	X
Plasma PK samples[n]			CCI	CCI	CCI	CCI	CCI	CCI		CCI	CCI	CCI	CCI
Urine PK			CCI										
Lipid panel, (fasting)[o]	CCI		CCI			CCI	CCI		CCI	CCI	CCI	CCI	CCI
CCI			CCI			CCI	CCI		CCI	CCI	CCI		CCI
ApoB (fasting)			CCI			CCI	CCI		CCI	CCI	CCI		CCI
Stored samples (fasting)			P				X	X	X	X	D43, 57, 85, 169		
ISR assessments			Following spontaneous report from participant, complete ISR CRF and Pain VAS assessment										
Immunogenicity			CCI					CCI		CCI	CCI		CCI
AE/concomitant medications	X	X	X	X	X	X	X	X	X	X	CCI	X	X

PCSK9	X		P			X	X	X	X	X	CCI [redacted]	X	X
HbA1c	X		P						X		CCI		X

Abbreviations: AE = adverse event; ApoB = apolipoprotein B; BP = blood pressure; COVID-19 = Coronavirus disease 2019; CRF = case report form; CRU = clinical research unit; D = day; ECG = electrocardiogram; ET = early termination; h = hour(s), FSH = follicle-stimulating hormone; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; I/E = inclusion/exclusion; ISR = injection-site reaction; LDL-C = low-density lipoprotein cholesterol; CCI [redacted] min = minutes; P = predose; PCSK9 = proprotein convertase subtilisin/kexin type 9; PCR = polymerase chain reaction; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; PR = pulse rate; Q2W = once every 2 weeks; PUC = preparative ultracentrifugation; Q4W = once every 4 weeks; RR = respiration rate; SC = subcutaneous; TEAE = treatment-emergent AE; TG = triglyceride; VAS = visual analog score; VLDL-C = very low-density lipoprotein cholesterol.

a All follow-up visits should take place in the morning after an overnight fast of at a minimum [redacted] hours. Water is permitted *ad libitum* during the fasting period.

b After Day CCI [redacted], once any treatment related AEs are resolved and PCSK9 levels return to at least CCI [redacted]% of baseline, the Monitoring Extension visits may be discontinued. The final visit of a participant who completes the study will be the first scheduled Monitoring Extension visit after they report no ongoing AEs, and after PCSK9 levels have returned to at least 80% of baseline in a blood sample collected at one of the preceding visits. At the participant's final visit, they will receive the assessments performed at ET, except for the collection of a blood sample for PCSK9 assessment.

c Outpatient follow-up visits on Days CCI [redacted] will be conducted through a remote telehealth visit assessing AE/concomitant medications.

d On Day -1 prior to randomization review AEs, concomitant medications, and compliance to Inclusion/Exclusion criteria.

e Discharge from CRU after all assessments have been completed.

f All doses of study intervention will be administered SC in the morning after an overnight fast of approximately 8 hours duration.

g Complete physical examination performed at Screening, ET and last visit., and symptom-directed examinations at all other visits.

h Body weight is measured at any time before breakfast.

i A COVID-19 PCR test will be performed at Screening and on Day -1 prior to dosing. If test results are positive for the virus the participant will be excluded from the study.

j A serum pregnancy will be performed at screening. Urine pregnancy tests may be performed at all other visits. If a urine test result is positive, the result will be confirmed with a serum test.

k A serum FSH test will be performed in women at screening to confirm postmenopausal status.

l If the HCV antibody test is positive, it must be followed by an HCV RNA test. Participants who are positive for HCV antibody and negative for HCV RNA may be enrolled. See Exclusion Criterion #8, Section 5.2.

m Single 12-lead ECG at screening, safety follow-up and ET visit. Three triplicate 12-lead ECGs at pre-dose 2 minutes apart to establish baseline. Triplicate 12-lead ECGs at all other scheduled times. The actual day and time must be documented in the CRF.

n PK samples identified with an X may be obtained at any time within the scheduled days; the exact date and time of blood sample collection must be recorded in the CRF.

o Lipid panel: TG, total cholesterol, LDL-C (PUC), VLDL-C (calculated), HDL-C, non-HDL-C (calculated).

1.3.2. Part B Study Schedule (Repeat Dose Cohort)

Procedure	Screening	Inpatient Visit 1			Outpatient Follow-up Visits[a]					Inpatient Visit 2			Outpatient Follow-up Visits[a]							ET
													Post-Dose						Monitoring Extention[b]	
Week																				
Informed Consent	X																			
Demographics	X																			
Medical history	X	X																		
Review/confirm I/E criteria	X	X[d]																		
Randomization		X																		
Admit to CRU		X								X										
Discharge from CRU[e]				X								X								
Administer study intervention[f]			X								X									
Physical examination[g]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X
Height	X																			
Weight[h]	X	X							X							X				X
COVID-19 PCR test[i]	X	X								X										
Pregnancy test[j]	X	X								X									X	X
FSH[k]	X																			
Hepatic serologies[l]	X																			
Urine drug screen and ethanol	X	X																		
Urinalysis	X	X			X	X							X	X						
Safety laboratory tests	X		P	X	X	X	X	X	X		P	X	X	X	X	X	X		X	X
Body Temperature[m]	X		P								P									X
Vital signs -- PR/BP/RR	X				X	X	X	X	X	X			X	X	X	X	X		X	X
12-lead ECG[n, v]	X				X								X						X	X
Transient Elastography[o]	X																			
MRI-PDFF and MR	X									X							X			
Plasma PK samples[p]																				
Lipid panel (fasting)[q]																				
ApoB (fasting)																				
Stored samples (fasting)																				

Procedure	Screening	Inpatient Visit 1			Outpatient Follow-up Visits[a]					Inpatient Visit 2			Outpatient Follow-up Visits[a]							ET
													Post-Dose						Monitoring Extention[b]	
Week			CCI		CCI	CCI	CCI	CCI	CCI	CCI			CCI	CCI	CCI	CCI	CCI	CCI	CCI	
Day	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	CCI	
ISR assessments			Following spontaneous report from participant, complete ISR CRF and Pain VAS assessment																	
Immunogenicity			CCI			CCI					CCI			CCI		CCI		CCI		CCI
AE/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X		P								P						X	D260		X
PCSK9	CCI		CCI			CCI	CCI		CCI		CCI			CCI	CCI		CCI	CCI	CCI	
CCI [r]	X		P			X		X			P			X			X	D176, 260	X	

Abbreviations: AE = adverse event; Apo = apolipoprotein; BP = blood pressure; CAP = controlled attenuation parameter; CCI ; COVID-19 = Coronavirus disease 2019; CRF = case report form; CRU = clinical research unit; CCI ; D = day; ECG = electrocardiogram; CCI ; ET = early termination; CCI ; h = hour(s), FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; I/E = inclusion/exclusion; ISR = injection-site reaction; LDL-C = low-density lipoprotein cholesterol; CCI ; min = minutes; MRI-PDFF = magnetic resonance imaging proton density fat fraction; CCI ; CCI ; P = predose; PCR = polymerase chain reaction; PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamics; PK = pharmacokinetics; PR = pulse rate; CCI ; PR = pulse rate; RR = respiration rate; SC = subcutaneous; TEAE = treatment-emergent AE; TG = triglyceride; VAS = visual analog score; VLDL-C = very low-density lipoprotein cholesterol.

a All follow-up visits should take place in the morning after an overnight fast of at minimum 8 hours. Water is permitted ad libitum during the fasting period.

b After Day 260, once any treatment related AEs are resolved and PCSK9 levels return to at least CCI % of baseline, the Monitoring Extension visits may be discontinued. The final visit of a participant who completes the study will be the first scheduled Monitoring Extension visit after they report no ongoing AEs, and after PCSK9 levels have returned to at least CCI % of baseline in a blood sample collected at one of the preceding visits. At the participant's final visit, they will receive the assessments performed at ET, except for the collection of a blood sample for PCSK9 assessment.

c Outpatient follow-up visits on Days CCI and CCI will be conducted through a remote telehealth visit assessing AE/concomitant medications.

d On Day -1 prior to randomization review AEs, concomitant medications, and compliance to protocol restrictions.

e Discharge from CRU after all assessments have been completed.

f All doses of study intervention will be administered SC in the morning after an overnight fast of at minimum 8 hours. Water is permitted ad libitum during the fasting period.

g Complete physical examination at screening; symptom-directed examinations at all other visits.

h Body weight is measured at any time before breakfast.

i A COVID-19 PCR test will be performed at Screening. and on Days -1 and 84 upon admission to CRU. If test results are positive for the virus the participant will be excluded from the study.

j A serum pregnancy will be performed at screening. Urine pregnancy tests will be performed at all other visits. If a urine test result is positive, the result will be confirmed with a serum test.

k A serum FSH test should be performed in women at screening to confirm postmenopausal status.

l If the HCV antibody test is positive, it must be followed by an HCV RNA test. Participants who are positive for HCV antibody and negative for HCV RNA may be enrolled. See Exclusion Criterion #8, Section 5.2.
m Temperature also measured at any additional time points as clinically indicated.
n Single 12-lead ECG at screening, safety follow-up and/ ET visit. Three triplicate 12-lead ECGs at pre-dose 2 minutes apart to establish baseline. Triplicate 12-lead ECGs at all other scheduled times. The actual day and time must be documented in the CRF.
o Participants must meet the CAP inclusion criteria prior to MRI assessment (Section 5.1). If CAP has been completed within 4 weeks before screening, this test does not need to be repeated.
p Recording times identified with an X may be obtained at any time within the scheduled days; the exact date and time of recording must be recorded in the CRF.
q Lipid panel: TG, total cholesterol, LDL-C, VLDL-C (calculated), HDL-C, non-HDL-C (calculated).
r CCI

2. Introduction

LY3885125 CCI is a novel Dicer-substrate small interfering ribonucleic acid (DsiRNA) conjugated to N-acetylgalactosamine CCI designed to specifically knock down sterol regulatory element binding protein (SREBP) cleavage activating protein (SCAP) messenger ribonucleic acid (mRNA) in the liver. SCAP regulates the activation of SREBPs, which are transcription factors that govern *de novo* lipogenesis, cholesterol biosynthesis, and metabolism pathways. LY3885125 is being developed to reduce hepatic SCAP mRNA levels and thereby reduce SCAP protein expression. CCI

2.1. Study Rationale

CCI Given these effects, there is potential for LY3885125 as a treatment for dyslipidemia and nonalcoholic fatty liver disease (NAFLD).

Study J4N-MC-YFAA is a first-in-human (FIH) placebo-controlled study, which will evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single ascending subcutaneous (SC) doses of LY3885125 in participants with dyslipidemia (Part A), and of repeated SC doses of LY3885125 in participants with NAFLD and CCI (Part B). In Part A, response to LY3885125 will be assessed based on changes in circulating proprotein convertase substilisin/kexin type 9 (PCSK9) concentration. In Part B the effect of LY3885125 compared with placebo on liver fat content (LFC) will be evaluated through changes in magnetic resonance imaging proton density fat fraction (MRI PDFF).

