Protocol J2A-GH-GZGX(b)

A Multiple Dose Titration Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Chinese Participants who have Obesity or are Overweight with Weight-related Comorbidities

NCT06023095

Approval Date: 15 March 2024

Title Page

Protocol Title: A Multiple Dose Titration Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Chinese Participants who have Obesity or are Overweight with Weight-related Comorbidities

Protocol Number: J2A-GH-GZGX

Amendment Number: (b)

Compound: LY3502970

Brief Title: Effect of LY3502970 in Chinese participants who have obesity or are overweight with weight-related comorbidities.

Study Phase: Phase 1

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana USA 46285

Approval Date: Protocol Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-124963

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	26-Jul-2023
Original Protocol	08-Dec-2022

Amendment (b)

Overall Rationale for the Amendment:

Protocol J2A-GH-GZGX has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to the protocol are described in the following table. Note that minor edits may have been made throughout the protocol, which are not captured in the amendment summary table.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis Section 4.1. Overall Design Section 9.5. Sample Size Determination	Number of participants to be enrolled changed from 'up to 24' to 'approximately 24'.	To allow more flexibility in enrolment.
Section 10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments Section 10.11. Appendix 11: Clinical Laboratories and Specimen Disposal Units	Hepatitis D virus total antibody test replaced with hepatitis D virus IgG and IgM antibody tests.	Updated following laboratory discontinuation of the hepatitis D virus total antibody test.
Section 10.11. Appendix 11: Clinical Laboratories and Specimen Disposal Units	CCI [redacted], Ltd removed as reference laboratory for hepatitis D virus testing.	Updated following laboratory discontinuation of the hepatitis D virus total antibody test.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multiple Dose Titration Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Chinese Participants who have Obesity or are Overweight with Weight-related Comorbidities

Brief Title: Effect of LY3502970 in Chinese participants who have obesity or are overweight with weight-related comorbidities.

Rationale: Study J2A-GH-GZGX (GZGX) is a Phase 1, multiple dose titration study designed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3502970 following oral administration of multiple once daily (QD) doses for 16 weeks in Cohort 1 and 24 weeks in Cohort 2 in Chinese participants who have obesity or are overweight with weight-related comorbidities.

PK data from previous Phase 1 clinical studies supports QD administration of LY3502970 and found LY3502970 to be safe and well tolerated in the proposed dose ranges for this study. A single-ascending dose and multiple ascending dose LY3502970 study (Study J2A-JE-GZGB) has been performed in Japanese participants with type 2 diabetes mellitus (T2DM). The current study is intended to obtain sufficient safety, tolerability, PK, and PD data with preliminary efficacy measurements to support identification of an appropriate dose range for subsequent clinical studies of LY3502970 in the Chinese population.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of LY3502970 following multiple oral QD doses in Chinese participants with obesity or who are overweight with weight-related comorbidities.	• Number and incidence of TEAEs and SAEs.
Secondary	
• To characterize the PK profile of LY3502970 following multiple oral QD doses in Chinese participants with obesity or who are overweight with weight-related comorbidities. • To characterize the PD effects of LY3502970 following multiple oral QD doses in Chinese participants with	• C_{max} and $AUC_{(0-24)}$. • Changes from baseline in: – body weight – body mass index

obesity or who are overweight with weight-related comorbidities.	– waist circumference. • Changes from baseline in: – fasting plasma glucose – fasting insulin – HbA1c – lipid profiles.

Abbreviations: $AUC_{(0-24)}$ = area under the concentration versus time curve from time 0 to 24 hour time point; C_{max} = maximum observed drug concentration; HbA1c = glycated hemoglobin; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design

Study GZGX is a Phase 1, investigator- and participant-blind, 2-cohort, randomized, placebo-controlled, 16-week (Cohort 1) and 24-week (Cohort 2) multiple dose titration study in Chinese participants with obesity or who are overweight with weight-related comorbidities.

Screening

All participants will be screened within 28 days prior to Day 1.

Treatment and Assessment Period

Participants may be admitted to the CRU in advance if judged to be required by the investigator. It is intended that eligible participants will attend an inpatient visit at the clinical research unit (CRU) on Days -1, 56, and 112 for Cohort 1, and on Days -1, 28, 84, 140, and 168 for Cohort 2.

On Day 1, participants will be randomized 10:2 to either LY3502970 or placebo, and 1:1 to Cohort 1 or 2, with a computer-generated allocation code using an interactive web-response system.

Overall, approximately 24 Chinese participants may be enrolled. Approximately 12 participants in each cohort will be randomized (10 participants to LY3502970 and 2 participants to placebo) to ensure approximately 8 participants receiving LY3502970 in each cohort complete the study.

From Day 1 to Day 112 of Cohort 1, participants will receive an oral QD dose of LY3502970 at 4 dose levels, or placebo. From Day 1 to Day 168 of Cohort 2, participants will receive an oral QD dose at 6 dose levels of LY3502970, or placebo.

Prior to discharge from the CRU (Day 3), participants will be instructed on the symptoms and treatment of hypoglycemia. Participants may be allowed to leave the CRU after completing assessments on Days 3, 57, and 114 for Cohort 1 and on Days 3, 29, 85, 141, and 170 for Cohort 2, or later at the investigator's discretion. Participants will return for outpatient visits for PK sampling and PD and safety assessments at predefined times. Participants may be required to remain at the CRU longer than the planned days at the investigator's discretion.

Progression of Cohorts through Study GZGX

Two cohorts are planned. Participants will be randomized to 1 of 2 cohorts comprising approximately 12 participants each. Participants will be randomized to receive stepwise dose titration of either LY3502970 or corresponding placebo for 16 weeks in Cohort 1 and 24 weeks in Cohort 2. Participants will receive a stepwise dose titration of LY3502970 or placebo, with each dose level administered for 4 weeks as shown:

- Cohort 1
  - LY3502970 Level 1; [redacted] mg for 4 weeks,
  - LY3502970 Level 2; [redacted] mg for 4 weeks,
  - LY3502970 Level 3; [redacted] mg for 4 weeks,
  - LY3502970 Level 4; [redacted] mg for 4 weeks.
- Cohort 2
  - LY3502970 Level 1; [redacted] mg for 4 weeks,
  - LY3502970 Level 2; [redacted] mg for 4 weeks,
  - LY3502970 Level 3; [redacted] mg for 4 weeks,
  - LY3502970 Level 4; [redacted] mg for 4 weeks,
  - LY3502970 Level 5; [redacted] mg for 4 weeks,
  - LY3502970 Level 6; [redacted] mg for 4 weeks.

In Cohort 2, the duration of titration steps may be amended, and additional step-through doses may be added based on data obtained from Cohort 1. In addition, the dosage and dose titration scheme for either cohort may be further modified based on emerging safety and tolerability data. Any changes to the planned dose will be reviewed and approved by the sponsor and the investigator.

Safety data review will be planned for progression between stepwise dose titration within cohorts. The investigator and Lilly clinical pharmacologist or clinical research physician will review all available safety data including adverse events, vital signs, electrocardiograms, body weight, safety laboratory measurements, and physical assessments. Any available PK or PD data may also be considered for dose titrations. Individual patient data will not be made available to the investigator to avoid unblinding.

If the investigator decides not to up-titrate the dose level as planned for individual participants for any reason, participants should be discontinued for doses equal to or less than [redacted] mg. Participants may remain at the current dose level for doses greater than [redacted] mg through to the last planned dose on Day 112 for Cohort 1 or on Day 168 for Cohort 2.

Follow-up Period

Following the final assessments between Days 113 and 116 for Cohort 1 and Days 169 to 172 for Cohort 2, as detailed in the SoA, a follow-up visit approximately 2 weeks after the last dose of study intervention will be performed.

Brief Summary:

The purpose of this study is safety observation and to measure PK and PD of LY3502970 capsules in participants who have obesity or are overweight with weight-related comorbidities.

Study details include:

- The study duration, including screening, will be up to 157 days for Cohort 1 and 213 days for Cohort 2.
- The treatment duration will be up to 112 days for Cohort 1 and 168 days for Cohort 2.
- The visit frequency will be approximately once every 2 weeks.

Study Population:

Participants will be native Chinese males or females, between 18 and 65 years of age, inclusive. Participants will have a body mass index (BMI) of greater than 30.0 kg/m^2, or a BMI between 27.0 up to 30.0 kg/m^2 with at least 1 weight-related comorbidity.

Number of Participants:

Approximately 24 Chinese participants who have obesity or are overweight with weight-related comorbidities may be enrolled so that 20 participants complete the study. The use of a 10:2 LY3502970:placebo ratio is intended to ensure that approximately 8 participants complete all planned LY3502970 doses in each cohort.

Intervention Groups and Duration:

All participants will be screened within 28 days prior to Day 1. A single oral dose of LY3502970 or placebo in a capsule formulation will be administered QD as per the planned cohort dosing levels until Day 112 in Cohort 1, or Day 168 in Cohort 2. Participants will be followed through until Day 126 in Cohort 1 or Day 182 in Cohort 2.