2.2. Background

NAFLD is characterized by hepatic steatosis when no other causes for hepatic fat accumulation can be identified. NAFLD ranges from simple steatosis (nonalcoholic fatty liver), NASH with or without fibrosis through to cirrhosis (Rinella et al. 2023). The prevalence of NAFLD is increasingly becoming a leading cause of chronic liver disease worldwide (Powell et al. 2021). In the USA 25% to 30% of the adult population suffers from NAFLD (Rinella et al. 2023). Obesity, Type 2 diabetes mellitus (T2DM), and dyslipidemia are considered important risk factors for NAFLD (Younossi et al. 2016; Chalasani et al. 2018). NAFLD is seen in 47.3 to 63.7% of people with T2DM and up to 80% of people with obesity (Younossi et al. 2019; Polyzos et al. 2019). NAFLD has become the most rapidly increasing cause of liver-related mortality worldwide and is an important cause of end-stage liver disease, primary liver cancer, and liver transplantation (Powell et al. 2021). NASH is the progressive stage of NAFLD and is characterized histologically by steatosis, lobular inflammation and hepatocyte injury (ballooning) with or without fibrosis (Chalasani et al. 2018). Patients with NASH have increased overall and liver -specific mortality (Singh et al. 2015; Younossi et al. 2016), and they have increased risks

of cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (Chalasani et al. 2018). The burden of NASH is expected to increase in line with the global epidemic of obesity, T2DM, and metabolic syndrome (Estes et al. 2018). There are currently no approved pharmacological therapies available for treatment of NAFLD and NASH. The beneficial effects of weight loss on NAFLD and NASH are well-documented (Vilar-Gomez et al. 2015; Chalasani et al. 2018; Semmler et al. 2021); therefore, currently diet and exercise are considered the standard treatment for NAFLD and NASH (Rinella et al. 2023).

SCAP is a sterol-sensing protein that plays a critical role in cholesterol homeostasis in mammalian cells. It is a transmembrane protein that normally resides in the endoplasmic reticulum (ER). When cells are deprived of cholesterol, SCAP escorts SREBPs from the ER to the Golgi. Two Golgi proteases (site-1 protease [S1P], and site-2 protease [S2P]) then sequentially cleave SREBPs, releasing their active NH2-terminal transcription factor domains, which travel to the nucleus and activate genes involved in lipid metabolism (Brown et al. 2018). There are several SREBP isoforms: SREBP2 regulates cholesterol synthesis and uptake, SREBP1 isoform c (SREBP1c) regulates fatty acid and TG biosynthesis, while SREBP1 isoform a (SREBP1a) regulates both pathways.

SCAP is expressed in the liver and extrahepatic tissues. Liver-specific knockout of SCAP in mouse models led to significant inhibition of de novo synthesis of free fatty acid and cholesterol. In the leptin-deficient (ob/ob) mouse model and the diet-induced-obesity (DIO) mouse model, SCAP deficiency led to significant suppression of liver TG levels and liver total cholesterol levels. In hamsters fed with a high-sucrose diet, reduction in SCAP mRNA expression by siRNA reduced liver TG and total cholesterol levels and normalized plasma TG levels (Moon et al. 2012). In rhesus monkeys, knockdown of SCAP mRNA by siRNA resulted in dose dependent reduction in serum TG and LDL-C, with minimal impact on high-density lipoprotein cholesterol (HDL-C) (Jensen et al. 2016). Based on these observations from preclinical models, inhibiting SCAP via siRNA may be of therapeutic benefit for the treatment of dyslipidemia and fatty liver disease, including NASH.

CCI [redacted]

2.2.1. Summary of Nonclinical Data

The cynomolgus monkey and Sprague Dawley rat were selected as the species for safety assessment. Due to the homology of the SCAP mRNA target sequence with humans, cynomolgus monkeys (and not rat) are pharmacologically responsive to LY3885125 and allow assessment of adverse effects related to the intended pharmacologic activity. This species selection strategy allows for evaluation of off-target and oligonucleotide-related class effects in both species and potential exaggerated pharmacology in monkeys. This is an accepted approach for the safety evaluation of oligonucleotides (Kornbrust et al. 2013; FDA/CDER Onpattro NDA 210922).

A single-dose monkey study CCI [redacted] was conducted to assess cytokine and complement activation after a single administration of LY3885125. Administration of CCI [redacted] or CCI [redacted] mg/kg LY3885125

to male cynomolgus monkeys (*Macaca fascicularis*) once via SC injection resulted in no LY3885125-related effects on mean body weight, clinical observations, coagulation or clinical chemistry parameters, or effects on cytokine (CCI) and complement (CCI) parameters.

A standalone cardiovascular study was conducted to evaluate the potential cardiovascular effects of LY3885125 in instrumented male cynomolgus monkeys (CCI). CCI male cynomolgus monkeys were administered by SC injection single doses of control CCI or CCI mg LY3885125/kg via SC injection (CCI males per group).

No LY3885125-related qualitative electrocardiogram (ECG) abnormalities or quantitative changes in PR interval, QRS duration, QT interval, or individual heart rate-adjusted QT (QTc) interval were noted up to CCI postdose following administration of CCI .

Monkeys administered CCI LY3885125 were noted to have a transient increase in heart rate (of up to CCI bpm) from CCI hours postdose, which resolved by CCI postdose; a transient increase in systolic (CCI), diastolic (CCI), and mean arterial blood pressure CCI from CCI postdose, which resolved by CCI ; and an increase in body temperature (CCI) from CCI postdose, which resolved by CCI postdose. No heart rate, blood pressure, or body temperature changes were noted in monkeys administered CCI

No LY3885125-related changes in arterial pulse pressure or dP/dtmax (maximal rate of rise in pressure), or changes in locomotor activity were noted up to CCI following administration of CCI

The toxicity of LY3885125 was evaluated in GLP CCI -month repeat-dose studies in cynomolgus monkeys CCI and Sprague Dawley rats (CCI). Administration of LY3885125 was not associated with significant toxicological findings in the rat and monkey studies. CCI

In conclusion, the available nonclinical pharmacology, PK, and toxicology data support the use of LY3885125 in the proposed clinical trial.

The margin of safety for SC injection of LY3885125 in humans based on administered dose and predicted exposure from nonclinical studies is presented in Table 2.1.

Additional details of the nonclinical studies are provided in the Investigator's Brochure (IB).

Table 2.1 Margin of Safety for Subcutaneous Injection of LY3885125 Based on Administered Dose and Predicted Exposure

	Dose (mg/kg)	Dose (mg/m^2)	Dose Multiple[a]	AUC (ng·h/mL)	Exposure Multiple[e]
Human Starting Dose (5 mg)[b]	CCI	CCI	–	CCI	
Rat NOAEL[c]	CCI	CCI	CCI	CCI	CCI
Monkey NOAEL[d]	CCI	CCI	CCI	CCI	CCI
Human Maximum Dose (CCI mg)[b]	CCI	CCI	–	CCI	
Rat NOAEL[c]	CCI	CCI	CCI	CCI	CCI
Monkey NOAEL[d]	CCI	CCI	CCI	CCI	CCI

Abbreviations: AUC = area under the plasma concentration time curve; NOAEL = no-observed-adverse-effect level; SC = subcutaneous.

[a] Dose multiple is the dose in animals/dose in humans based on mg/m^2 using a human body weight of 70 kg. Exposure multiple is the calculated AUC in animals / predicted AUC in humans (see Section 4.2.3 of the Investigator's Brochure).

[b] Assume human body weight = 70 kg to predict human exposure. The maximum dose for the study will be limited to CCI mg until additional data from Part A cohorts are available to inform the safety, tolerability, and impact on PCSK9 as a biomarker of CCI knockdown. A protocol amendment will be submitted with supporting data if doses above CCI mg are to be evaluated.

[c] CCI-month (CCI-dose) rat toxicology study, Day CCI $AUC_{0\text{-}48}$ exposure (CCI).

[d] CCI-month (CCI-dose) monkey toxicology study, Day CCI $AUC_{0\text{-}48}$ exposure (CCI).

[e] AUC multiple: based on predicted human $AUC_{0\text{-}\infty}$ using allometric scaling from rat. Allometric slopes are fixed to 0.75 for clearance (CL) and 1 for volume of distribution (V). Bioavailability (F) is approximately CCI% based on rat data at CCI mg/kg SC.

2.3. Benefit/Risk Assessment

The nonclinical safety information for LY3885125 adequately supports the transition from preclinical status to a clinical study.

Based on the nonclinical data, LY3885125 is not considered to be a high-risk compound. The nonclinical cardiovascular safety data CCI [redacted] SCAP is expressed in the liver and extrahepatic tissues. CCI [redacted]

CCI [redacted]

In summary, while the clinical safety profile of LY3885125 is not yet established, the available information suggests a low likelihood of significant toxicity. LY3885125 has not been administered to humans previously. This FIH study with LY3885125 will mitigate risks by a design that is in accordance with principles outlined in the Guideline on Strategies to Identify and Mitigate Risks for FIH and Early Clinical Trials with Investigational Medicinal Products. The important potential safety risks are summarized in Table 2.2. Any potential risks are considered monitorable and manageable in dyslipidemia and NAFLD participants. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of LY3885125 may be found in the IB.

Table 2.2 Important Potential Safety Risks with LY3885125

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation/Monitoring Strategy
Hypersensitivity or allergic reactions	Not specific to LY3885125. Oligonucleotide therapies, both marketed and those in development, have been associated with hypersensitivity events.	Monitor for hypersensitivity reactions in participants. Assess spontaneously reported adverse events for their likelihood to represent hypersensitivity reactions. Once identified, investigative site personnel will collect additional information to characterize the type of reaction using standardized forms. Qualified staff will have received training and have access to supportive measures to manage the reactions.
Injection-site reactions	Not specific to LY3885125. As this molecule is an injectable therapeutic, there is the potential risk of localized injection-site reactions.	Qualified staff will have received training and have access to supportive measures to manage the reactions.
CCI [redacted]	Specific to LY3885125. CCI [redacted] Further information is provided in the IB.	Vital signs and ECG will be recorded across multiple scheduled time points following single and multiple doses.
CCI [redacted]	CCI [redacted] CCI [redacted]	CCI [redacted]

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Part A: • To determine the safety and tolerability of LY3885125 after a single SC dose in participants with dyslipidemia.	• AEs. • Serious adverse events (SAEs).
Part B: • To determine the safety and tolerability of LY3885125 after 2 SC doses on Days CCI in participants with NAFLD and elevated ALT.	• AEs. • SAEs.
Secondary	
Part A: • To assess the PK and PD of LY3885125 after a single SC dose.	• LY3885125 area under the concentration-time curve (AUC), maximum observed concentration (C_{max}), time of C_{max} (T_{max}). • Changes in PCSK9 and apolipoprotein B (ApoB) from baseline relative to placebo.
Part B: • To assess the PK and PD of LY3885125 following 2 SC doses on Days CCI.	• LY3885125 AUC, C_{max}, T_{max}. • Relative change of liver fat content from baseline to Weeks CCI by magnetic resonance imaging proton density fat fraction (MRI-PDFF) compared with placebo. • Changes in PCSK9 and ApoB from baseline relative to placebo.

Objectives	Endpoints
Exploratory	
CCI • CCI	• CCI • CCI
CCI • CCI • CCI	• CCI • CCI

4. Study Design

4.1. Overall Design

Study J4N-MC-YFAA is a Phase 1, multicenter, randomized, placebo-controlled, double-blind, 2-part study in participants with dyslipidemia, and participants with NAFLD and elevated ALT. The study design includes:

- **Part A (Cohorts 1 to 6)**: placebo-controlled, Investigator- and participant-blind, single SC dose of LY3885125 in participants with dyslipidemia:
  - To evaluate the safety, tolerability, PK, and PD of a single ascending dose (SAD) of LY3885125 in up to 6 Cohorts.
  - Data from Part A will inform the dose for Part B.
- **Part B (Cohort 7)**: placebo-controlled, Investigator- and participant-blind, repeat SC doses of LY3885125 in participants with NAFLD and CCI :
  - To evaluate the safety, tolerability, PK, PD, and change of LFC from baseline to Weeks CCI by MRI-PDFF of a repeated dose of LY3885125 at CCI .
  - The dose and dosing frequency in Part B will be based on data from Part A. The protocol will be amended prior to initiation of Part B.