Ethical Considerations of Benefit/Risk:

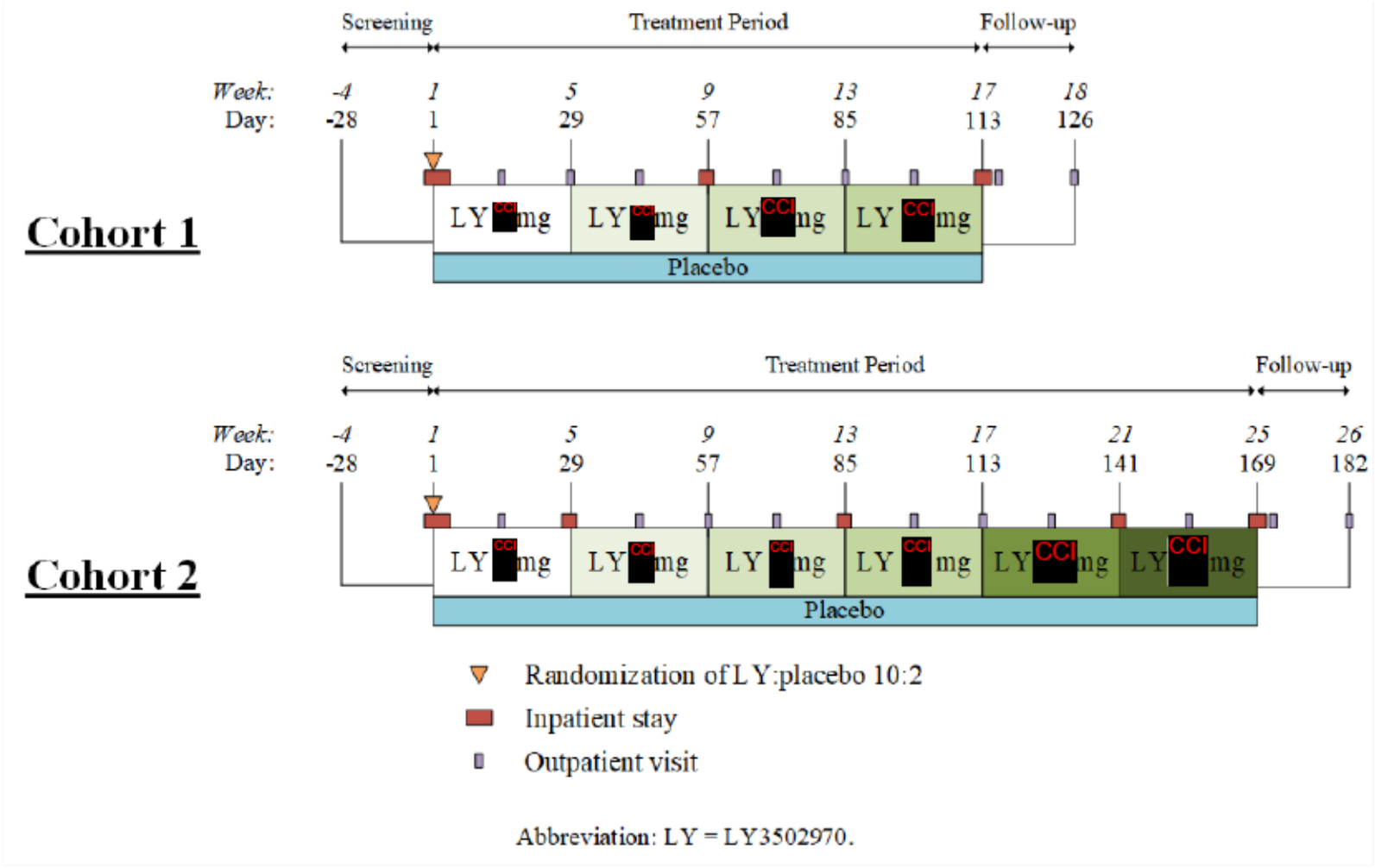
No safety or tolerability concerns that preclude further investigation of LY3502970 have been identified in 173 healthy participants and 51 participants with T2DM to date, up to the highest single dose given of [redacted] mg and multiple dose given of [redacted] mg. No clinically significant safety or tolerability concerns have been identified in participants to date for LY3502970 up to [redacted] mg in participants with T2DM.

To mitigate the well-known gastrointestinal tolerability issues of glucagon-like peptide-1 receptor agonist, participants will be assigned a treatment regimen that includes a starting dose of [redacted] mg daily and increasing or escalating doses of LY3502970. Before each dose-titration step, the CP or CRP may assess the safety and tolerability data of each participant and decide if they should continue with the assigned treatment regimen. It is anticipated that these dose-titration steps will occur approximately every 4 weeks to a maximum of [redacted] mg in Cohort 1 and [redacted] mg in Cohort 2.

Data from Phase 1 studies indicate that LY3502970 treatment may result in a decrease in body weight. These data support improved weight management in participants with obesity or are overweight with weight-related comorbidities.

Data Monitoring Committee: No.

1.2. Schema



Abbreviation: LY = LY3502970.

1.3. Schedule of Activities

Schedule of Activities – Cohort 1

Procedure	Screening	Treatment Period													Follow-up Period				ED	Notes
Visits	1	2				3	4	5	6		7	8	9	10				11		
Weeks	-4 to -1	-1	1			3	5	7	8	9	11	13	15	16	17			18		
Days	-28 to -2	-1	1	2	3	15	29	43	56	57	71	85	99	112	113	114	116	126		
Window (days)						±2	±1	±2	±1		±2	±1	±2	±1				±3		
Informed consent	X																			
Inclusion and exclusion criteria	X	X																		
Randomization			X																	
Participant admission to CRU		X							X					X						
Inpatient stay at CRU		X	X	X	X				X	X				X	X	X				
Participant discharge from CRU					X					X						X				
Outpatient visit	X					X	X	X			X	X	X				X	X		
Fasting	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	Overnight fasting of at least 8 hours.
Study intervention																				
Study intervention dispense			X				X			X		X								
Diary dispense					X		X			X		X								
Clinical Assessment																				
Medical history	X	X																		

Procedure	Screening	Treatment Period													Follow-up Period				ED	Notes
Visits	1	2				3	4	5	6		7	8	9	10				11		
Weeks	-4 to -1	-1	1			3	5	7	8	9	11	13	15	16	17			18		
Days	-28 to -2	-1	1	2	3	15	29	43	56	57	71	85	99	112	113	114	116	126		
Window (days)						±2	±1	±2	±1		±2	±1	±2	±1				±3		
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Complete physical examination at screening, and symptom-directed at other visits and as clinically indicated.
Height	X																			
Weight	X		P			P	P	P		P	P	P	P		X			X	X	Weight will be measured twice for each participant in a consistent way using a calibrated scale.
Waist circumference	X		P			P	P	P		P	P	P	P		X			X	X	
Vital signs	X	X	P	X		P	P	P		P	P	P	P		X			X	X	Vital signs must be measured before blood sample collections, if applicable.
Body temperature	X																			
Single 12-lead ECG	X		P	X		P	P	P		P	P	P	P		X			X	X	ECG must be recorded before collecting blood samples or vital signs measurements, close to the time of the blood draw, and in a fasted state.
Hypoglycemia training					X															See Section 8.2.7.3.
PHQ-9	X		X						X					X				X	X	
C-SSRS screening/ baseline	X																			

Procedure	Screening	Treatment Period													Follow-up Period				ED	Notes
Visits	1	2			3	4	5	6		7	8	9	10					11		
Weeks	-4 to -1	-1	1		3	5	7	8	9	11	13	15	16		17			18		
Days	-28 to -2	-1	1	2	3	15	29	43	56	57	71	85	99	112	113	114	116	126		
Window (days)						±2	±1	±2	±1		±2	±1	±2	±1				±3		
C-SSRS since last assessed			X			X	X	X	X		X	X	X	X				X	X	
Concomitant medication review	←	→	←																X	
AE/SAE review	←	→	←																X	
Laboratory Assessment																				
Screening tests	X																			Including ethanol testing, drug screen, HBV, HCV, and HIV related testing, thyroid-stimulating hormone, and others. See Section 10.2.
Calcitonin	X														X				X	
Pancreatic amylase	X		P												X				X	
Fasting lipase	X		P												X				X	
Pregnancy test (females only)	X		P												X			X	X	Serum pregnancy testing at screening. Urine pregnancy testing for WOCBP at all other time points.
FSH	X																			For females only whose menopausal status needs to be determined.
Hematology	X		P		P	P	P	P		P	P	P	P		X			X	X	P samples will be collected on dosing days.
Clinical chemistry	X		P		P	P	P	P		P	P	P	P		X			X	X	
Urinalysis	X		P		P	P	P	P		P	P	P	P		X			X	X	

Procedure	Screening	Treatment Period												Follow-up Period				ED	Notes
Visits	1	2			3	4	5	6		7	8	9	10				11		
Weeks	-4 to -1	-1	1		3	5	7	8	9	11	13	15	16	17			18		
Days	-28 to -2	-1	1	2	3	15	29	43	56	57	71	85	99	112	113	114	116	126		
Window (days)						±2	±1	±2	±1		±2	±1	±2	±1				±3		
PK sampling			P, 0.5, 1, 2, 4, 6, 8, and 12h	24 h (P)			P		P, 0.5, 1, 2, 4, 6, 8, and 12h	24h (P)		P		P, 0.5, 1, 2, 4, 6, 8, 12h	24h	48h	96h			See Section 8.4 for PK collection time windows for each time point.
Pharmacodynamic Laboratory Assessment																			
HbA1c	X		P							P					X				X	P samples will be collected on dosing days. Samples of HbA1c, fasting plasma glucose, fasting insulin, and fasting lipid panel will be analyzed at the central laboratory except screening.
Fasting plasma glucose	X		P				P			P		P			X				X	
Fasting insulin			P				P			P		P			X				X	
Fasting lipid panel	X		P				P			P		P			X				X	

Abbreviations: AE = adverse event; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; h = hour; HBV = hepatitis B virus; HbA1c = glycated hemoglobin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; P = predose; PHQ-9 = patient health questionnaire-9; PK = pharmacokinetic; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Schedule of Activities – Cohort 2

Procedure	Screening		Treatment Period											Notes
Visits	1		2			3	4		5	6	7	8		
Weeks	-4 to -1	-1	1			3	4	5	7	9	11	12	13	
Days	-28 to -2	-1	1	2	3	15	28	29	43	57	71	84	85	
Window (days)						±2	±1		±2	±1	±2	±1		
Informed consent	X													
Inclusion and exclusion criteria	X	X												
Randomization			X											
Participant admission to CRU		X					X					X		
Inpatient stay at CRU		X	X	X	X		X	X				X	X	
Participant discharge from CRU					X			X					X	
Outpatient visit	X					X			X	X	X			
Fasting	X		X	X	X	X	X	X	X	X	X	X	X	Overnight fasting of at least 8 hours.
Study intervention														
Study intervention dispense			X					X		X			X	
Diary dispense					X			X		X			X	
Clinical Assessment														
Medical history	X	X												
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	Complete physical examination at screening, and symptom-directed at other visits and as clinically indicated.
Height	X													
Weight	X		P			P		P	P	P	P		P	Weight will be measured twice for each participant in a consistent way using a calibrated scale.
Waist circumference	X		P			P		P	P	P	P		P	
Vital signs	X	X	P	X		P		P	P	P	P		P	Vital signs must be measured before blood sample collections, if applicable.
Body temperature	X													