The study will begin with Part A, with Dose Escalation Meetings of the DEC between each cohort, and will proceed to Part B after reviewing emerging data from Part A and potentially use modelling to select an appropriate dose and frequency of dosing.

During Part A of the study, there will be ongoing reviews of safety, tolerability, and PK data as described in Section 6.3.1. Based on these reviews, the following may be adjusted:

- Planned dose levels;
- Sample collection schedule;
- Safety measurement schedules;
- Length of inpatient stay.

In addition to oversight by the DEC, a SRC will meet CCI throughout the study to evaluate the safety and tolerability of LY3885125. The SRC may make recommendations regarding conduct of the study as described in Section 4.5 and in the SRC Charter.

The study schema is presented in Section 1.2.

Participants should complete the study assessments and procedures as specified in the Schedule of Activities (SoA) in Section 1.3.

4.1.1. Part A - Single Ascending Dose (SAD) Cohorts 1-6 (Cohort 6 optional)

Part A will consist of up to 6 single-dose levels, Cohorts 1 to 6, with the following numbers of participants randomized to LY3885125 or placebo as follows and also summarized in Table 4.1:

- Cohorts 1 and 2: a total of CCI participants (CCI per cohort) randomized 6:2 to LY3885125:placebo.
- Cohorts 3 through 5: total of CCI participants (CCI per cohort) randomized 9:2 to LY3885125:placebo.
- Cohort 6 (optional): total of CCI participants randomized 10:9 to LY3885125:placebo. This cohort will consist of participants with dyslipidemia on a stable moderate or high -intensity dose of statin; CCI

Table 4.1 Part A Design

Part A Cohort	n	Randomization (LY3885125:placebo)
1-2	CCI	6:2
3-5	CCI	9:2
6 (optional)	CCI	10:9

The single doses of LY3885125 planned to be administered in Part A to Cohorts 1 to 5 are as follows: CCI mg, CCI mg, CCI mg, CCI mg, and CCI mg . The doses specified are the planned doses; the actual doses will be selected during the Dose Escalation Meetings based on the available safety and PK data, with projected levels of systemic exposure within limits determined by margin of safety to the NOAEL as described in Section 4.3 (Justification for Dose). Data from the Part A cohorts will provide safety, tolerability, available PK, and PD data to inform the Part B dose and dosing frequency.

For the optional Cohort 6 of Part A (CCI) the planned dose of LY3885125 will not exceed the dose administered in Cohort 5.

Sentinel dosing will be used in Part A to reduce the risk of exposing all participants in a cohort to study intervention and the potential for unexpected AEs occurring simultaneously. Two participants from each SAD cohort will be included in the sentinel dosing regimen to allow for one participant treated with study intervention and one participant treated with placebo to be dosed prior to dosing the remaining participants in the cohort. There will be CCI in each Part A cohort.

4.1.1.1. Screening (Part A)

Participant eligibility for Part A will be determined at a screening visit within 28 days prior to dosing with study intervention (LY3885125 or placebo) on Day 1.

4.1.1.2. Treatment Period (Part A)

In each period, participants will be admitted to the clinical research unit (CRU) on the day prior to dosing (Day -1) for 4 overnight stays. Participants will be monitored as inpatients in the CRU up to Day [redacted].

Participants will be given a SC dose of LY3885125 or placebo on Day 1.

The single doses planned to be administered in Part A are as follows: [redacted]mg, [redacted] mg, [redacted] mg, [redacted] mg, and [redacted] mg.

The safety data to be reviewed at each dose level will include, but are not limited to, AEs, clinical laboratory safety tests, vital signs, ECGs, physical examination (symptom-directed). The dose level for each cohort may be adjusted based on emerging safety, tolerability, and available PK and PD data from preceding cohorts.

After review of these data, the DEC will decide if the planned dose needs to be modified The magnitude of dose escalations may be reduced following data review.

The conduct of DEC meetings is described in Section 6.3.1, the dose escalation stopping criteria are described in Section 4.5.1, and the temporary stopping criteria are described in Section 4.5.2

Details of assessments and their timing in Part A are provided in the SoA (Section 1.3.1) and in Section 8 (study assessments and procedures).

4.1.1.3. Follow-up (Part A)

Participants will attend follow-up visits as outpatients as outlined in the SoA (Section 1.3.1). Each participant enrolled in a Part A cohort will be followed [redacted]

4.1.2. Part B – Repeat Dose – Cohort 7

Part B may be initiated, at the earliest, after review of safety, tolerability, PK, and PD data from Part A. The dose administered in Part B will not exceed what has been studied in Part A. The protocol will be amended prior to initiation of Part B to define the dose and dosing frequency.

Changes in biomarkers of drug pharmacology other than [redacted] in Part A may guide the Part B dose selection

For Part B (Cohort 7) a total of approximately 44 participants (NAFLD participants with [redacted]) will be randomized into 3 treatment arms to receive 2 SC doses of study intervention (LY3885125 or placebo), one on [redacted] and one on [redacted]. [redacted]. The assignment of study intervention (LY3885125 or placebo) in each treatment arm and number of participants is shown in Table 4.2.

The proposed dosing interval of [redacted] days between the two doses administered on [redacted] and [redacted] of Part B will be confirmed or modified, if necessary, when the protocol amendment is submitted prior to initiation of Part B. [redacted]

Table 4.2 Part B Design

Part B (Cohort 7) Treatment Arm	n	First Dose (CCI)	Second Dose (CCI)
1	11	LY3885125	LY3885125
2	11	LY3885125	Placebo
3	22	Placebo	Placebo

[a] The dose administered on CCI (first dose) and CCI (second dose) will be the same dose level

4.1.2.1. Screening (Part B)

Participant eligibility for Part B will be determined at a screening visit within CCI days prior to dosing with study intervention (LY3885125 or placebo) on Day 1. The participants will undergo assessment of CCI during the screening period to assess their eligibility for the study. CCI assessment may be deferred if CCI assessment has been done within CCI weeks of the screening visit. Participants must meet the CCI inclusion criteria prior to MRI assessment.

4.1.2.2. Treatment Period (Part B)

For Part B treatment period, participants will be admitted to the CRU on the days prior to dosing (CCI and CCI) and will stay in the CRU for CCI nights. Participants will be monitored as inpatients in the CRU up to 2 days after dosing (to CCI and CCI, respectively).

Participants will be given an SC dose of LY3885125 or placebo on CCI and CCI. The dose will be based on review of data from Part A.

Details of assessments and their timing in Part B are provided in the SoA (Section 1.3.2).

4.1.2.3. Follow-up (Part B)

Participant will attend follow-up visits as outpatients as outlined in the SoA (Section 1.3.2).

4.2. Scientific Rationale for Study Design

Study J4N-MC-YFAA is a FIH study of LY3885125 with 2 parts, a single ascending dose in participants with dyslipidemia, and repeated dose in participants with NAFLD and CCI . Both study parts are Investigator- and participant-blinded and placebo-controlled to avoid bias in the collection and evaluation of data. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment related or reflective of the study conditions. A sentinel dosing strategy for all dose levels in Part A will be used, as the study drug has not previously been administered to participants. There will be a minimum interval of CCI between the administration of the Investigational Product to the sentinel pair and the remaining participants in each Part A cohort.A DEC will meet between each cohort to review safety and available PK and PD data to determine if adjustments to the planned dose are needed. The DEC will also review the data against the dose escalation and temporary stopping criteria. If any of these criteria are met, the SRC will be convened to review available data and make recommendations regarding continued study conduct.

CCI . In Part A, the single-dose escalation design is appropriate to assess the LY3885125 safety profile in a way that minimizes participant risk. The number of participants is adequate to explore safety, tolerability, PK, and PD across a broad range of doses to determine appropriate dosage regimens to evaluate in future studies. The potential of LY3885125 to reduce ApoB concentration will be assessed in all cohorts. CCI for repeated SC doses of LY3885125. Part B will use a 3-arm design and assess the safety, tolerability, PK and PD effects of LY3885125. Potential effects of LY3885125 use during pregnancy and lactation are not known. To minimize potential risk, this first-in-human study is excluding women of childbearing potential and including contraception requirements for men (Section 10.4.2.2). Additional details can be found in the IB.

ApoB

In Part A, the potential for LY3885125 to reduce ApoB concentration will be assessed in all cohorts. Apo B is a key structural component of lipoproteins, each lipoprotein particle carrying one ApoB molecule. Consequently, the ApoB level can also provide a measure of the number of circulating lipoprotein particles and is also a potential biomarker for cardiovascular disease (Harper and Jacobson, 2010; Lu et al. 2022).

PCSK9

In Part A, the effect of LY3885125 will be assessed based on changes in circulating PCSK9 concentration. PCSK9 is a circulating protein that is mainly produced by the liver. It plays an important role in cholesterol metabolism. PCSK9 inhibition leads to improvement in dyslipidemia. PCSK9 mRNA expression is directly regulated by the SCAP-SREBP pathway. CCI These data support circulating PCSK9 as a biomarker for SCAP siRNA in human trials.

MRI

In Part B, the effect of LY3885125 compared with placebo on liver fat content will be evaluated through changes in MRI Proton Density Fat Fraction (PDFF). MRI-PDFF is a quantitative [redacted] which provides accurate, quantitative assessment of liver fat. MRI-PDFF has been validated as an accurate imaging biomarker when compared with liver histology (Loomba et al. 2020). MRI-PDFF is reproducible and is a sensitive method to assess hepatic steatosis. Studies have shown that MRI-PDFF is sensitive to small longitudinal changes (<5%) of liver fat (Middleton et al. 2017) and ≥30% relative decrease in MRI-PDFF (Tamaki et al. 2022) is an independent predictor of improvement in NAFLD activity score and liver fibrosis. Previous studies have also shown correlation between improvement in liver fat measured by MRI-PDFF and non-invasive biomarkers like enhanced liver fibrosis score, [redacted], and cytokeratin-18 (Stine et al. 2021). MRI-PDFF has the advantage of being non-invasive and can provide longitudinal quantitative change of liver fat in clinical trials.

In addition, [redacted] will be determined as an exploratory endpoint in all Part B participants. [redacted] has been shown to correlate with fibroinflammatory activity on liver biopsy and to have high diagnostic accuracy to identify participants with NAFLD, NASH, and NASH with higher stages of fibrosis. Furthermore, studies suggest [redacted] at greatest risk of disease progression (Andersson et al. 2021).

4.3. Justification for Dose

Doses of LY3885125 selected for this study are based on Good Laboratory Practice (GLP) toxicology results, nonclinical pharmacology studies in mouse and monkey, and predicted human PK. The planned single SC dose levels are [redacted] mg, [redacted] mg, [redacted] mg, [redacted] mg, and [redacted] mg.

4.3.1. Starting Dose

The NOAELs in the [redacted]-month toxicity studies were [redacted] mg/kg in both rat and monkey. Starting dose was determined from the NOAELs in the [redacted]-week toxicity studies in rats and monkeys extrapolated to a human equivalent dose and applying a safety factor (FDA 2005). The starting dose of [redacted] mg is expected to have minimal pharmacological effect, given that humans are expected to respond more like monkey than mouse to SCAP knockdown. The [redacted] mg starting dose has a safety margin of [redacted]-fold to [redacted]-fold dose margin to the NOAEL in rats and monkeys, respectively ([redacted]

4.3.2. Predicted Efficacious Dose

Based on SCAP mRNA knockdown and PCSK9 inhibition in hydrodynamic injection (HDI) and DIO mouse models, the predicted human efficacious dose range is [redacted] mg to [redacted] mg. The monkey pharmacology study at [redacted] mg/kg demonstrated [redacted]% to [redacted]% reduction in SCAP mRNA, and the effect lasted for at least [redacted] weeks. When this dose is scaled allometrically to human, the efficacious dose is expected to be approximately [redacted] to [redacted] mg ([redacted] to [redacted] mg/kg). Therefore, considering both the mouse and monkey models, the predicted efficacious dose range is [redacted] mg to [redacted] mg.

4.3.3. Maximum Dose

A maximum dose of CCI mg (Table 4.3) allows for the assessment of a dose range to cover the predicted human efficacious dose and has approximately [redacted]-fold to CCI-fold dose margin to the NOAEL in rats and monkeys, respectively (Table 2.1). At a dose of CCI mg, approximately CCI% to CCI% reduction in SCAP mRNA is predicted, based on the range of estimates from the mouse and monkey modelsTable 4.3).

While a CCI-mg dose is specified as the maximum dose for Cohort 5, the actual dose administered may be lower, depending on the safety and available pharmacokinetic (PK) data from preceding cohorts. Data to be reviewed during dose escalation meetings by the DEC will ultimately drive dose selection for any given cohort, as described in Section 6.3.1.

The maximum dose for the study will be limited to CCI mg until additional data from Part A cohorts are available to inform the safety, tolerability, and impact on PCSK9 as a biomarker of SCAP mRNA knockdown. A protocol amendment will be submitted with supporting data if doses above CCI mg are to be evaluated.

Table 4.3 Projected Human Dose Range Based on SCAP mRNA Knockdown and PCSK9 Inhibition-Based on Mouse and Monkey Models

Human Dose (mg)	SCAP mRNA Knockdown Based on Mouse Model	Serum PCSK9 Inhibition in Based on Mouse Model	SCAP Knockdown Based on Rhesus Monkey Model
[redacted]	CCI	CCI	CCI
CCI	CCI	[redacted]	[redacted]
CCI	CCI	[redacted]	[redacted]
CCI	[redacted]	CCI	[redacted]
CCI	[redacted]	[redacted]	[redacted]

Abbreviations: PCSK9 = proprotein convertase substilisin/kexin type 9; SCAP = sterol regulatory element binding protein (SREBP) cleavage activating protein.

4.3.4. Part B Dose

The dose of LY3885125 for Cohort 7 in Part B will not exceed what has already been dosed in Part A. The primary criteria for selection of dose for the first dose level in Part B will be safety and tolerability data from Part A. Additionally, changes in biomarkers of drug pharmacology in Part A may guide the dose selection. The protocol will be amended prior to initiation of Part B to define the dose and dosing frequency.

Although the predicted plasma half-life ($t_{1/2}$) of LY3885125 is relatively short, the maximum effect is expected to be reached after [redacted] or more weeks and may take [redacted] months or longer to return to baseline levels after a single dose. The suitability of the proposed dosing interval of CCI days between the two doses to be administered in Part B will be informed by the rate of return of PCSK9 plasma concentrations in Part A study participants.

4.4. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the SoA for the last participant in Part B or last participant meets the discontinuation criteria outline in the SoA (Section 1.3.1).

4.5. Medical Oversight and Safety Reviews

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

- monitoring and assessing the safety information collected during the trial both in real time and periodically;
- reviewing safety data for trends that need action, and
- identifying potential adverse drug reactions.

The Dose Escalation Committee (DEC) will meet between each cohort in Part A to assess the safety and tolerability of the individual dose cohorts. The timing, structure, and data that will be reviewed in the meetings are described in Section 6.3.1.

The DEC will include the following individuals, none of whom will have interactions with site-facing personnel:

- PK/PD scientist
- Clinical pharmacologist experienced with siRNA therapeutics
- Liver safety expert
- Clinical development lead for the molecule
- Asset manager for the molecule

The DEC will determine if the planned dose for the next cohort is appropriate, should be adjusted, or if further analysis of the data is warranted before proceeding. The DEC will consider the criteria outlined in Sections 4.5.1, 4.5.2, and 4.5.3.

4.5.1. Dose Escalation Stopping Criteria

A dose level will not be repeated or exceeded, if

- the results of safety evaluations for that dose level give the Sponsor or Investigator cause for concern, or
- the Investigator or Sponsor considers the dose level to be poorly tolerated.

4.5.2. Temporary Stopping Criteria

If any of the following scenarios occur, dosing in all ongoing cohorts will be temporarily halted until written guidance from the Sponsor pending a full review of safety and available PK and PD data by the Safety Review Committee (SRC):

- CCI meet individual participant discontinuation criteria for liver function test elevations in a given cohort (see Section 7.1.1)
- CCI meet individual participant discontinuation criteria for QTcF prolongation in a given cohort (see Section 7.1.2); or
- CCI hypersensitivity reactions.

Individual participant or study discontinuation criteria are provided in Section 7.1.

If the DEC recommends temporary suspension of the trial due to emerging safety issues, the SRC will be convened to perform a full review of available safety data.

The SRC will be comprised of the following personnel, none of whom will have any interactions with site-facing personnel:

- SRC chairperson: Chief Medical Officer for Chorus, a division of Lilly Research Laboratories
- SRC Secretary: Head of Global Regulatory Affairs for Chorus, a division of Lilly Research Laboratories
- Sponsor Representative: expert from Lilly's Global Patient Safety department
- Other SRC members will include:
    - Team's PK/PD scientist (will not have a vote given study team affiliation)
    - Statistician unaffiliated with the study team, and
    - Medical representatives, 1 with relevant clinical pharmacology and siRNA experience, and 1 with extensive liver safety experience.

Neither the principal investigator for the study nor the Sponsor's medical monitor for the study will be members of the SRC. The SRC will review blinded data initially and may be unblinded if certain criteria are met.

The SRC will meet CCI while the study is being conducted to perform review of emerging safety data CCI

An ad hoc meeting can be convened in response to emerging safety signals (for example, based on recommendations from the DEC or Investigator). An SRC meeting must be convened if there is a recommendation to temporarily pause study drug intervention or enrollment in the study.

The SRC meetings will be focused on reviewing the overall safety and tolerability of LY3885125. The SRC will document outcomes and recommended actions regarding:

- No safety findings of concern, recommend study proceed without modification
- Identified safety concerns that should be monitored more closely, recommend modifications to the study protocol/procedures, Investigator's Brochure, and/or Informed Consent Forms
- Identified safety concerns that the SRC would like to explore further, recommend unblinding the SRC members for further analysis and communication to senior management
- Identified safety concerns that are concerning, recommend study drug intervention or enrollment to be paused while additional analyses are performed and escalation to senior management.

4.5.3. Early Study Termination Criteria Based on Safety

The Sponsor reserves the right to terminate the study at any time for any reason. The study will be discontinued if Lilly judges it is necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice.

The SRC will use the following criteria when considering if the study should be terminated early due to safety concerns:

- CCI develop the same treatment emergent adverse event (TEAE) or serious adverse event (SAE) regardless of causality 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;
- CCI develop any TEAE or SAE regardless of attribution to study drug that has life-threatening consequences or requires urgent intervention;
- Death of any subject at any time related to adverse event.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the Institutional Ethics Committees/Institutional Review Boards, the regulatory authorities, and any contract research organization used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participants and assure appropriate participant therapy and/or follow-up.

5. Study Population

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

The eligibility of participants for enrollment in 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.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening (Days -28 to -1), and prior to randomization when participants arrive at the clinic on Day -1 only.

Screening will occur up to CCI days prior to enrollment. Participants who are not enrolled within CCI days of screening may undergo additional medical assessment, clinical measurements, or both to confirm their eligibility. In such instances, the following screening tests and procedures will be repeated: medical assessment, vital signs, clinical laboratory tests, and ECG.

5.1. Inclusion Criteria

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

Participants in Part A and B:

1. Males, or females not of childbearing potential (also see Section 10.4).
    a. Males who agree to use highly effective or effective methods of contraception may participate in this trial.
        i. All men must refrain from sperm donation for duration of the study and for 3 months following the last dose of study intervention.
        ii. Men with partners of childbearing-potential must either remain abstinent (if this is their preferred and usual lifestyle), or must use condoms during intercourse for the duration of the study, and for CCI days following the last dose of study intervention.
    b Female participants must be of nonchildbearing potential. If female, the participant must be either of nonchildbearing potential, defined as either surgically sterilized or at least 1 year postmenopausal (confirmed as FSH >40 IU/L at screening).
2. 18 to 70 years of age inclusive, at the time of signing the informed consent.
3. On a stable diet for the 3 months prior to randomization and plan to continue approximately the same stable diet during the study.
4. Reliable and willing to be available for the duration of the study and willing to follow study procedures, and have given signed informed consent approved by the Sponsor and the Independent Ethics Committee (IEC) governing the site, prior to beginning any study-specific procedures.

Additional Inclusion Criteria for Part A Participants:

5. Dyslipidemic with following fasted blood levels at screening:
    a. CCI mg/dL ≤TG CCI mg/dL.
    b. LDL-C CCI mg/dL.
6. Body mass index (BMI) in range 18.5 to 45.0 kg/m^2.

Additional Inclusion Criteria for Part A Cohort 6 Participants:

7. Cohort 6 only: Must be on a CCI [redacted] before screening and plan to remain on the same medication and dose for the duration of the study.

Additional Inclusion Criteria for Part B Participants:

8. NAFLD with liver fat content CCI % as determined by MRI-PDFF.
9. Serum ALT CCI U/L and less than CCI × upper limit of normal (ULN) (as described in Exclusion Criteria, Section 5.2).
10. Controlled attenuation parameter (CAP) CCI dB/m by transient elastography done at screening visit or done within CCI days of screening visit. Participants must meet the CAP inclusion criteria prior to MRI assessment.
11. BMI CCI and CCI kg/m^2.

5.2. Exclusion Criteria

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

Participants in Part A and B:

1. Sponsor (Eli Lilly and Company) employees, contract research organization (CRO) employees, Investigator or site personnel directly affiliated with this study or their immediate families (spouse, parent, child, or sibling, whether biological or legally adopted).
2. Treatment with another investigational drug, biological agent, or device within 30 days of Screening Visit or 5 half-lives of investigational agent, whichever is longer.
3. History or presence of medical illness including, but not limited to, any cardiovascular, thromboembolism or bleeding disorder, hepatic, respiratory, hematological, endocrine, immune, psychiatric, or neurological disease, convulsions, or any clinically significant laboratory abnormality that, in the judgment of the Investigator, indicate a medical problem that would preclude study participation.
4. Supine heart rate greater than CCI bpm. A repeat measure is permitted.
5. Uncontrolled hypertension with a resting blood pressure ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic at visit 1; a repeat assessment is permitted.
6. Have had any of the following within the past CCI days prior to screening: myocardial infarction, unstable angina, coronary artery bypass graft, percutaneous coronary intervention (diagnostic angiograms are permitted), transient ischemic attack, cerebrovascular accident, hospitalization due to heart failure.
7. Have New York Heart Association functional Classification III-IV congestive heart failure.
8. Current infection with Coronavirus disease 2019 (COVID-19).
9. Current infection with hepatitis B virus (HBV), that is, positive for hepatitis B surface antigen (HBsAg) and/or polymerase chain reaction (PCR) positive for HBV deoxyribonucleic acid (DNA).