Procedure	Screening		Treatment Period											Notes
Visits	1		2			3	4		5	6	7	8		
Weeks	-4 to -1	-1	1			3	4	5	7	9	11	12	13	
Days	-28 to -2	-1	1	2	3	15	28	29	43	57	71	84	85	
Window (days)						±2	±1		±2	±1	±2	±1		
Single 12-lead ECG	X		P	X		P		P	P	P	P		P	ECG must be recorded before collecting blood samples or vital signs, close to the time of the blood draw, and in a fasted state.
Hypoglycemia training					X									See Section 8.2.7.3.
PHQ-9	X		X				X					X		
C-SSRS screening/baseline	X													
C-SSRS since last assessed			X			X	X		X	X	X	X		
Concomitant medication review	←	→	←										→	
AE/SAE review	←	→	←										→	
Laboratory Assessment														
Screening tests	X													Including ethanol testing, drug screen, HBV, HCV, and HIV related testing, thyroid-stimulating hormone, and others. See Section 10.2.
Calcitonin	X													
Pancreatic amylase	X		P											
Fasting lipase	X		P											
Pregnancy test (females only)	X		P											Serum pregnancy testing at screening. Urine pregnancy testing for WOCBP at all other time points.
FSH	X													For females only whose menopausal status needs to be determined.
Hematology	X		P		P	P		P	P	P	P		P	P samples will be collected on dosing days.
Clinical chemistry	X		P		P	P		P	P	P	P		P	
Urinalysis	X		P		P	P		P	P	P	P		P	

Procedure	Screening		Treatment Period											Notes
Visits	1	2			3	4		5	6	7	8			
Weeks	-4 to -1	-1	1			3	4	5	7	9	11	12	13	
Days	-28 to -2	-1	1	2	3	15	28	29	43	57	71	84	85	
Window (days)						±2	±1		±2	±1	±2	±1		
PK sampling			P, 0.5, 1, 2, 4, 6, 8, and 12h	24h (P)			P, 0.5, 1, 2, 4, 6, 8, and 12h	24h (P)		P		P, 0.5, 1, 2, 4, 6, 8, and 12h	24h (P)	See Section 8.4 for PK collection time windows for each time point.
Pharmacodynamic Laboratory Assessment														
HbA1c	X		P							P				P samples will be collected on dosing days. Samples of HbA1c, fasting plasma glucose, fasting insulin, and fasting lipid panel will be analyzed at the central laboratory except screening.
Fasting plasma glucose	X		P					P		P			P	
Fasting insulin			P					P		P			P	
Fasting lipid panel	X		P					P		P			P	

Abbreviations: AE = adverse event; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FSH = follicle-stimulating hormone; h = hour; HBV = hepatitis B virus; HbA1c = glycated hemoglobin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; P = predose; PHQ-9 = patient health questionnaire-9; PK = pharmacokinetic; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Schedule of Activities – Cohort 2 (Continued)

Procedure	Treatment Period							Follow-up Period				ED	Notes
Visits	9	10	11	12		13	14				15		
Weeks	15	17	19	20	21	23	24	25			26		
Days	99	113	127	140	141	155	168	169	170	172	182		
Window (days)	±2	±1	±2	±1		±2	±1				±3		
Participant admission to CRU				X			X						
Inpatient stay at CRU				X	X		X	X	X				
Participant discharge from CRU					X				X				
Outpatient visit	X	X	X			X				X	X		
Fasting	X	X	X	X	X	X	X	X			X	X	Overnight fasting of at least 8 hours.
Study intervention													
Study intervention dispense		X			X								
Diary dispense		X			X								
Clinical Assessment													
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	Complete physical examination at screening, and symptom-directed at other visits and as clinically indicated.
Weight	P	P	P		P	P		X			X	X	Weight will be measured twice for each participant in a consistent way using a calibrated scale.
Waist circumference	P	P	P		P	P		X			X	X	
Vital signs	P	P	P		P	P		X			X	X	Vital signs must be measured before any blood sample collections, if applicable.
Single 12-lead ECG	P	P	P		P	P		X			X	X	ECG must be recorded before collecting blood samples or vital signs measurements, close to the time of the blood draw, and in a fasted state.
PHQ-9				X			X				X	X	
C-SSRS since last assessed	X	X	X	X		X	X				X	X	

Procedure	Treatment Period							Follow-up Period				ED	Notes
Visits	9	10	11	12		13	14				15		
Weeks	15	17	19	20	21	23	24	25			26		
Days	99	113	127	140	141	155	168	169	170	172	182		
Window (days)	±2	±1	±2	±1		±2	±1				±3		
Concomitant medication review	←	←	←	←	←	←	←	←	←	←	→	X	
AE/SAE review	←	←	←	←	←	←	←	←	←	←	→	X	
Laboratory Assessment													
Calcitonin								X				X	
Pancreatic amylase								X				X	
Fasting lipase								X				X	
Pregnancy test (females only)								X			X	X	Serum pregnancy testing at screening. Urine pregnancy testing for WOCBP at all other time points.
Hematology	P	P	P		P	P		X			X	X	P samples will be collected on dosing days
Clinical chemistry	P	P	P		P	P		X			X	X	
Urinalysis	P	P	P		P	P		X			X	X	
PK sampling		P		P, 0.5, 1, 2, 4, 6, 8, and 12h	24h (P)		P, 0.5, 1, 2, 4, 6, 8, and 12h	24h	48h	96h			See Section 8.4 for PK collection time windows for each time point.
Pharmacodynamic Laboratory Assessment													
HbA1c		P						X				X	P samples will be collected on dosing days. Samples of HbA1c, fasting plasma glucose, fasting insulin, and fasting lipid panel will be analyzed at the central laboratory except screening.
Fasting plasma glucose		P			P			X				X	
Fasted insulin		P			P			X				X	
Fasting lipid panel		P			P			X				X	

Abbreviations: AE = adverse event; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; h = hour; HBV = hepatitis B virus; HbA1c = glycated hemoglobin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; P = predose; PHQ-9 = patient health questionnaire-9; PK = pharmacokinetic; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

2. Introduction

LY3502970 is a chemically synthesized, oral GLP-1RA being developed as a daily oral therapy as an adjunct to diet and exercise to improve weight management in adults who have obesity or are overweight with weight-related comorbidities.

2.1. Study Rationale

Study J2A-GH-GZGX (GZGX) is a Phase 1, multiple dose titration study designed to investigate the safety, tolerability, PK, and PD of LY3502970 following oral administration of multiple QD doses for 16 weeks in Cohort 1 and 24 weeks in Cohort 2 in Chinese participants who have obesity or are overweight with weight-related comorbidities.

PK data from previous Phase 1 clinical studies supported QD administration of LY3502970 and found LY3502970 to be safe and well tolerated in the proposed dose ranges for this study. A SAD and MAD LY3502970 study (Study J2A-JE-GZGB) has been performed in Japanese participants with T2DM. The current study is intended to obtain sufficient safety, tolerability, PK, and PD data with preliminary efficacy measurements to support identification of an appropriate dose range for subsequent clinical studies of LY3502970 in the Chinese population.

2.2. Background

LY3502970 is being investigated for its potential use in weight management. LY3502970 is a chemically synthesized molecule that shows agonist activity for GLP-1 receptor. To date, the safety profile of LY3502970 is consistent with other GLP-1RAs.

The GLP-1RAs are highly effective drugs that mimic the incretin hormone GLP-1 (Werner et al. 2010; Lau et al. 2015; Scheen 2017). The hormone is secreted from the intestine upon food consumption, and its effects include augmented glucose-dependent insulin secretion, prolonged satiety, reduced glucagon release, and delayed gastric emptying (Bayliss and Starling 1902; Baggio and Drucker 2007; Nauck et al. 1997). The GLP-1RAs have demonstrated beneficial effects on weight management (Frias et al. 2018; Newsome et al. 2019). Furthermore, liraglutide and semaglutide (SAXENDA® package insert, 2014; WEGOVY™ package insert, 2021) both injectable peptide GLP-1RAs, have been shown to be safe and effective for weight management and have established cardiovascular safety.

Obesity is a chronic disease, and its increasing prevalence is a public health concern associated with rising incidence of T2DM, increased risk for premature death, and increased risk for some cancers (American Medical Association 2013; Council on Science and Public Health 2013; Lauby-Secretan et al. 2016). There remains an unmet need in the pharmacologic treatment of obesity for drugs that are safe, efficacious, well tolerated, and easy to use. There are currently only a few FDA-approved medications for long-term use for the treatment of obesity that yield a placebo adjusted average weight loss between 3% and 7% (Srivastava and Apovian 2018; FDA 2020). Although moderate weight loss of 5% to 10% in individuals with obesity or overweight has long been shown to yield significant metabolic benefits, including improvements in cholesterol, BP, and glucose parameters (Goldstein 1992; Wing et al. 2011), greater weight loss can maximize these benefits and may be required to realize clinically meaningful improvements in other weight-related comorbidities, such as sleep apnea, nonalcoholic steatohepatitis, and

cardiovascular disease (Ryan and Yockey 2017). In addition to moderate efficacy, some centrally acting weight-loss agents to date have had adverse neurocognitive, psychiatric, or cardiovascular effects, further limiting their application in clinical practice (Srivastava and Apovian 2018). The development program for LY3502970 is to demonstrate that this oral non-peptide molecule has benefits on weight management and glucose control similar to that observed with injectable GLP-1RAs with the convenience of an oral medication.

The safety, tolerability, and PK/PD of LY3502970 has been evaluated in 5 Phase 1 clinical pharmacology studies, J2A-MC-GZGA (GZGA), J2A-MC-GZGC (GZGC), J2A-MC-GZGD(GZGD), J2A-MC-GZGJ (GZGJ), and J2A-MC-GZGF (GZGF). Study J2A-MC-GZGG (GZGG) was an additional completed study in which LY3502970 was not administered. Study GZGA was a SAD and a 4-week MAD study in healthy volunteers that evaluated the safety, tolerability, PK, and PD of LY3502970. Study GZGC was a multiple dose study in participants with T2DM designed to evaluate the safety, tolerability, PK, and PD of LY3502970 following 12 weeks of treatment. Study GZGD was a randomized, partially participant-blind, crossover study in healthy participants to investigate the safety, tolerability, and PK of multiple oral doses of LY3502970 formulation prototypes in healthy participants. Study GZGJ was a randomized, open-label, crossover study that was conducted to assess PK, safety, and tolerability of LY3502970 in healthy participants in fed and fasted state. Study GZGF was an open-label study to determine the disposition of radioactivity and PK of LY3502970 and total radioactivity in healthy male participants .

In **Study GZGA**, the SAD part of the study evaluated single oral doses of CCI mg. The MAD part of the study evaluated 28 daily LY3502970 doses of CCI mg and weekly dose escalation doses evaluating different dose escalation schemes that ranged from CCI mg through CCI mg with terminal doses of CCI mg. In both parts, GI-related AEs were the most commonly reported AEs, consistent with GLP-1 agonist pharmacology (Nauck et al. 2009; Dungan et al. 2014; Giorgino et al. 2015; Jendle et al. 2016; Nauck et al. 2016). All AEs were mild or moderate in severity and consistent with other GLP-1RAs; the incidence of GI AEs decreased with continued dosing in the MAD, thus demonstrating tachyphylaxis to the GI AEs. The MAD showed that LY3502970 initially delayed gastric emptying, an effect that was greatly diminished with continued exposure similar to marketed GLP-1RA drugs. Furthermore, LY3502970 showed a decrease in glucose and body weight. This study also assessed the effect of food on the PK of LY3502970. The effect of food on the PK of LY3502970 was a slight decrease in the AUC.

There has been no apparent concentration-dependent increase in systolic or diastolic BP after single or multiple doses or in PR after single doses. There has been a trend in an increase in PR after multiple doses of LY3502970, similar to that observed with other GLP-1RAs. However, 1 known effect of GLP-1RAs is to increase HR, usually with either no change or a mild reduction in BP (Lorenz et al. 2017). Changes in HR attenuate over time (Sun et al. 2015; Marso et al. 2016; Holman et al. 2017; Lorenz et al. 2017), and in long-term cardiovascular outcomes studies, GLP-1RAs have been associated with reduced risk for major adverse cardiovascular events (Drucker et al. 2018). The mechanisms by which GLP-1RAs increase HR are not fully understood, with recent studies suggesting direct stimulation of the sinoatrial node, although activation of the sympathetic nervous system, or reduction of systemic vascular resistance has not been excluded (Bharucha et al. 2008; Mendis et al. 2012; Smits et al. 2017).

LY3502970 PK was studied across a range of doses administered as single doses or multiple doses (28 doses) via a QD dosing regimen. LY3502970 PK appeared dose proportional over the dose range studied after a single and multiple doses from CCI mg. Peak concentrations were observed at approximately 4 to 16 hours postdose, and the half-life was approximately 24.6 to 35.3 hours for single doses and 48.1 to 67.5 hours for multiple doses.

Study GZGC evaluated LY3502970 treatment for 12 weeks in participants with T2DM controlled with diet and physical activity with or without a stable dose of metformin. Study GZGC included 5 dosing cohorts evaluating different target doses and dose escalations. Dose escalations occurred weekly to the target dose and then maintained at the target dose for the duration of the study. The following were the dosing cohorts:

- Cohort A: CCI mg,
- Cohort B: CCI mg,
- Cohort C: CCI mg,
- Cohort D: CCI mg, and
- Cohort E: CCI mg.

Preliminary data indicate that the most frequently reported AEs in Study GZGC were nausea, decreased appetite, and vomiting. Consistent with other GLP-1RAs, the AEs were more frequent early in the study and at the initiation of each dose escalation but diminished with continued dosing. No off-target AEs have been observed to date. LY3502970 treatment demonstrated a decrease in serum glucose and a decrease in 6-point self-monitoring blood glucose levels. There also has been a decrease in HbA1c and body weight. An increase in PR has been observed, which is of a similar magnitude as seen in other early-phase studies of GLP-1RAs. There have been no clinically significant effects on ECG parameters or other laboratory parameters noted to date.

Study GZGJ evaluated LY3502970 treatment in Asian healthy participants under fasted and fed state. Study GZGJ consisted of dose titration period and test period. Within-treatment dose escalation was applied following several intermediate dose levels and up to a final dose for testing.

Following multiple oral stable doses of LY3502970 CCI mg QD to healthy participants during test periods, overall mean exposure to LY3502970 based on $AUC_{(0-24)}$ and C_{max} was approximately 17.6% to 20.9% lower when administered after a high-fat, high-calorie meal than in the fasted state, whereas median t_{max} was unaffected between the feeding states.

The safety profile of LY3502970 from the study is consistent with the known safety profiles of other compounds in the GLP-1RA pharmaceutical class.

2.3. Benefit/Risk Assessment

No safety or tolerability concerns that preclude further investigation of LY3502970 have been identified in 173 healthy participants and 51 participants with T2DM to date, up to the highest single dose given of CCI mg and multiple dose given of CCI mg. No clinically significant safety or tolerability concerns have been identified in participants to date for LY3502970 up to CCI mg in participants with T2DM.

To mitigate the well-known GI tolerability issues of GLP-1RA, participants will be assigned a treatment regimen that includes a starting dose of [redacted] mg daily and increasing or escalating doses of LY3502970. Before each dose-titration step, the CP or CRP may assess the safety and tolerability data of each participant and decide if they should continue with the assigned treatment regimen. It is anticipated that these dose-titration steps will occur approximately every 4 weeks to a maximum of [redacted] mg in Cohort 1 and [redacted] mg in Cohort 2.

Data from Phase 1 studies indicate that LY3502970 treatment may result in a decrease in body weight. These data support improved weight management in participants with obesity or are overweight with weight-related comorbidities.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY3502970 are described in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of LY3502970 following multiple oral QD doses in Chinese participants with obesity or who are overweight with weight-related comorbidities.	• Number and incidence of TEAEs and SAEs.
Secondary	
• To characterize the PK profile of LY3502970 following multiple oral QD doses in Chinese participants with obesity or who are overweight with weight-related comorbidities. • To characterize the PD effects of LY3502970 following multiple oral QD doses in Chinese participants with obesity or who are overweight with weight-related comorbidities.	• C_{max} and $AUC_{(0-24)}$ • Changes from baseline in: – body weight – body mass index – waist circumference. • Changes from baseline in: – fasting plasma glucose – fasting insulin – HbA1c – lipid profiles.

Abbreviations: $AUC_{(0-24)}$ = area under the concentration versus time curve from time 0 to 24 hour time point; C_{max} = maximum observed drug concentration; HbA1c = glycated hemoglobin; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study J2A-GH-GZGX (GZGX) is a Phase 1, investigator- and participant-blind, 2-cohort, randomized, placebo-controlled, 16-week (Cohort 1) and 24-week (Cohort 2) multiple dose titration study in Chinese participants with obesity or who are overweight with weight-related comorbidities. See Inclusion Criteria [5] in Section 5.1 for the definition of weight-related comorbidities.

The schema in Section 1.2 illustrates the study design. Safety, PD, and PK assessments will be performed according to the SoA in Section 1.3.

Screening

All participants will be screened within 28 days prior to Day 1 and screening procedures will be conducted according to Section 1.3.

Treatment and Assessment Period

Participants may be admitted to the CRU in advance if judged to be required by the investigator. It is intended that eligible participants will attend an inpatient visit at the CRU on Days -1, 56, and 112 for Cohort 1 and on Days -1, 28, 84, 140, and 168 for Cohort 2.

On Day 1, participants will be randomized 10:2 to either LY3502970 or placebo, and 1:1 to Cohort 1 or 2, with a computer-generated allocation code using an IWRS, as detailed in Section 6.3.

Overall, approximately 24 Chinese participants may be enrolled. Approximately 12 participants in each cohort will be randomized (10 participants to LY3502970 and 2 participants to placebo) to ensure approximately 8 participants receiving LY3502970 in each cohort complete the study.

From Day 1 to Day 112 of Cohort 1, participants will receive an oral QD dose of LY3502970 at 4 dose levels, or placebo. From Day 1 to Day 168 of Cohort 2, participants will receive an oral QD dose at 6 dose levels of LY3502970, or placebo.

Prior to discharge from the CRU (Day 3), participants will be instructed on the symptoms and treatment of hypoglycemia. Participants may be allowed to leave the CRU after completing assessments on Days 3, 57, and 114 for Cohort 1 and on Days 3, 29, 85, 141, and 170 for Cohort 2, or later at the investigator's discretion. Participants will return for outpatient visits for PK sampling and PD and safety assessments at predefined times. Participants may be required to remain at the CRU longer than the planned days at the investigator's discretion.

Progression of Cohorts through Study GZGX

Two cohorts are planned. Participants will be randomized to 1 of 2 cohorts comprising approximately 12 participants each. Participants will be randomized to receive stepwise dose titration of either LY3502970 or corresponding placebo for 16 weeks in Cohort 1 and 24 weeks in Cohort 2. Participants will receive a stepwise dose titration of LY3502970 or placebo, with each dose level administered for 4 weeks as shown:

- Cohort 1
  - LY3502970 Level 1; [redacted] mg for 4 weeks,
  - LY3502970 Level 2; [redacted] mg for 4 weeks,
  - LY3502970 Level 3; [redacted] mg for 4 weeks,
  - LY3502970 Level 4; [redacted] mg for 4 weeks.
- Cohort 2
  - LY3502970 Level 1; [redacted] mg for 4 weeks,
  - LY3502970 Level 2; [redacted] mg for 4 weeks,
  - LY3502970 Level 3; [redacted] mg for 4 weeks,
  - LY3502970 Level 4; [redacted] mg for 4 weeks,
  - LY3502970 Level 5; [redacted] mg for 4 weeks,
  - LY3502970 Level 6; [redacted] mg for 4 weeks.

In Cohort 2, the duration of titration steps may be amended, and additional step-through doses may be added based on data obtained from Cohort 1. In addition, the dosage and dose titration scheme for either cohort may be further modified based on emerging safety and tolerability data. Any changes to the planned dose will be reviewed and approved by the sponsor and the investigator.

Safety data review will be planned for progression between stepwise dose titration within cohorts. The investigator and Lilly CP or CRP may review all available safety data including AEs, vital signs, ECGs, body weight, safety laboratory measurements, and physical assessments. Any available PK or PD data may also be considered for dose titrations. Individual patient data will not be made available to the investigator to avoid unblinding.

If the investigator decides not to up-titrate the dose level as planned for individual participants for any reason, participants should be discontinued for doses equal to or less than [redacted] mg. Participants may remain at the current dose level for doses greater than [redacted] mg through to the last planned dose on Day 112 for Cohort 1 or on Day 168 for Cohort 2, as detailed in Section 6.6. See Section 6.6.3 for more information on dose up-titration stopping criteria.

Follow-up Period

Following the final assessments between Days 113 and 116 for Cohort 1 and Days 169 to 172 for Cohort 2, as detailed in the SoA, a follow-up visit approximately 2 weeks after the last dose of study intervention will be performed.