10. Hepatitis C as defined by presence of hepatitis C virus (HCV) RNA. Participants treated for hepatitis C (and diagnosed as cured) must have a RNA test at screening and be RNA negative for at least 2 years prior to screening to be eligible for the study.
11. Human immunodeficiency virus (HIV) infection.
12. Average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females), or are unwilling to stop alcohol consumption from 48 hours prior to admission to and while resident at the CRU (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).
13. CCI
14. CCI for the reference range.
15. CCI ULN for the reference range (except for cases of known Gilbert's Syndrome).
16. Platelet count CCI /mm^3.
17. Clinical, laboratory, histological or imaging evidence of cirrhosis.
18. Clinical evidence of hepatic decompensation as defined by the presence of any of the following abnormalities:
    a. Serum albumin CCI
    b. International normalized ratio (INR) CCI.
    c. Direct bilirubin CCI
    d. History of CCI
19. CCI
20. CCI
21. Taken drugs associated with hepatic steatosis (e.g., amiodarone, valproic acid, methotrexate, tamoxifen) for more than 2 weeks in the 3 months prior to screening visit. Note: If the use of such drugs is anticipated to be medically necessary within the next 6 months, the participant should also be excluded
22. Receiving chronic CCI) systemic glucocorticoid therapy (excluding topical, intra ocular, intranasal, or inhaled preparations) or have received such therapy within 3 months prior to screening visit.
23. eGFR less than or equal to CCI , calculated by Chronic Kidney Disease Epidemiology (CKD-EPI) at screening.
24. Hypersensitivity to LY3885125 or to any of the excipients.
25. Any recent or recurrent infection within 14 days before dosing.
26. Type 1 diabetes mellitus or any other type of diabetes mellitus other than T2DM.
    a. Poorly controlled T2DM with glycated hemoglobin (HbA1c) of CCI is excluded.
27. Unwillingness to discontinue over-the counter (OTC) herbal medications that in the opinion of the Investigator can interfere with the study (see Section 6.9).

28. Initiation of an OTC medication in the 7 days prior to dose administration, or a new prescription medication in the 14 days prior to dose administration (including any medications for the treatment of obesity), except for hormone replacement therapy, vitamin and mineral supplements, low-dose aspirin, and occasional use of acetaminophen or ibuprofen. Additionally:
    a. A stable dose of statin medication for at least 8 weeks prior to screening is allowed;
    b. For participants with T2DM, stable treatment for at least 3 months prior to screening visit consisting of:
        i. Either diet/physical activity alone; or
        ii. Stable (CCI change) dose of basal insulin and/or oral antihyperglycemic medications (CCI [redacted]; see Exclusion Criteria 19).
    c. For participants with hypertension, a stable dose of up to 2 antihypertensive medications for CCI months prior to screening is allowed.
    d. Hormone replacement therapy in postmenopausal women is allowed, but women must be on stable therapy for CCI months prior to screening.
    e. If any medications (other than those that are specifically allowed) are taken, an otherwise suitable participant may be included following the agreement between the Investigator and the Sponsor.
29. Treatment with any oligonucleotide (siRNA and Antisense Oligonucleotide) therapy within the past CCI months.
30. Treatment with GLP-1 RA and GIP/GLP-1 RA and approved or experimental agents that target PCSK9 within CCI months prior to screening visit.
31. Thyroid-stimulating hormone (TSH) levels outside the normal reference range for the central laboratory at screening visit. Participants with hypothyroidism who are clinically euthyroid and on stable thyroid replacement therapy for at least 2 months prior to screening visit and who are anticipated to remain on this dose throughout the trial period are acceptable exceptions to this criterion.
32. Blood donation of CCI mL within the previous CCI weeks of study screening or a blood transfusion or severe blood loss within the prior CCI months, or have a hemoglobin value CCI (males) or CCI (females).
33. Unable to abide by investigative site restrictions on smoking and nicotine containing products.
34. Positive result on urine drug test for drugs of abuse at screening and/or randomization. One re-test for a positive result may be allowed. A positive test for a medically appropriate drug in the opinion of the Investigator is not exclusionary.
35. Are unwilling to comply with the dietary restrictions required for this study.

Additional Exclusion Criteria for Part B Participants:

1. Evidence of other forms of chronic liver disease.
2. Transferrin saturation[redacted] except when it has been demonstrated that a diagnosis of hemochromatosis has been excluded by genetic testing or when a previous liver biopsy has demonstrated no evidence of iron overload.
3. Initiated treatment with, or changed dose of, medications that may cause significant weight gain or weight loss, within [redacted] months prior to the screening visit.
4. Have a self-reported change in body weight [redacted] months prior to screening visit.
5. Prior surgical/endoscopic/device-based treatment/procedure for obesity. However, the following are allowed if performed >1 year before screening visit: liposuction, abdominoplasty, cryolipolysis. Prior device-based therapy is acceptable if device removal was more than 180 days prior to the screening visit.
6. Contraindication to MRI, such as persons with cardiac pacemaker or implants made of metal (for example, cochlear implant, nerve stimulators, magnetic vascular clips, or metallic heart valve) other contraindications for MRI or have claustrophobia (note: other condition that precludes completion of an MRI examination.

5.3. Lifestyle Considerations

- Participants will be instructed to abstain from alcohol and foods containing poppy seeds 48 hours prior to screening and prior to admission on Day 1 for Part A and Day 1 and Day [redacted] for Part B.
- Lifestyle considerations which constitute exclusion criteria are provided in Section 5.2. Reproductive and contraceptive guidance is provided in Appendix 4 (Section 10.4).

5.3.1. Meals and Dietary Restrictions

Participants will fast overnight for at minimum 8 hours prior to dosing with study intervention and prior to all follow-up visits. Water is permitted *ad libitum* during the fasting period. All doses of study intervention will be administered SC in the morning after the overnight fast. All follow-up visits should also take place in the morning after the overnight fast.

Standard meals will be provided during the stay at the CRU. Otherwise, participants will maintain their own dietary habits throughout the duration of the study.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

- While inpatients at the CRU, participants will be allowed to maintain their regular caffeine consumption throughout the study period.
- No alcohol will be allowed at least 24 hours before each CRU admission and each outpatient visit, and throughout the duration of each CRU visit. Between CRU visits, weekly alcohol intake should not exceed 21 units for males and 14 units for females (a unit is defined in Exclusion Criterion 23, Section 5.2).
- During the study, participants should not intentionally change their consumption of tobacco-containing products, except while inpatient at the CRU, when participants should abide by CRU restrictions on smoking and nicotine-containing product.

5.3.3. Activity

Participants must refrain from strenuous exercise during the in-house period of the study and within 72 hours prior to scheduled blood sample collections for clinical safety labs.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol. The study intervention used in this protocol is LY3885125 and matching placebo (commercially available sterile 0.9% saline, USP).

6.1. Study Intervention(s) Administered

LY3885125 or placebo will be administered as SC injections in the morning. Participants in Part A of the study will receive a single SC dose on Day 1 of Part A. Participants in the Part B will receive 2 SC doses, one on CCI of Part B and one on CCI of Part B.

This table lists the interventions used in this clinical study.

Intervention Name	LY3885125	Placebo
Dosage Level(s)	Part A: Cohorts 1 to 5: single ascending doses from [redacted] mg to CCI mg on Day 1. Cohort 6 (optional): Single dose to participants with dyslipidemia on stable moderate or high- intensity dose of statin.	Part A: Cohorts 1 to 5: single dose on Day 1. Cohort 6 (Optional): Single dose to participants with dyslipidemia CCI [redacted]
	Part B: Cohort 7 (NAFLD participants with elevated ALT): Single dose on CCI and on CCI. Data review in Part A will inform Part B dose.	Part B: Cohort 7 (NAFLD participants with CCI): Single dose on CCI and on CCI.
Route of Administration	Subcutaneous	Subcutaneous

Packaging and labeling

Study interventions will be supplied by the Sponsor or its designee in accordance with current Good Manufacturing Practice (GMP). Study interventions will be labeled as appropriate for country requirements.

6.2. Preparation, Handling, Storage, and Accountability

- The Investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study personnel.
- The Investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the laboratory manual.

6.3. Assignment of Study Intervention

On Day -1 participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to the study intervention, according to the randomization schedule generated prior to the study by the statistics department at the Sponsor or designee. Each participant will be dispensed blinded study intervention, labeled with the participant's unique randomization number, throughout the study. The blinding procedures for this study are provided in Section 6.4.

Details of assignment of study intervention in Part A and B of the study, as well as stopping criteria are provided below.

6.3.1. Dose Escalation in Part A

Participants in Part A (Cohort 1 through 6) of the study will receive a single SC dose of LY3885125 or placebo on Day 1 of Part A, randomized as described in the following table:

Part A Cohort	n	Randomization (LY3885125:placebo)
1-2	CCI	6:2
3-5	CCI	9:2
6 (optional)	CCI	10:9

Dose Escalation Committee

The DEC will meet once data are available from at least [redacted] participants in Cohorts 1 and 2, and at least [redacted] participants in Cohorts 3 to 5. There will be 2 parts to each DEC meeting: an open session and a closed session.

In the open session, aggregate safety data from each cohort will be reviewed in blinded manner. The Investigator and medical monitor will be in attendance along with the DEC members who will have access to the treatment assignment of individual participants if required. No unblinded data will be shared during the open session.

In the closed session, DEC members with access to the treatment assignment of individual participants across all completed and ongoing cohorts will agree on proceeding to the next cohort as planned. The DEC will also consider whether the next intended dose level is appropriate or whether this should be adjusted (for example, a lower dose given) in the next cohort. Decisions will be based on criteria described in Section 4.5.1 (dose escalation stopping criteria) and 4.5.2 (temporary stopping criteria).

The DEC will review all safety data, laboratory parameters, and available PK/PD data as described in Table 6.1.

Table 6.1 Data Reviewed by Dose Escalation Committee (DEC)

		Safety and Tolerability	Pharmacokinetics
Part A (SAD)	Dose Progression	*Cohort 2* All data from [redacted] or more participants from the prior SAD cohort, up to at least CCI at the prior dose level *Cohorts 3 to 5* All data from [redacted] or more participants from the prior SAD cohort, up to at least CCI at the prior dose level	Available data
Part B	Initiation of First dose	Part B (Cohort 7) will be initiated after the review of all available data, including CCI data, up to at least CCI of Cohort 5 in Part A.	Available cumulative data, including data up to at least CCI

SAD = single ascending dose

6.3.2. Dosing in Part B

For Part B (Cohort 7) a total of approximately 44 participants will be randomized into 3 treatment arms to receive 2 SC doses of study intervention (LY3885125 or placebo), one dose on CCI and one dose approximately CCI weeks later on CCI

The assignment of study intervention (LY3885125 or placebo) in each treatment arm and number of participants is shown in Section 4.1.2. The dose for Part B will not exceed the dose tested and deemed to be safe in Part A as shown above in Table 6.1. The protocol will be amended prior to initiation of Part B to define the dose level and frequency of dosing.

6.4. Blinding

This study will be participant- and Investigator-blind. Site-facing Sponsor personnel will also be blinded throughout the study. Non-site-facing Sponsor personnel may be unblinded as necessary, and this information will be recorded.

Blinding will be maintained throughout the conduct of the study. One set of sealed envelopes containing the randomization code will be made available to the investigator at the start of the trial. A code envelope, which reveals the treatment for a specific study participant, may be opened during the study only if the participant's well-being requires knowledge of the participant's treatment assignment. In case of an emergency, the Investigator has responsibility for determining if the unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, it is the responsibility of the Investigator to promptly document the decision and rationale and notify Sponsor study personnel as soon as possible.

If an Investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from treatment. In cases where there are ethical reasons to have the participant remain in the study, the Investigator must obtain specific approval from the Sponsor's Clinical Research Physician (CRP) for the participant to continue in the study.

6.5. Study Intervention Compliance

Not applicable.

6.6. Dose Modification

For dose modification see Section 6.3.

6.7. Continued Access to Study Intervention after the End of the Study

Not applicable.

6.8. Treatment of Overdose

For this study, any dose of study intervention greater than assigned through enrollment will be considered an overdose.

In the event of an overdose, the Investigator or the treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as until the study intervention no longer has a clinical effect or can no longer be detected systemically (at least 10 days).
- Obtain a plasma sample for PK analysis as soon as possible.
- Document the quantity of excess dose as well as the duration of the overdose in the case report form (CRF).