4.2. Scientific Rationale for Study Design

This study will evaluate the multiple dose titration regimen of LY3502970 in Chinese participants with obesity or who are overweight with weight-related comorbidities. Participants with obesity or who are overweight with weight-related comorbidities will be enrolled, rather than healthy participants, to evaluate the body weight loss effects of LY3502970 more accurately. The doses will be escalated within each treatment group in order to reach higher dose exposures and improve the GI tolerability for GLP-1RA class. The 16- and 24-week treatment durations for Cohorts 1 and 2 will provide sufficient data to assess the safety, tolerability, PK, and PD of LY3502970.

The 2-cohort study design will allow up-titration regimens to 2 anticipated medium and high treatment dose levels that are consistent with pivotal studies in participants with obesity or weight-related comorbidities. The use of 2 concurrent cohorts will allow dense PK sampling at each LY3502970 dose level without subjecting participants to excessive blood collection, and will also increase the probability of participant compliance and completion of the study. Low ethnic sensitivity of LY3502970 is anticipated, partially based on previous results including Study GZGJ which was conducted in Singapore using healthy Asian participants mostly composed of Chinese participants. PK data of CCI mg QD LY3502970 doses was generally comparable to data from previous studies conducted using non-Asian participants under testing dose, with consistent safety profiles. Study GZGX will investigate the PK of higher LY3502970 doses (CCI mg) in Chinese-only participants.

Participants with a BMI equal to or greater than 30.0 kg/m^2 or a BMI between 27.0 up to 30.0 kg/m^2, with at least 1 weight-related comorbidity were chosen to align with other completed or upcoming LY3502970 studies. The BMIs chosen fit Chinese criteria for obese and overweight participants.

Safety and tolerability assessments will be made across all dose levels, including AE and SAE review, evaluation of ECGs, vital signs, and clinical safety laboratory tests during the study.

The participant- and investigator-blinded, randomized, placebo-controlled design minimizes the bias on safety and tolerability assessments and allows for a strong comparison between LY3502970 and placebo.

To minimize the potential confounding effect of changes in concomitant medications, participants will be permitted to use concomitant medications that do not interfere with the assessment of efficacy or safety characteristics of the study intervention.

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

4.3. Justification for Dose

LY3502970 doses of CCI mg administered orally QD were selected based on the following:

- In the single and a 4-week multiple dose study in healthy participants, GZGA, LY3502970 doses through CCI mg were safe and well tolerated following dose titration.
- In the 12-week study, GZGC, in participants with T2DM, LY3502970 doses between CCI mg were safe and well tolerated following dose titration. Furthermore, LY3502970 doses through CCI mg appear to lower glucose and body weight.
- In the 7-week multiple dose study in healthy participants, GZGJ, LY3502970 doses through CCI mg were safe and well tolerated following dose titration.
- A low ethnic sensitivity of the GLP-1RA drug class has been observed in early phase studies, and for participants with T2DM, chronic weight management, or both.

High acute doses of GLP-1RAs, including LY3502970, are often poorly tolerated due to GI symptoms, whereas a more gradual dose titration scheme to reach a high dose has been shown to improve GLP-1RA tolerability. Dosing algorithms starting at a low dose of CCI mg accompanied by dose up-titration every 4 weeks would permit adequate time for development of

tolerance to GI events and are predicted to minimize GI tolerability concerns. The selected dose range and titration scheme would enable further evaluation of benefit and risk considerations of LY3502970.

4.4. End of Study Definition

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

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit shown in the SoA in Section 1.3. If any assessments are missed, the designation of completer can be determined by the sponsor.

5. Study Population

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 ECGs. 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 only unless otherwise specified, and not continuously throughout the trial.

Screening may occur up to 28 days prior to enrollment. Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and clinical measurements to confirm their eligibility. In such instances, repeat the following screening tests and procedures: medical assessments (for example, medical history, concomitant medicine, vital signs, and physical examination) and clinical measurements at the discretion of the investigator.

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

5.1. Inclusion Criteria

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

Age

1. are 18 to 65 years of age, inclusive, at the time of signing the informed consent .

Type of Participant and Disease Characteristics

2. are native Chinese. To qualify as native Chinese, the participant, the participant's biological parents, and all 4 of the participant's biological grandparents must be of Chinese origin.
3. have had a stable body weight, in other words, less than 5% body weight change for the 3 months prior to randomization.
4. have clinical laboratory test results within a normal range for the population or investigative site (if not defined according to the protocol), or results with acceptable deviations that are judged to be not clinically significant by the investigator.

Weight

5. have a BMI:
   - equal to or greater than 30.0 kg/m^2, or
   - between 27.0 up to 30.0 kg/m^2, with at least 1 of the following weight-related comorbidities including:
     a. hypertension: on BP -lowering medication or having systolic BP equal to or greater than 130 mmHg or diastolic BP equal to or greater than 80 mmHg at screening,
     b. dyslipidemia:
        i. on lipid lowering medication,

ii. having low-density lipoprotein equal to or greater than 160 mg/dL (4.1 mmol/L),

iii. triglycerides equal to or greater than 150 mg/dL (1.7 mmol/L),

iv. or -high density lipoprotein less than 40 mg/dL (1.0 mmol/L) for men or -high density lipoprotein less than 50 mg/dL (1.3 mmol/L) for women at screening,

c. cardiovascular disease: (for example, ischemic cardiovascular disease, New York Heart Association Functional Classification Class I-II heart failure. See Section 10.8), or

d. obstructive sleep apnea (only in participants greater than 30 years of age).

Sex and Contraceptive/Barrier Requirements

are male or female. WOCBP and WNOCBP may participate in this trial. Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Appendix 4 in Section 10.4.

Informed Consent

6. are capable of giving signed informed consent as described in Appendix 1 in Section 10.1.2, which includes compliance with the requirements and restrictions listed in the ICF and this protocol.

Other Inclusion Criteria

7. have venous access sufficient to allow for blood sampling as per the protocol.
8. are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

5.2. Exclusion Criteria

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

Medical Conditions

9. have any prior diagnosis of T1DM or T2DM, or rare forms of diabetes mellitus.
10. are overweight or have obesity induced by other endocrinological disorders, for example, Cushing's syndrome, diagnosed monogenetic, or syndromic forms of obesity, for example, Melanocortin 4 Receptor deficiency or Prader-Willi Syndrome.
11. have significant previous or current history of comorbidities capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data.
12. have a history or presence of psychiatric disorders.
13. are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.

14. have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS **or** have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS, **and** the ideation or behavior occurred within the past month.
15. have a moderately severe or severe depression status by PHQ-9 score of 15 or more.
16. have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
17. have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty, if performed greater than 1 year prior to screening).
18. have or plan to have endoscopic or device based therapy for obesity or have had device removal within the last 6 months prior to screening including but not limited to:
    - mucosal ablation,
    - gastric artery embolization,
    - intragastric balloon, and
    - duodenal-jejunal endoluminal liner.
19. have any of the following cardiovascular conditions within 3 months prior to screening:
    - acute myocardial infarction,
    - stroke,
    - unstable angina,
    - hospitalization due to CHF,
    - coronary artery bypass graft,
    - transient ischemic attack, or
    - percutaneous coronary intervention (diagnostic angiograms are permitted)

    .
20. have a history of New York Heart Assocation Functional Classification III or IV CHF.
21. ongoing or history of frequent intermittent or chronic tachyarrhythmia syndromes.
22. have a history of additional risk factors for Torsades de Pointes (for example, heart failure, hypokalemia, or family history of Long QT Syndrome).
23. have a known clinically significant gastric emptying abnormality , or have undergone gastric bypass (bariatric) surgery, sleeve gastrectomy, or restrictive bariatric surgery.
24. have a history of acute or chronic pancreatitis. A participant with a history of acute pancreatitis caused by gallstones may be included in the study if the participant has a cholecystectomy to resolve the problem.
25. have a history of clinically significant gallbladder disease. However, participants with cholecystectomy may be included in the study.
26. have signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease.
27. have evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone that, in the opinion of the investigator, would pose a risk to participant safety. Participants on a stable dose of thyroid replacement therapy for at least the prior 3 months who are clinically euthyroid and who are

anticipated to remain on this dose throughout the trial period may be eligible if they meet the other criteria.

28. have a known self or family history, specifically a first-degree relative, of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma.
29. have evidence of a significant, uncontrolled endocrine abnormality in the opinion of the investigator.
30. have evidence of a significant, active autoimmune abnormality that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids during the study period.
31. have other acute, chronic, or uncontrolled medical conditions including recent, in other words, within the past year, active suicidal ideation, behavior, or laboratory abnormality that may increase the risk associated with study participation, study intervention administration, or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy

32. have used or intend to use any prescription or over-the-counter medications or traditional Chinese treatments within 3 months prior to screening and throughout the study with the exception of vitamin or mineral supplements, occasional paracetamol, and prescription medications for the treatment of concurrent medical conditions such as thyroid replacement, antihypertensive agents, antiplatelet drugs, or lipid-lowering agents with a stable dose for at least 3 months prior to enrollment .
33. are receiving or have received, within 3 months prior to screening, chronic (which is defined as occurring for greater than 2 weeks), systemic glucocorticoid therapy.
34. are receiving or have received within 3 months prior to screening, medications that may cause significant weight gain. Participants at a stable dose for greater than 6 months and with no expectation that the dose will change within the next year, and who are weight stable for the last 6 months on these medications may be included in the study.
35. have started subcutaneous, intramuscular, implantable, or injectable contraceptives within 18 months prior to screening.
36. are receiving or have taken within 3 months prior to screening, prescribed or over the counter medications or alternative remedies including herbal or nutritional supplements intended to promote weight loss.
37. are receiving or have taken within 3 months prior to screening, metformin, or any other glucose-lowering medication.
38. initiated or changed hormone therapy, for example, estrogen and progesterone, within 3 months prior to screening. Hormone replacement therapy in postmenopausal women is allowed but women must be on stable therapy for 3 months prior to screening.
39. are receiving strong CYP3A inhibitors, strong CYP3A inducers, strong OATP inhibitors, or drugs that are P-gp or BCRP substrates with a narrow therapeutic index. See Appendix 12 in Section 10.12 for examples of excluded concomitant medication.

40. use concomitant medications that prolong the QT/QTc interval.
41. are chronically taking medications that directly affect GI motility.
42. are currently taking a central nervous system stimulant with the exception of caffeinated beverages.

Prior/Concurrent Clinical Study Experience

43. have known allergies to GLP-1RAs, LY3502970, related compounds, any components of the formulation, or have a history of significant atopy.
44. have had any exposure to GLP-1 analogs, or other related compounds within the prior 3 months.
45. have participated, within the last 30 days or 5 half-lives, whichever is longer, in a clinical study involving an investigational product.
46. have previously completed or withdrawn from this study or any other study investigating LY3502970.

Diagnostic Assessments

47. have at least 1 laboratory value suggestive of diabetes during screening, including 1 or more HbA1c level of 6.5% (48 mmol/mol) or above, fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or above, or random glucose level of 200 mg/dL (11.1 mmol/L) or above.
48. have at least 1 laboratory value suggestive of liver disease during screening, including ALT level greater than 3.0× ULN for the reference range, ALP level greater than 1.5× ULN for the reference range, or TBL greater than 1.5× ULN for the reference range (except for cases of known Gilbert's Syndrome).
49. have triglycerides greater than 500 mg/dL (5.7 mmol/L). If the participant is on lipid-lowering therapies, doses must be stable for 3 months prior to enrollment.
50. have a serum calcitonin level of:
    - equal to or greater than 20 ng/L, if eGFR is greater than or equal to 60 mL/min/1.73 m^2, or
    - equal to or greater than 35 ng/L if eGFR less than 60 mL/min/1.73 m^2.
51. have renal impairment measured as eGFR less than 30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology Collaboration as determined at screening.
52. have poorly controlled hypertension indicated by systolic BP of equal to or greater than 160 mmHg or diastolic BP equal to or greater than 100 mmHg at screening (excluding white-coat hypertension; therefore, if a repeated measurement shows values within the range, the participant can be included in the trial).
53. have a resting pulse rate of greater than 100 bpm or less than 50 bpm.
54. have an ECG with abnormalities, as considered by the investigator, that increase the risks associated with participating in the study, such as QTcF greater than 450 msec for male participants or QTcF greater than 470 msec for female participants or QRS interval greater than 120 msec for all participants.
55. show evidence of HIV infection, or positive HIV antibodies, or both.

56. have evidence of current infection of hepatitis B and/or test positive for hepatitis B virus at screening, defined as:
    a. positive for hepatitis B surface antigen, or
    b. positive for anti-hepatitis B core antibody in conjunction with a positive confirmatory polymerase chain reaction for hepatitis B virus DNA.

Note: Participants who are positive for anti-hepatitis B core antibody and hepatitis B virus DNA negative may be enrolled in the study.

57. show evidence of hepatitis C and/or positive hepatitis C antibody.

Other Exclusion Criteria

58. are lactating.
59. regularly use known drugs of abuse or show positive findings on drug screening that is not consistent with their medication history.
60. have had a blood donation of equal to or greater than 500 mL within the previous 8 weeks of study screening, a blood transfusion or severe blood loss within the prior 3 months, or have any hematologic condition or hemoglobin value less than 11 g/dL in males or less than 10 g/dL in females that may interfere with HbA1c measurement.
61. have an average weekly alcohol intake that exceeds 21 units per week in males and 14 units per week in females or are unwilling to stop alcohol consumption from 24 hours prior to CRU admission days, until the participant has been discharged from the CRU. Number of units = (total volume of drink [mL] × alcohol by volume [%])/1000.
62. smoke more than 10 cigarettes per day, or equivalent, or are unable to abide by investigative site smoking restrictions.
63. in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.
64. are unwilling to comply with the dietary restrictions required for this study.
65. have previously completed or withdrawn from the study.
66. are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
67. are employees of Eli Lilly and Company or the investigative site.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants will be required to be in a fasting state, after an overnight fast of at least 8 hours, except for water, for outpatient and residential visits as specified in the SoA in Section 1.3.

While self-administering study intervention at home, participants will take their dose before breakfast in the morning, but if they forget, it can be taken later that day.

When not resident at the CRU, participants will be encouraged to maintain their usual dietary habits during the study.

Participants should follow the diet recommendations provided by the study site or given in Appendix 5 in Section 10.5.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

Caffeine

Participants will be allowed to maintain their regular caffeine consumption throughout the study period, unless CRU confinement period restrictions require otherwise.

Alcohol

Alcohol consumption is not permitted while participants are resident at the CRU and for 24 hours prior to each study visit.

Tobacco

Participants must abide by the CRU smoking restrictions during study visits and while resident at the CRU. Smoking, and use of other tobacco- or nicotine-containing products, will be limited during the study confinement according to the CRU guidelines. Smoking, and use of other tobacco- or nicotine-containing products, will also not be permitted for 1 hour before assessments of vital signs and ECG.

5.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity and exercise during the study, but will abstain from strenuous exercise for 24 hours prior to any visit in which laboratory safety tests will occur. While certain study procedures are in progress at the site, participants may be required to remain supine or sitting.

Participants should follow the physical activity recommendations provided by the study site or given in Appendix 5 in Section 10.5.

5.3.4. Other Restrictions

Study participants will be instructed not to donate blood or blood products during the study or for 90 days following the study.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened generally. If, in the opinion of the investigator, an ineligible laboratory test result is the result of an error or extenuating circumstance, then that parameter can be retested once soon during screening period.

5.5. Criteria for Temporarily Delaying Enrollment, Randomization, or Administration of Study Intervention of a Participant

Not applicable.

6. Study Interventions and Concomitant Therapy

Study intervention is defined as any investigational interventions, marketed products, placebo, or medical devices intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Interventions Administered

While inpatient in the CRU, LY3502970 or placebo will be administered orally each day with approximately 200 mL of room temperature water in the morning of each dosing day in a sitting position, following an overnight fast of at least 8 hours. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

When participants self-administer study intervention at home, they will be advised to take 1 capsule of the correct dosage of LY3502970 or a placebo capsule orally with approximately 200 mL of room temperature water before breakfast in the morning, but if they forget, it can be taken later that day and recorded in the participant diary.

lists the interventions used in this clinical study.

Table GZGX.1. Study Interventions Administered

Intervention Name	LY3502970	Placebo
Type	Drug	Placebo
Dose Formulation	Capsule	Capsule
Unit Dose Strength(s)	[redacted] mg capsule [redacted] mg capsule [redacted] mg capsule [redacted] mg capsule [redacted] mg capsule [redacted] mg capsule	Capsule of LY – placebo to match
Route of Administration	Oral	Oral
Use	Experimental	Placebo

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current good manufacturing practice. 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 interventions received and that 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 interventions 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 separately. In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention and cohort using an IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits summarized in SoA in Section 1.3. Returned study intervention should not be redispensed to the participants. This is a double-blind study in which participants, investigators, and site personnel are blinded to study intervention. The IWRS will be programmed with blind-breaking instructions.

6.4. Blinding

This is a participant- and investigator-blinded study. To preserve the blinding of the study for LY3502970 and placebo, all study site personnel will be blinded to treatment allocation.

All doses of study drug capsules appear the same. Furthermore, placebo capsules look like study drug capsules to maintain blinding.

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

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

Blinding will be maintained throughout the conduct of the study as described in the blinding and unblinding plan section of the SAP or in a separate document.

6.5. Study Intervention Compliance

When participants are dosed at the site, study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing by a member of the CRU staff other than the person administering the study intervention. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by review of the participants' diaries by site staff during the site visits. This will be documented in the source documents and CRF. Participants will be advised to self-administer study intervention before breakfast in the morning, but if they forget it can be taken later that day. Doses that are late by more than 12 hours as planned should not be made up and recorded in the dosing diary as missed. Reasons should be recorded for any missed dose. Vomiting after dosing should be noted in the diary and a vomited dose should not be re-dosed or replaced. A record of the number of capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and dose reductions, will also be recorded in the CRF.

Participants who are significantly noncompliant will be discontinued from the study. The assessment of study intervention compliance will be determined by:

- information about study intervention administered at home by the participant via the participant's diary,
- information about the participant's adherence to the SoA, and
- information about any other parameters the investigator considers necessary.

6.6. Dose Modification

6.6.1. Dose Titration

All available safety and tolerability data will be reviewed routinely. Safety data will be the primary criteria for the step-wise dose titration. Safety parameters to be assessed will include all available data from AEs, vital signs, ECGs, body weight, safety laboratory measurements, and physical assessments. In addition, if available at the time of the dose titration decision, PK and PD data may be used as supporting data for dose titration, but such data are not required.

If a dose is tolerated, the dose should be increased per original protocol dose titration. If it is decided not to up-titrate to the dose level as planned for individual participants for any reason, if the participant is at doses equal to or less than [redacted] mg that participant should be discontinued. A participant at doses equal to or greater than [redacted] mg may remain at the current dose level through to the last planned dose on Day 112 for Cohort 1 or on Day 168 for Cohort 2.

Dose levels, titration scheme, sampling schedule, timing of procedures, and length of CRU stay may be adjusted in view of emerging safety or PK or PD data during the study. These changes must be appropriately documented and communicated by the sponsor to the investigator.

6.6.2. Dose Titration Delay

Titration delay will be permitted once for a participant with study intervention at doses equal to or greater than [redacted] mg. Use of study treatment at the current dose level can be extended in a participant for up to 14 days due to a persisting drug-related AE or any other reason, at the discretion of the investigator and after consultation with Lilly. The participant may restart up-titration if it is considered tolerable and feasible to continue study intervention in the next dose level as soon as possible. This means that the participant may catch up with his or her original schedule and dose levels in the following titration decisions, if available. No treatment period extension and no skipping of dose levels will be allowed.

In order to maintain blinding to study intervention, the site should contact the IWRS help desk for next steps. Some unscheduled visits at the discretion of the investigator may be required. All dose interruptions and dose modifications, and the reasons for those changes, will be recorded.