6.9. Prior and Concomitant Therapy

In general, concomitant medication other than those specified should be avoided; however, OTC medications may be administered at the Investigator's discretion (e.g., acetaminophen for treatment of headache at doses ≤2 grams/24 hours).

If the need for concomitant medication (other than OTC medications) arises, inclusion or continuation of the participant may be at the discretion of the Investigator after consultation with the Sponsor.

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be documented along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose, route of administration, and frequency for concomitant therapy of special interest.

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

ACC/AHA Statin Therapies

Below in Table 6.2 are listed the different types of statin therapy by intensity according to the American College of Cardiology (ACC) and the American Heart Association (AHA) rating system (Stone et al. 2014).

Table 6.2 Statin Therapies According to American College of Cardiology (ACC) and American Heart Association (AHA) Classification[a]

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Daily dose lowers LDL-C by approximately ≥50%	Daily dose lowers LDL-C by approximately 30% to <50%
Atorvastatin 40 mg, 80 mg Rosuvastatin 20 mg, 40 mg	Atorvastatin 10 mg, 20 mg Rosuvastatin 5 mg, 10 mg Simvastatin 20 mg, 40 mg[b] Pravastatin 40 mg, 80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg twice daily Pitavastatin 2 mg, 4 mg

[a] Stone et al. 2014
[b] Simvastatin 80 mg is not allowed in this study.

Prohibited Medications

The following medications are prohibited throughout the study:

- GLP-1 RA or other incretin-based therapies and DPP-4 inhibitors.
- Medications intended to promote weight loss, including prescribed, OTC, or alternative remedies.
- Drugs reported to induce hepatic steatosis.
- Long-term (>14 days) systemic corticosteroid therapy.

Examples of medications prohibited throughout the study are presented in Table 6.3.

Table 6.3 Examples of Prohibited Medications

CCI	CCI	CCI
CCI	CCI	CCI
CCI		

6.9.1. Standard of Care for Participants with Type 2 Diabetes Mellitus

Patients with well-controlled T2DM may enroll in this study. Although it is not anticipated that LY3885125 will have an adverse effect on blood glucose levels, it is possible that glycemic control may worsen during this study due to the natural history of T2DM. Investigators and other study team members are expected to treat study participants according to the nationally established standards of care for diabetes management in respective participating countries, except where that treatment would be in conflict with the protocol-provided treatment requirements (see Section 6.9 prohibited medications). The investigators should follow current published standards of care from the American Diabetes Association (ADA) (ElSayed et al. 2023), and consensus guidelines of ADA and European Association for the Study of Diabetes (EASD) (Davies et al. 2022).

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

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

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention (applies only to Part B). If study intervention is permanently discontinued, the participant will remain in the study to complete procedures for an early termination visit and post-treatment follow-up, if applicable, as shown in the SoA (Section 1.3).

In Part B, prior to the repeat dose, all available safety data will be reviewed. Any clinically significant findings that may determine if further dosing should be discontinued will be determined by the Investigator in consultation with the Sponsor. A second dose will not be administered if the study participant experienced a hypersensitivity reaction after receiving the first dose in Part B of the study.

A participant should be permanently discontinued from study intervention if:

- The participant becomes pregnant during the study
- The participant decides to discontinue study intervention
- The Investigator decides that the participant should be discontinued due to AEs (the participant will be followed until the AE resolves)
- The participant has a SAE considered related to study treatment.

7.1.1. Liver Chemistry Stopping Criteria

Study intervention should be interrupted or discontinued if one or more of the conditions listed in Table 7.1 occur.

Table 7.1 Liver Chemistry Stopping Criteria

Participants with Normal or Near Normal Baseline ALT, AST, ALP (<1.5 × ULN)	**Participants with Elevated Baseline ALT, AST, ALP (≥1.5 × ULN)**
ALT or AST >5 × ULN	ALT or AST >3 × baseline
ALT or AST >3 × ULN and either TBL >2 × ULN or INR >1.5 (Except for participants with Gilbert's syndrome)[a]	ALT or AST >2 × baseline and either TBL >2 × ULN or INR >1.5 (Except for participants with Gilbert's syndrome)[a]
ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	ALT or AST >2 × baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
ALP >3 × ULN, when the source of increased ALP is the liver	ALP >2.5x baseline when the source of increased ALP is the liver
ALP >2.5x ULN and TBL > 2x ULN	ALP >2x baseline and TBL > 2x ULN
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	ALP >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines with minor modifications

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

[a] For participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2 × ULN.

Resumption of the study intervention can be considered only in consultation with the Sponsors designated medical monitor and only if the liver test results return to baseline and if a self-limited non drug-etiology is identified (see Section 8.2.5.1 for further details). Otherwise, the study intervention should be discontinued. Participants who discontinue from study intervention due to the abnormal liver tests will undergo monitoring as described in Appendix 5 (Section 10.5).

7.1.2. QTcF Stopping Criteria

If a clinically significant finding is identified on ECG, including, but not limited to changes from Day 1 predose baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. QTcF > 500 confirmed from the average of triplicate ECGs is a criterion to stop dosing in a participant. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE. The predose baseline used for the calculation of the change in QTc value is the average of the triplicate ECG taken closest to the time point of dosing on Day 1.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- At any time at the participant's own request for any reason or without providing any reason.
- At the request of the participant's designee (for example, parents or legal guardian).
- At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
- If the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to the introduction of the new agent.

At the time of discontinuation from the study, if possible, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA (Section 1.3). If the participant has not already discontinued study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the participant from the study.

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

7.3. Lost to Follow-up

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

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Complete physical examinations and symptom-directed physical assessment will be conducted at the visits specified in the SoA (Section 1.3). Symptom-directed physical assessment may also be conducted at other visits, as determined by the Investigator, if a participant presents with complaints:

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded as noted in the SoA.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to the clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, vital signs measurements will be conducted at the visits specified in the SoA (Section 1.3) and as clinically indicated. Participants must be supine for approximately 5 minutes before blood pressure and pulse rate collection and remain supine but awake during measurement. Systolic and diastolic blood pressure and pulse rate should be measured after the ECG is recorded (if the ECG is recorded at the same time point) and before other procedures.

8.2.3. Electrocardiograms

Triplicate 12-lead ECGs will be obtained on the days and times specified in the SoA (Section 1.3). ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary:

- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but at least 1 minute apart.
- The ECGs must be recorded before collecting any blood samples. Participants must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high-quality records.

ECGs will be interpreted by a qualified physician, the Investigator, or qualified designee at the site as soon after the time of ECG collection as possible. Ideally, the Investigator should be present:

- To determine whether the participant meets entry criteria at screening; and
- For immediate participant management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/QTc interval from baseline) after enrollment, the Investigator will determine if the participant can continue in the study (Section 7.1.2). The Investigator, or qualified designee, is responsible for determining if any change in participant management is needed and must document his/her review of the ECG printed at the time of evaluation. Any new clinically relevant finding should be reported as an AE.

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

8.2.4. Clinical Safety Laboratory Tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency of tests.
- The Investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an Investigator-designated local laboratory require a change in participant management or are considered clinically significant by the Investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.5. Safety Monitoring

The Sponsor's CRP will monitor safety data throughout the course of the study.

The Sponsor will review SAEs within time frames mandated by company procedures. When appropriate, the Sponsor CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

The medical monitor will periodically review the following data:

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

8.2.5.1. Hepatic Safety

Close Hepatic Monitoring

Laboratory tests (Section 10.2), including ALP, ALT, AST, TBL, direct bilirubin, GGT, and creatine kinase (CK) should be repeated within CCI hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

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

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

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

Comprehensive Hepatic Evaluation

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

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

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

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

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

- Hepatitis D virus (HDV)
- Cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- Acetaminophen levels
- Acetaminophen protein adducts
- Urine toxicology screen
- Wilson's disease
- Blood alcohol levels
- Urinary ethyl glucuronide; and
- Blood phosphatidylethanol

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

- Hepatologist or gastroenterologist consultation
- Magnetic resonance cholangiopancreatography (MRCP)
- Endoscopic retrograde cholangiopancreatography (ERCP)
- Cardiac echocardiogram; or
- Liver biopsy

Additional Hepatic Data Collection (Hepatic Safety CRF) in Study Participants who have Abnormal Liver Tests during the Study

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

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

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

8.2.6. Pregnancy Testing

Pregnancy testing will occur as indicated in the SoA (Section 1.3).

8.2.7. Injection Site Reactions (ISR)

Symptoms of a local ISR may include:

- Erythema
- Induration
- Pain
- Pruritus, and
- Edema

If an ISR is reported by a participant or investigator, the ISR Case Report Form (CRF) will be used to capture additional information about this reaction (for example, degree and area of erythema, induration, pruritus, and edema).

All positive responses of pain will require an additional assessment using the Pain Visual Analog Scale (Pain VAS). Pain measurements will be quantified using the 100-mm VAS pain score.

Management of ISRs will consist of ice packs and may include topical administration of antihistamines to alleviate itching.

8.2.8. Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the Sponsor in the electronic CRF. If the Investigator, after consultation with the Sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction has occurred related to study drug administration, the participant should be permanently discontinued from further study intervention.

The investigative sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated with systemic antihistamines, intravenous steroids, and in case of a severe allergic reaction (for example, anaphylactic reaction), epinephrine (in accordance with severity of the reaction and local standard of care).

Additional information will be collected on the CRF, including signs and symptoms related to the main event, as well as relevant medical history and the participant's potential risk factors. If the study participant experiences changes in blood pressure or pyrexia/fever, additional vital sign information, including blood pressure, temperature, and pulse, should be collected. The timing of the AE and any treatments administered should also be collected.

In case of generalized urticaria or anaphylaxis, additional blood samples should be collected as described below.

Laboratory assessments (hypersensitivity laboratory testing kit) will be performed if the participant experiences generalized urticaria or if anaphylaxis is suspected. The sample will be collected after the participant has been stabilized, and CCI . Samples may, however, be obtained CCI after the event occurred as analytes can remain altered for an extended period of time. The time the sample was collected will be recorded. A follow-up sample will be CCI , whichever is later.

The samples will be analyzed to determine levels of the following:

- LY3885125 concentrations
- Tryptase
- N-methylhistamine
- Basophil activation test
- Complement (C3, C3a, and C5A)
- Cytokine panel (IL-6, IL-1β, and IL-10)

Samples will be taken and stored for future immunogenicity testing and analysis for drug-specific immunoglobulin E (IgE).

In the event of a hypersensitivity reaction, participants will continue to be followed according to the schedule of activities.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3 (Section 10.3):

- AEs
- SAEs
- Product complaints.

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

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

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

After the initial report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events:

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – after participant's study participation has ended **and** the Investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	The predicted time until estimated plasma levels of partner would be below the level of toxicologic concern, plus 93 days	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the Investigator	N/A
PC (if Investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event

*Serious adverse events should not be reported unless the Investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of Pregnancy Information

Male participants with partners who become pregnant:

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant within 93 days of last visit while the male participant is in this study. This applies only to male participants who receive study intervention.
- After learning of a pregnancy in the female partner of a study participant, the Investigator will:
  - Obtain a consent to release information from the pregnant female partner directly; and
  - Within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the Sponsor.

  The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant:

Female participants must be considered of nonchildbearing potential to participate in the study (see Sections 5 and 10.4). However, in the event a participant becomes pregnant, the following action must be taken:

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in protocol Section 8.3.1. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant discontinues the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Events of Special Interest

Not applicable

8.4. Pharmacokinetics

In Parts A and B blood samples will be collected to determine plasma concentrations of LY3885125. The blood samples will be collected on the days and times specified in the SoA (Section 1.3). The plasma samples will be prepared for analysis as detailed in the laboratory manual provided separately to sites.

The PK of LY3885125 will be assessed in Part A after a single SC dose of LY3885125 on CCI CCI on CCI and CCI. The PK endpoints to be determined include AUC, C_{max}, T_{max}.

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of sampling may be altered during the study based on newly available data (for example, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the site. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of LY3885125 plasma concentration may also be used to evaluate LY3885125 pharmacology or safety aspects related to concerns arising during or after the study.

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 study intervention administration will be collected, pooled, and refrigerated. At the end of the collection period, the total urine volume will be recorded. Urine samples will be used to determine creatinine, quantification of LY3885125 and if applicable major metabolite and exploratory metabolite identification. Assessment of renal clearance will be an exploratory assessment; therefore, failure to collect samples or analyze all collected samples will not be a deviation.

8.5. Pharmacodynamics

PCSK9 and Apo Panel

In Parts A and B blood samples will be collected to determine plasma levels of PCSK9 and ApoB/Apo panel as markers of the PD of LY3885125:

- For Part A, the changes in PCSK9 and ApoB from baseline relative to placebo after the single dose of LY3885125 on Day 1 will be determined; and
- For Part B, the changes in PCSK9 and ApoB from baseline to Weeks [redacted] and [redacted] relative to placebo will be determined.

Fasting blood samples will be collected at visits and times specified in the SoA (Section 1.3), and the samples prepared for analysis as detailed in the laboratory manual provided separately to sites.

Liver Fat Content

In Part B liver fat content will be estimated on MRI-PDFF, which will be performed at visits and times specified in the SoA (Section 1.3), and as detailed in the laboratory manual.

The relative change in liver fat content (relative percent) from Baseline to Weeks [redacted] and [redacted] by MRI-PDFF compared to placebo following the 2 SC doses on Days [redacted] and Day [redacted] will be assessed.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Lipid Profile

[redacted]

8.8. Biomarkers

Serum Biomarkers

[redacted]

Blood samples will be collected at the visits and times in the SoA (Section 1.3), and the serum samples prepared for analysis as detailed in the laboratory manual provided separately to sites.

The Sponsor may store the samples for up to 15 years after the end of the study to achieve study objectives. Additionally, with participants' consent, samples may be used for further research by the Sponsor.

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[redacted]

8.9. Immunogenicity Assessments

Antibodies targeting or binding to LY3885125 will be evaluated in serum collected from all participants at the visits and times in the SoA (Section 1.3).

Serum samples will be screened for antibodies binding to study intervention, and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to study intervention and/or further characterize the immunogenicity of study intervention.

The detection and characterization of antibodies to study intervention will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study intervention will also be evaluated for study intervention serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last study visit at a facility selected by the Sponsor to enable further analysis of immune responses to study intervention.

8.10. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable

9. Statistical Considerations

9.1. Statistical Hypotheses

No inferential analyses are planned for either Part A or Part B, so no formal statistical hypotheses are defined. Only descriptive summary statistics will be provided for endpoints of interest.

9.1.1. Multiplicity Adjustment

No inferential analyses are planned for either Part A or Part B, so no adjustment for multiplicity is necessary.

9.2. Analyses Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set / Population	Description
Full analysis set (FAS)	All randomized participants.
Safety analysis set	All participants who are exposed to study intervention.
Pharmacodynamics (PD) analysis set	All participants in the Safety analysis set who have at least one PD assessment
Pharmacokinetics (PK) analysis set	All participants who have received at least one dose of LY3885125 and have sufficient concentration-time data to estimate PK parameters.

The full analysis set is used to analyze disposition and baseline characteristics, the safety analysis set is used to analyze the endpoints and assessments related to safety, the PD analysis set is used to analyze PD endpoints, and the PK analysis set is used for the PK analyses.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of the Sponsor or its designee. Details of statistical analysis methods will be described in the Statistical Analysis Plan (SAP).

Bayesian analyses will be performed using the primary PD marker – change from baseline in PCSK9 in Part A and relative change of liver fat content (percent) by MRI-PDFF in Part B at Weeks CCI . All other analyses will only provide descriptive statistics tabulated by cohort. Some descriptive summaries, e.g., participant accounting, study disposition, and participant demographics, will also provide descriptive statistics for all cohorts pooled together.

Incidence based summaries and analyses with binomial outcomes will use all observed data for participants in the respective analysis set with presentation of number and percent of participants.

Summaries for continuous variables will include the number of participants in the analysis, mean, standard deviation, median, minimum, and maximum.

Any change to the data analysis methods described in the protocol will require a protocol amendment ONLY if it changes a principal feature of the protocol. Any other changes to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or clinical study report (CSR).

Handling of missing, unused, and spurious data will be addressed in the SAP, where appropriate. Adjustments to the planned analyses will be described in the final CSR.

SAS software version 9.4 or higher will be used to perform statistical analyses, unless otherwise specified.

9.3.2. Primary Endpoint(s) Analysis

The primary endpoints in Part A and in Part B are AEs and SAEs. The analyses for AEs and SAEs will focus on events that emerge or worsen after the first dose of LY3885125. Events that occur after the last follow-up visit or early termination visit will only be included in an analysis if the investigation believes the event is at least possibly related to LY3885125.

9.3.3. Secondary Endpoint(s) Analysis

The secondary endpoints in Part A are:

- PK - LY3885125 AUC, C_{max}, T_{max}.
- PD - Changes in PCSK9 and ApoB from baseline relative to placebo.

The secondary endpoints in Part B are:

- PK - LY3885125 AUC, C_{max}, T_{max}.
- PD - Relative change of liver fat content (percent) from baseline to CCI by MRI-PDFF compared to placebo.
- PD - Changes in PCSK9 and ApoB from baseline relative to placebo.

9.3.4. Exploratory Endpoint(s) Analysis

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9.3.5. Safety Analyses

Safety analyses will be conducted on all participants who received at least one dose of study treatment. No statistical comparisons of treatment groups will be completed for safety endpoints.

Adverse events will be summarized and listed. Quantitative measurements, such as clinical laboratory safety tests, vital signs and ECGs, will be descriptively summarized by treatment group using number of participants, mean, median, standard deviation, minimum and maximum. Categorical endpoints will be summarized using number of participants, frequency, and percentages. Additional analysis will be performed if warranted upon review of the data.

9.3.6. Other Analyses

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.

9.4. Interim Analysis

No interim analyses are planned for this study.

9.5. Sample Size Determination

Enrollment for Part A will enable completion of approximately 68 participants in up to 6 cohorts. Enrollment of 19 participants, randomized 10:9 to LY3885125:placebo in Cohort 6 was CCI [redacted]

Enrollment for Part B will enable completion of approximately 44 participants in a single cohort that consists of 3 treatment arms with 2 doses administered per arm. The sample size for Part B was CCI [redacted]

Participants may be replaced at the discretion of the sponsor for adequate evaluation of study endpoints.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (for example, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethic Committees (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations.
  - Reporting to the Sponsor or designee significant issues related to participant safety, participant rights, or data integrity.
- Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement (CTA).

10.1.2. Financial Disclosure

Not applicable for Phase 1 study.

10.1.3. Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant and is kept on file.

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

10.1.4. Data Protection

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

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by the Sponsor to all Investigators (for example, by phone and/or

email) as soon as possible. It will be a requirement that Investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any Investigator not responding will be followed up by Sponsor personnel prior to any further planned dosing. If a dose is planned imminently, Sponsor personnel will immediately, and continually, use all efforts to reach Investigators until contact is made and instructions verified.

Reports

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

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

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

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (for example, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source data may include laboratory tests, medical records, and clinical notes.
- The Investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the Sponsor. All completed CRFs must be signed prior to archival.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (for example, CROs).
- The Sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

Data collected via the CRO data capture system will be stored by the CRO. The Investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the Investigator will receive or access an archival copy of pertinent data for retention.

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

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

10.1.6. Source Documents

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

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) (CRO[s]) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

10.1.8. Publication Policy

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

10.1.9. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the Sponsor, will participate as Investigators in this clinical trial.

10.1.10. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3885125 or after LY3885125 become(s) commercially available.

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

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

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

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

Sample Type	Custodian	Retention Period After Last Participant Visit*
Pharmacokinetics	Sponsor or Designee	2 years
Biomarkers	Sponsor or Designee	15 years

10.2. Appendix 2: Clinical Laboratory Tests

- The clinical laboratory safety tests detailed in the table below will be performed by the designated central and local laboratories.
- In circumstances where the Sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

Clinical laboratory test results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

<table>
<tr><th colspan="2">Safety Laboratory Tests</th></tr>
<tr><td>Hematology:
Hematocrit
Hemoglobin
Erythrocyte/red blood cell (RBC) count
Mean cell volume
Mean cell hemoglobin
Mean cell hemoglobin concentration
Leukocytes/white blood cell (WBC) count
Platelets

Differential WBC [Absolute counts and %] of:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils

Coagulation:
International normalized ratio (INR)
Prothrombin Time (PT)
Activated partial thromboplastin Time (aPTT)

Glycated hemoglobin (HbA1c)</td><td>Clinical Chemistry:
Sodium
Potassium
Bicarbonate
Chloride
Calcium total
Phosphorus
Magnesium[a]
Glucose (random)
Creatinine
Blood urea nitrogen (BUN)
Total protein
Albumin
Direct bilirubin
Total bilirubin (TBL)
Alkaline phosphatase (ALP)
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Creatine kinase (CK)
Gamma-glutamyl transferase (GGT)
Lactate dehydrogenase (LDH)
Iron
Transferrin
Transferrin saturation[a]
Estimated glomerular filtration rate (eGFR) calculated by Chronic Kidney Disease Epidemiology (CKD-EPI)[a]</td></tr>
<tr><td>Urinalysis:
Specific gravity
pH
Protein
Glucose
Ketones
Bilirubin
Urobilinogen
Blood
Nitrite

CCI
[redacted]</td><td>Lipids:
Total cholesterol
Triglycerides (TG)
Low-density lipoprotein (LDL)
High-density lipoprotein (HDL)
Very low-density lipoprotein (VLDL)
CCI [redacted]

PCSK9 (Proprotein convertase subtilisan/kexin type 9) and ApoB

Ethanol testing[a,b]
Urine drug screen[a,b]
Hepatic serologies:[a]
Hepatitis B surface antigen (HBsAg)
HBV DNA
Hepatitis C antibody
HCV RNA

Stored sample
Human immunodeficiency virus (HIV)[a]
COVID-19 PCR test[c]
Pregnancy test[d]
Follicle-stimulating hormone (FSH)[e]
Thyroid-stimulating hormone (TSH) [a]</td></tr>
</table>

FIB-4 formula = Age (years) × AST (IU/L) / {platelet count (10^9/L) × ALT (IU/L)$^{1/2}$}

a Performed at screening only.

b Urine drug screen and ethanol level must be repeated prior to admission to the clinical research unit (CRU) and at other times indicated in the Schedule of Activities (SoA) in Section 1.3.

c A COVID-19 PCR test will be performed at Screening. and on Day 1 prior to dosing. If test results are positive for the virus the participant will be excluded from the study.

d Serum pregnancy test at screening; urine pregnancy test may be performed at all other timepoints and at other times indicated in Schedule of Activities (SoA)

e A serum FSH test should be performed in women at screening to confirm postmenopausal status if applicable.

f CCI

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

10.3.1. Definition of Adverse Event (AE)

AE Definition

- An adverse event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (that is, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after administration of study intervention even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of study intervention, including signs, symptoms, or clinical sequelae.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- Results in death.
- Is life-threatening:
    - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization:
    - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity:
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect:
    - Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Other situations:
    - Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention When the ability to use the study intervention safely is impacted, the following are also product complaints:
    - Deficiencies in labeling information, and
    - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the Investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the Investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.
- Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) in their assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The Investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via Paper Form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the Sponsor, or designee.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SAE Report.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met:

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Term	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they: • Have a congenital anomaly such as Müllerian agenesis; • Are infertile due to surgical sterilization; or • Are postmenopausal (the last menstrual period was at least 12 months ago, and follicle-stimulating hormone (FSH) at screening confirms post-menopausal status). Examples of surgical sterilization include total hysterectomy, bilateral tubal ligation, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Post-menopausal state	The postmenopausal state is defined as: no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

10.4.2. Contraception Guidance

10.4.2.1. Female Participants

Only women not of childbearing potential (WNOCBP) can participate in this trial. See Section 10.4.1 for definitions.