6.6.3. Dose Up-titration Stopping Criteria

If any of the following scenarios occur, a safety review will be triggered to decide if the study treatment may be discontinued or the dose level may be decreased if participants are at the CCI [redacted] mg dose levels, in which case participants may continue with a daily dose of equal to or greater than [redacted] mg. If in the group the following scenarios occur, then a safety review will be triggered to decide if titration to the corresponding dose level will be stopped after notification of the investigator or designee:

- one treatment-emergent SAE considered related to LY3502970 treatment (unless due to anticipated pharmacology of LY3502970, for example, hypoglycemia).
- two or more clinically significant events (see Appendix 7; Section 10.7) considered related to LY3502970 treatment, defined as moderate-to-severe symptoms, clinical signs, and/or clinical laboratory findings that could cause harm to health and would preclude further dosing of a participant who experiences this effect. Clinically significant events will be determined by the investigator or suitable designee and may include findings that do not fulfill the criteria for SAEs.
- equal to or greater than 40% of participants in a dose level experience a symptomatic hypoglycemic episode with plasma glucose values lesser than 3.0 mmol/L (54 mg/dL) and these events are deemed to be related to LY3502970 administration.
- two or more participants develop persistent (greater than 1 week) symptoms suggestive of acute pancreatitis. Refer to algorithm for the monitoring of asymptomatic hyperenzymemia in Section 8.2.7.1.

Participants experiencing clinically significant events thought to be related to the study intervention will be encouraged to complete a 14-day follow-up period before study discharge.

6.6.4. Dose Reduction

No dose reductions are permitted for dose up-titration to and including [redacted] mg LY3502970 QD. A decrease in dose that is one dose level lower than the highest tolerated or highest received dose (that is, from CCI [redacted] mg, CCI [redacted] mg, or CCI [redacted] mg) is permitted at any time if an individual participant is unable to tolerate the CCI [redacted] -mg dose levels. One dose reduction is

permitted per participant. If a dose is reduced, the participant will continue at the decreased dose level through to the last planned dosing on Day 112 for Cohort 1 or on Day 168 for Cohort 2. Participants who are unable to tolerate study intervention after a decrease in dose level may discontinue study intervention at the discretion of the investigator (Section 7.1). In order to maintain blinding to study intervention, the site should contact the IWRS help desk for next steps.

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

LY3502970 will not be made available to participants after conclusion of the study.

6.8. Treatment of Overdose

For this study, any dose of LY3502970 greater than the doses assigned according to the up-titration regimen through randomization within a 24-hour time period will be considered an overdose.

The treatment for overdose is supportive care; refer to the IB.

In the event of an overdose, the investigator 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 or SAE and laboratory abnormalities until, for example, LY3502970 no longer has a clinical effect or can no longer be detected systemically (on Day 121 for Cohort 1 and Day 177 for Cohort 2), and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.9. Prior and Concomitant Therapy

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

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

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

Treatment with medications that are excluded in the inclusion and exclusion criteria, as detailed in Section 5.2, is not permitted.

Participants should abstain from use any prescription or over-the-counter medications or traditional Chinese treatments within 3 months prior to screening and throughout the study with the exception of vitamin or mineral supplements, occasional paracetamol, thyroid replacement, and prescription medications for the treatment of concurrent medical conditions such as antihypertensive agents, antiplatelet drugs, or lipid-lowering agents with a stable dose for at least 3 months prior to enrollment. Medications that may cause significant weight gain are not permitted unless the participant is on a stable dose for greater than 6 months with no expectation that the dose will change within the next year, and who are weight stable for the last 6 months on these medications. Hormone replacement therapy in postmenopausal women is allowed but women must be on stable therapy for 3 months prior to screening. Participants should not take strong CYP3A inhibitors or strong CYP3A inducers, or drugs that are sensitive P-gp substrates with a narrow therapeutic index or BCRP substrates with a narrow therapeutic index. Participants should not concomitantly take strong OATP inhibitors. See Appendix 12 in Section 10.12 for examples of concomitant medications of these types to exclude.

Participants should not use concomitant medications that prolong the QT/QTc interval. Medications that are taken chronically and directly affect GI motility are not permitted. Central nervous system stimulants are not permitted, with the exception of caffeinated beverages.

Participants on stable concomitant medications at the time of study entry should continue their regular, unchanged doses throughout the study. Allowed concomitant medications should be taken according to label directions or in the discrepancy of investigator. Medications that may be affected by an increase in gastric pH should be separated from study drug administration by at least 2 to 4 hours. See Appendix 12 in Section 10.12 for examples of such drugs that might be affected by an increase in gastric pH.

Additional new medications are to be avoided during the study, unless required to treat an AE or for the treatment of an ongoing medical problem.

Nausea, vomiting, or both, during this study may be treated with antiemetics but these medications should not be used prophylactically. Nonsteroidal anti-inflammatory medications (including ibuprofen, aspirin), acetaminophen (at doses of up to 3 g per day), cough suppressants, antihistamines, vitamin/mineral supplements, antibiotics, and topical ointments may be used on an as-needed basis without notifying the sponsor and are not restricted by the stable dosing requirements listed earlier.

If the need for additional concomitant medication arises, the participant may be continued in the study or on study medication if, in the investigator's opinion, the addition of the new medication does not pose a safety risk. If an additional concomitant medication is started, the sponsor should be informed as soon as possible.

Initial doses of LY3502970 may delay gastric emptying and have the potential to transiently impact the rate of absorption of concomitantly administered oral medicinal products. LY3502970 should be used with caution in participants receiving oral medicinal products that require rapid gastrointestinal absorption following the initial doses of LY3502970 as exposure to oral medications may be increased.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or the study as a whole is handled as part of Appendix 1 in Section 10.1.

7.1. Discontinuation of Study Intervention

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

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention (treatment), thereby discontinuing the treatment period, and will remain in the study to complete procedures for an ED visit and post-treatment follow-up, if applicable, as shown in the SoA.

Discontinuation of study intervention should be considered by the investigator if any of the following occurs in a participant:

- experience an AE that is considered to be intolerable,
- acute pancreatitis is diagnosed,

  experience an abnormal safety laboratory test result, determined to be clinically significant by the investigator,
- experience any of the following circumstances:
  - diagnosis of cirrhosis after randomization,
  - pancreatitis or pancreatic cancer,
  - diagnosis of medullary thyroid cancer after randomization,
  - diagnosis of an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization, or
  - diagnosis of T1DM or latent autoimmune diabetes in adults.
- a clinically significant finding is identified in ECG parameters including, but not limited to, QTc greater than 500 msec or an increase from baseline of equal to or greater than 60 msec, from at least 2 consecutive readings, the participant will be discontinued. For other clinically significant findings, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as AE,
- the participant has a PHQ-9 score of 15 or more, the participant has answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, or the participant has answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

Note: A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

- given any non-study medication for weight loss for more than 1 week,

- the participant becomes pregnant during the study, or
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons.

Participants may be temporarily discontinued for up to 2 days, before resuming the previous dose of study intervention and continue on to dose titration, at the investigator or designee's discretion.

7.1.1. Liver Chemistry Stopping Criteria

The discontinuation values required below pertain to participants enrolled with normal or near normal hepatic biochemical tests including ALT equal to or less than 1.5× ULN, TBL equal to or less than 1.5× ULN, or ALP equal to or less than 1.5× ULN. In participants with abnormal hepatic biochemical tests at baseline, the discontinuation values may need to be adjusted on a case-by-case basis. For example, those enrolled with baseline ALT greater than 1.5× ULN, for example nonalcoholic fatty liver disease, the discontinuation value may need to be ALT greater than 2× baseline plus symptoms instead of ALT greater than 3× ULN plus symptoms. Similarly, in those with elevated TBL (for example Gilbert's syndrome) or elevated ALP (for example underlying bone disease) at baseline, the discontinuation values will increase and will be based on direct bilirubin levels and hepatic ALP-isoenzyme levels respectively.

In study participants with normal or near normal baseline liver tests including ALT, AST, ALP less than 1.5× ULN, the study drug should be interrupted and close hepatic monitoring initiated as described in Section 8.2.7.2 if 1 or more of these conditions occur:

Elevation	Exception
ALT or AST >5×ULN	
ALT or AST >3×ULN and either TBL >2×ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2×ULN.
ALT or AST >3×ULN 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 >2.5×ULN and TBL >2×ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2×ULN.
ALP >2.5×ULN 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

In study participants with abnormal baseline liver tests including ALT, AST, ALP equal to or greater than 1.5× ULN, the study drug should be interrupted if one or more of these conditions occur:

Elevation	Exception
ALT or AST >3×baseline	
ALT or AST >2×baseline and either TBL >2×ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2×ULN.
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 >2.5×baseline when the source of increased ALP is the liver	
ALP >2×baseline and TBL >2×ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2×ULN.
ALP >2×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.	

Resumption of the study drug can be considered only in consultation with the Lilly designated-medical monitor and only if the liver test results return to baseline and if a self-limited non-drug etiology is identified. Otherwise, the study drug should be discontinued.

7.1.2. QTc Stopping Criteria

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

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

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, or

- 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 introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an ED visit and post-treatment follow-up, if applicable, as shown in the SoA in Section 1.3. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue 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 are otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA in Section 1.3.

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

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based on emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF. Failure or being late, that is, outside stipulated time allowances to perform procedures or obtain samples due to legitimate clinical issues such as equipment technical problems, venous access difficulty, or participant defaulting or turning up late on an agreed scheduled procedure will not be considered as protocol deviations, but the CRU will still be required to notify the sponsor in writing via a file note.

Appendix 2 in Section 10.2 lists the laboratory tests that will be performed for this study.

Appendix 2 in Section 10.2.1 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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

8.1. Efficacy Assessments

Efficacy parameters will be explored through the PD measures specified in Section 8.5.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Physical examinations and routine medical assessments will be conducted as specified in the SoA in Section 1.3 and as clinically indicated.

A complete physical examination at screening will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological systems. Height, weight, and waist circumference will also be measured and recorded. Investigators should pay special attention to clinical signs related to previous serious illnesses.

A symptom-directed physical examination will be performed at other visits, as deemed necessary by the investigator.

8.2.2. Vital Signs

For each participant, vital signs, and body temperature measurements should be conducted according to the SoA in Section 1.3. BP and pulse rate should be measured after at least 5 minutes in the supine position.

Unscheduled vital signs should be assessed in the orthostatic position, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes. If the participant feels unable to stand, supine vital signs only will be recorded. Additional vital signs may be measured during each study period if warranted.

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained according to the SoA in Section 1.3. Refer to Section 7.1.2 for QTc stopping criteria and any additional QTc readings that may be necessary.

ECGs must be recorded before collecting any blood samples or vital signs measurements. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

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

If a clinically significant finding is identified after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed and must document his or her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2 in Section 10.2 for the list of clinical laboratory tests to be performed and the SoA in Section 1.3 for the timing and frequency.