10.4.2.2. Male Participants

The table below describes contraceptive guidance for men.

Males who agree to use highly effective or effective methods of contraception may participate in this trial.

All men must refrain from sperm donation for duration of the study and for 93 days following the last dose of study intervention.

Men with partners of childbearing potential must either remain abstinent (if this is their preferred and usual lifestyle), or must use condoms during intercourse for the duration of the study, and for 93 days following the last dose of study intervention.

Topic	Guidance
For all men	All men should refrain from sperm donation for the duration of the study and for and for 93 days following the last dose of study intervention.
Contraception for men with partners of childbearing potential	• Either remain abstinent (if this is their preferred and usual lifestyle); or • Must use condoms during intercourse for the duration of the study; and • For 93 days following the last dose of study intervention.
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

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

Topic	Guidance
Highly effective contraception	• Combination of oral contraceptive pill and mini-pill • Implanted contraceptives • Injectable contraceptives • Contraceptive patch (only women <198 pounds or 90 kg) • Total abstinence • Vasectomy (if only sexual partner) • Fallopian tube implants (if confirmed by hysterosalpingogram) • Combined contraceptive vaginal ring, or • Intrauterine devices
Effective contraception	• Male or female condoms with spermicide • Diaphragms with spermicide or cervical sponges • Barrier method with use of a spermicide • Condom with spermicide • Diaphragm with spermicide, or • Female condom with spermicide Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.
Ineffective forms of contraception	• Spermicide alone • Immunocontraceptives • Periodic abstinence • Fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • Withdrawal • Post-coital douche • Lactational amenorrhea

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

Close Hepatic Monitoring

In case of a hepatic abnormality, laboratory tests should be repeated within 48 to 72 hours to confirm the abnormality. These laboratory tests should include, at a minimum:

- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- alkaline phosphatase (ALP)
- total bilirubin (TBL)
- direct bilirubin (DBL)
- gamma-glutamyl transferase (GGT), and
- creatine kinase (CK).

These results should be used to determine if it is increasing or decreasing if 1 or more of these conditions occur.

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

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

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests, should be initiated by the investigator in consultation with the study physician. At a minimum, this evaluation should include physical examination and a thorough medical history, including:

- Symptoms
- Recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures)
- Recent travel
- History of concomitant medications (including over-the-counter [OTC])
- Herbal and dietary supplements
- History of alcohol drinking, and
- Other substance abuse.

Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive Hepatic Evaluation

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

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

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

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

At a minimum, this evaluation should include a physical examination and a thorough medical history, as outlined above, as well as:

- Tests for prothrombin time-international normalized ratio
- Tests for viral hepatitis A, B, C, or E
- Tests for haemolysis
- Tests for autoimmune hepatitis; and
- An abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the study physician, including tests for

- Hepatitis D virus
- Cytomegalovirus
- Epstein-Barr virus
- Acetaminophen levels
- Acetaminophen protein adducts
- Urine toxicology screen
- Wilson's disease
- Blood alcohol levels
- Urinary ethyl glucuronide, and
- Blood phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant to their primary physician for further management.

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

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

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

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

10.5.1. Hepatic Evaluation Testing

See Section 7.1.1 for Hepatic stopping criteria.

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

Hepatic Haematology Panel:	**Hepatic Clinical Chemistry Panel:**
Haemoglobin	Total bilirubin
Haematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry:**
Basophils	Alkaline phosphatase isoenzymes[d]
Eosinophils	Haptoglobin
Platelets	Immunoglobulin IgA (quantitative)
Cell morphology (RBC and WBC)	Immunoglobulin IgG (quantitative)
Hepatic Coagulation Panel:	Immunoglobulin IgM (quantitative)
Prothrombin time, INR (PT-INR)	**Urine Chemistry:**
Hepatitis A virus (HAV) testing:	Drug screen
HAV total antibody	Ethyl glucuronide (EtG)[d]
HAV IgM antibody	Epstein-Barr virus (EBV) testing:
Hepatis B virus (HBV) testing:	EBV antibody [d]
Hepatitis B surface antigen (HBsAg)	EBV DNA[b,d]
Hepatitis B surface antibody (anti-HBs)	Cytomegalovirus (CMV) testing:
Hepatitis B core total antibody (anti-HBc)	CMV antibody[d]
Hepatitis B core IgM antibody	CMV DNA[b,d]
HBV DNA[b, d]	Herpes simplex virus (HSV) testing:
Hepatis C virus (HCV) testing:	HSV (Type 1 and 2) antibody[d]
HCV antibody	HSV (Type 1 and 2) DNA[b,d]
HCV RNA[b,d]	Liver kidney microsomal type 1 (LKM-1) antibody[d]
Hepatitis D virus (HDV) testing:	
HDV antibody	
Hepatitis E virus (HEV) testing:	
HEV IgG antibody[d]	
HEV IgM antibody[d]	
HEV RNA[b,d]	

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

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

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

[d] Assayed only by an investigator-designated qualified laboratory.

10.6. Appendix 6: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this Appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the Sponsor in partnership with the Investigator.

Exceptional Circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the Investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing Changes under Exceptional Circumstances

In an exceptional circumstance, after receiving the Sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the Sponsor grants written approval for changes in study conduct, the Sponsor will also provide additional written guidance, if needed.

Considerations for Making a Change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed Consent

Additional consent from the participant will be obtained, if required, for:

- Participation in remote visits, as defined in Section "Remote Visits", and
- Provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional Circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote Visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, symptom-directed physical assessments and evaluations of AEs.

Data Capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety Reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Return to On-Site Visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local Laboratory Testing Option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: PCSK9 and ApoB. The local laboratory must be qualified in accordance with applicable local regulations.

Screening Period Guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit are valid for a maximum of 28 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 28 days from screening to randomization visit: The participant will proceed to the next study visit per the usual Schedule of Activities (SoA, Section 1.3), provided that the randomization visit must be conducted within 28 days from first screening.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 28 days from screening to randomization visit: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting with the screening visit to ensure participant eligibility by randomization visit.

Adjustments to Visit Windows

Whenever possible and safe to do so, as determined by the Investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the Sponsor. This minimizes missing data and preserves the intended conduct of the study.

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Documentation of Changes to Study Conduct

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source Documents at Alternate Locations

Source documents generated at a location other than the study site should be part of the Investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.7. Appendix 7: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ACC	American College of Cardiology
ADA	American Diabetes Association
ADR	adverse drug reaction
AE	adverse event
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apo	apolipoprotein
ApoB	Apolipoprotein B
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
blinding/masking	A single-blind study is one in which the Investigator and/or the Investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the Sponsor is aware of the treatment but the Investigator and/the Investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the Investigator or Sponsor staff who are involved in the treatment or clinical evaluation of participants are aware of the treatment received.
BMI	body mass index
BUN	blood urea nitrogen
CAP	controlled attenuation parameter
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CCI	[redacted]
CKD-EPI	Chronic Kidney Disease Epidemiology
C_{max}	maximum observed plasma concentration
CMV	cytomegalovirus
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 study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019

Term	Definition
CRF	Case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor for each trial participant.
CRO	contract research organization
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
CSR	clinical study report
CT	computed tomography
CTA	Clinical Trial Agreement
DEC	Dose Escalation Committee
DIO	diet-induced-obesity
DNA	deoxyribonucleic acid
DPP-4i	dipeptidyl peptidase 4 inhibitor (gliptin)
DsiRNA	dicer-substrate small interfering RNA
DSUR	development safety update report
EASD	European Association for the Study of Diabetes
EBV	Epstein-Barr virus
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
CCI	[redacted]
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ER	endoplasmic reticulum
ERCP	endoscopic retrograde cholangiopancreatography
FDA	Food and Drug Administration
CCI	[redacted]
FIH	first-in-human
FSH	follicle-stimulating hormone
GalNAc	N-acetylgalactosamine
GalXC-SCAP-3339	LY3885125
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GIP RA	glucose-dependent insulinotropic polypeptide receptor agonist
GLP	Good Laboratory Practice
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GMP	Good Manufacturing Practice

Term	Definition
HbA1c	glycated hemoglobin
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	High-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HDI	hydrodynamic injection
HDV	hepatitis D virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IB	Investigator's Brochure
IEC	Independent Ethics Committee
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	International normalized ratio
IRB	Institutional Review Board
ISR	Injection-site reactions
LDH	lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
CCI	[redacted]
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that is either inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MRCP	magnetic resonance cholangiopancreatography

Term	Definition
CCI	[redacted]
MRI-PDFF	magnetic resonance imaging proton density fat fraction
mRNA	messenger ribonucleic acid
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
[redacted]	CCI [redacted]
NOAEL	no-observed-adverse-effect level
ob/ob	leptin-deficient
OTC	over-the-counter
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PCR	polymerase chain reaction
PCSK9	proprotein convertase substilisin/kexin type 9
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
CCI	[redacted]
PT	prothrombin time
PUC	preparative ultracentrifugation
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
S1P	site-1 protease
S2P	site-2 protease
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SRC	Safety Review Committee
SC	subcutaneous(ly)
SCAP	SREBP cleavage activating protein
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.
siRNA	small interfering RNA
SoA	Schedule of Activities
SREBP	sterol regulatory element-binding protein
SREBP1a	sterol regulatory element-binding protein 1 isoform a
SREBP1c	sterol regulatory element-binding protein 1 isoform c
SREBP2	sterol regulatory element-binding protein 2
$t_{1/2}$	half-life
T2DM	Type 2 diabetes mellitus (T2DM)

Term	Definition
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TG	triglyceride
T_{max}	time of maximum observed concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UK	United Kingdom
US	United States
USP	United States Pharmacopeia
VLDL	very low-density lipoprotein
WBC	white blood cell

10.8. Blood Sampling Schedule

10.8.1. Blood Volumes to be Collected in Part A

Purpose	Blood Volume (mL) Each sample	Number of Samples (n)	Total Volume (ml)	Comments
CCI	[redacted]	[redacted]	[redacted]	
CCI	[redacted]	[redacted]	[redacted]	
CCI	[redacted]	[redacted]	[redacted]	Includes HCV antibody test
CCI	[redacted]	[redacted]	[redacted]	
CCI	[redacted]	[redacted]	[redacted]	
CCI	[redacted]	[redacted]	[redacted]	
CCI	[redacted]	[redacted]	[redacted]	
CCI	[redacted]	[redacted]	[redacted]	
CCI	[redacted]	[redacted]	[redacted]	To be stored by Lilly specialist laboratory
CCI			[redacted]	

Abbreviations: CCI [redacted]

10.8.2. Proposed Approximate Blood Volumes to be Collected in Part B

Purpose	Blood Volume (mL) each sample	Number of Samples (n)	Total Volume (ml)	Comments
CCI				
CCI				
CCI				
CCI				
CCI				
CCI				
CCI				
CCI				
CCI				
CCI				
CCI				
CCI				
CCI				
CCI				

Abbreviations: CCI

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