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 or within the designated follow-up period after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal or 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 in Section 10.2, must be conducted in accordance with the SoA in Section 1.3, 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, AE, or dose modification, then the information will be reported as an AE.

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

8.2.5. Pregnancy Testing

Pregnancy testing will be performed for all female participants at screening, and for WOCBP the time points detailed in the SoA in Section 1.3.

Serum pregnancy testing will be performed at screening. Urine pregnancy testing will be performed at all other time points.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Participants who have obesity or are overweight are at increased risk for depression (Luppino et al. 2010). Depression can increase the risk for suicidal ideation and behavior. Therefore, study participants will be screened at trial entry and monitored during the study for depression, suicidal ideation, and behavior.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study medication in who experience signs of suicidal ideation or behavior, following a risk assessment.

Participants will be monitored for depression and suicidal ideation or behavior through AE collection and by using the C-SSRS and the PHQ-9 questionnaires. Scores of the questionnaires must be reviewed by the investigator at the time of each visit, and appropriate actions as described below should be taken.

The PHQ-9 questionnaire is a validated, participant-completed 9-item depression module of the Patient Health Questionnaire, which is used as a diagnostic instrument for common mental disorders. The PHQ-9 consists of 9 items each scored on a scale of 0 = "not at all" to 3 = "nearly every day" with a recall period of "the last 2 weeks." Major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least "more than half the days" in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia. As a severity measure, a higher score indicates greater severity.

C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the

National Institute of Mental Health trial group for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

See Section 8.3.3 for details.

8.2.7. Safety Monitoring

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

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

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

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

8.2.7.1. Pancreatic Monitoring

Diagnosis of acute pancreatitis

Acute pancreatitis is an AE of interest in all studies with LY3502970, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks 2006, Koizumi 2006):

- abdominal pain, characteristic of acute pancreatitis, that is, epigastric pain radiating to the back, often associated with nausea and vomiting,
- serum amylase including total, pancreatic, or both and/or lipase equal to or greater than 3× ULN, and/or
- characteristic findings of acute pancreatitis on CT scan or MRI.

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase,
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal MRI, and
- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone/gall bladder disease, hypertriglyceridemia, and concomitant medications.

Discontinuation for acute pancreatitis

If acute pancreatitis is diagnosed, the participant must discontinue use of study intervention.

Asymptomatic elevation of serum amylase and/or lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck et al. 2016; Steinberg et al. 2017a, 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic

enzymes (lipase and/or p-amylase equal to or greater than 3× ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

8.2.7.2. Hepatic Monitoring

Laboratory tests detailed in Appendix 6 in Section 10.6, including ALT, AST, ALP, TBL, direct bilirubin, and gamma-glutamyl transferase should be repeated, with additional tests for creatine kinase within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5× 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)

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

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab 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 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 ≥2× baseline (except for participants with Gilbert's syndrome)

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

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,
- viral hepatitis A, B, C, or E,
- 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 Lilly-designated medical monitor, including tests for

- hepatitis D virus,
- cytomegalovirus,
- Epstein-Barr virus,
- acetaminophen levels,

- acetaminophen protein adducts,
- urine toxicology screen,
- Wilson's disease,
- blood alcohol levels,
- urinary ethyl glucuronide, and
- 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 a

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

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

Additional hepatic safety data collection in 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 equal to or greater than 5× ULN on 2 or more consecutive blood tests (if baseline ALT is less than 1.5× ULN)
    - in participants with baseline ALT equal to or greater than 1.5× ULN, the threshold is ALT equal to or greater than 3× baseline on 2 or more consecutive tests.
2. elevated TBL to equal to or greater than 2× ULN (if baseline TBL is less than 1.5× ULN; except for cases of known Gilbert's syndrome)
    - in participants with baseline TBL equal to or greater than 1.5× ULN, the threshold should be TBL equal to or greater than 2× baseline.
3. elevation of serum ALP to equal to or greater than 2× ULN on 2 or more consecutive blood tests (if baseline ALP less than 1.5× ULN)
    - in participants with baseline ALP equal to or greater than 1.5× ULN, the threshold is ALP equal to or greater than 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.

8.2.7.3. Hypoglycemia Monitoring

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia.

Investigators should use the following classification of hypoglycemia:

Level 1 hypoglycemia:

Glucose less than 70 mg/dL (3.9 mmol/L) and equal to or greater than 54 mg/dL (3.0 mmol/L): Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

Level 2 hypoglycemia:

Glucose less than 54 mg/dL (3.0 mmol/L): Level 2 hypoglycemia is also referred to as documented or blood glucose confirmed hypoglycemia with glucose less than 54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, were semiconscious, unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.

If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

Nocturnal hypoglycemia: Nocturnal hypoglycemia is a hypoglycemia event (including severe hypoglycemia) that occurs at night and presumably during sleep.

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

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

- AEs,
- SAEs, and
- PCs.

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 LY3502970 study as described in Section 7.

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

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

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 or contacts. All SAEs and AESIs as defined in Section 8.3.4 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 PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and or causality, or both. Further information on follow-up procedures is provided in Appendix 3 in Section 10.3.4.

8.3.1. Timing and Mechanism for Collecting Events

Table GZGX.2 describes the timing, deadlines, and mechanism for collecting events.

Table GZGX.2. Timing 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 eCRF	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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	Day 126 in Cohort 1, Day 182 in Cohort 2, or upon ED	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; eCRF = electronic case report form; ED = early discontinuation; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

* SAEs 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 while the male participant is in this study. This applies only to male participants who receive LY3502970.

After learning of a pregnancy in the female partner of a study participant, the investigator will attempt to:

- obtain 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

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 less than 20 weeks' gestational age) or stillbirth (occurring at equal to or more than 20 weeks' gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. 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 be withdrawn from the study. If the participant is discontinued from the study, the standard discontinuation process should be followed, and the participant should continue directly to the ED visit. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Event Monitoring with a Systemic Questionnaire

Nonleading AE collection should occur prior to the collection of the PHQ-9 or C-SSRS.

If a suicide-related event is discovered *during the C-SSRS* but was not captured during the nonleading AE collection, sites should not change the AE form.

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

Participants will be referred to a mental health professional if, in the opinion of the investigator or designee, it is necessary for the safety of the participant or if the participant has any of the following:

- the participant has a PHQ-9 score of 15 or more,
- the participant has answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, or
- the participant has answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

8.3.4. Adverse Events of Special Interest

Nausea, vomiting, and diarrhea events are considered AESIs and will be recorded as AEs in the electronic CRF. For each event, assessment of severity, duration (start and stop dates and times), and investigator's opinion of relatedness to study treatment and protocol procedure will be captured. Other AESIs for this program include:

- pancreatic events,
- cardiovascular events,
- hepatic events, and
- hypoglycemia.

If any of these AESIs are reported, sites will be prompted to collect additional details and data.

8.4. Pharmacokinetics

At the visits and times specified in the SoA in Section 1.3, venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of LY3502970. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed on between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded. Differences from the time specified in the protocol are not considered protocol deviations as long as samples are collected and accurate dates and times are recorded in a timely manner on the appropriate forms.

Time window allowances for each PK collection time point are listed below:

PK Time Point	Time Window Allowance
0.5 hour	± 5 minutes
1 hour	± 5 minutes
2 hour	± 10 minutes

4 hour	± 10 minutes
6 hour	± 10 minutes
8 hour	± 10 minutes
12 hour	± 10 minutes
24 hour	± 10 minutes
48 hour	± 1 hour
96 hour	± 1 hour

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

8.4.1. Bioanalysis

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

Concentrations of LY3502970 will be assayed using a validated liquid chromatography mass spectrometry method. Analyses of samples collected from participants who received placebo are not planned.

Bioanalytical samples collected to measure LY3502970 concentrations will be retained for a maximum of 1 year following the last participant visit for the study.

8.5. Pharmacodynamics

The following secondary PD measures will be collected as specified in the SoA in Section 1.3:

- body weight,
- BMI,
- waist circumference,
- fasting plasma glucose,
- fasting insulin,
- Hb1Ac, and
- lipid profiles.

See Appendix 10 in Section 10.10 for details of height, weight, and waist circumference measurement procedures.

8.6. Genetics

Not applicable.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

The SAP will be finalized prior to first participant first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypothesis

The primary objective is to investigate the safety and tolerability of LY3502970 following multiple oral QD doses for 16 weeks in Cohort 1 and 24 weeks in Cohort 2, in Chinese participants who have obesity or are overweight with weight-related comorbidities. There are no formal statistical hypotheses confirmed for this study.

9.2. Analyses Sets

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

Participant Analysis Set	Description
Enrolled	All participants randomly assigned to study intervention or placebo.
Safety analysis set	All participants who are exposed to at least 1 dose of study intervention or placebo. Participants will be analyzed according to the intervention they actually received.
PK analysis set	All enrolled participants who receive at least 1 dose of study intervention and have evaluable PK data.
PD analysis set	All enrolled participants who receive at least 1 dose of study intervention or placebo and have evaluable PD data.

Participants may be excluded from the PK and PD summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median t_{max}.

9.3. Statistical Analyses

9.3.1. General Considerations

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

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety, PD, and population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final clinical study report.

9.3.2. Primary Endpoint Analysis

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

The incidence of AEs for each treatment in each part will be presented by severity and by association with study intervention as perceived by the investigator. AEs reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

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

9.3.2.1. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.3.3. Secondary Endpoints Analysis

9.3.3.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3502970 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max} and $AUC_{(0-24)}$ of LY3502970. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported. If deemed necessary, additional model-based analysis may be performed. Full details of the PK parameters to be calculated will be provided in the SAP.

9.3.3.2. Pharmacokinetic Statistical Inference

All PK parameters will be listed and summarized using descriptive statistics. Steady-state PK data will be evaluated to estimate dose proportionality over the dose range in Cohort 1 and Cohort 2. Log-transformed C_{max} and $AUC_{(0-24)}$ will be evaluated using a power model (where the log of the dose will be an explanatory variable) to estimate ratios of dose-normalized geometric means and the corresponding 90% CIs. The estimated ratio between the highest and lowest doses will be used to assess dose proportionality. The interparticipant coefficient of variation will be derived.

9.3.3.3. Pharmacodynamic Parameter Estimation

Inferences will be sought regarding the effect of LY3502970 on the PD endpoints. Such effects will be explored over different doses of LY3502970 and at applicable time points as per the SoA in Section 1.3.

9.3.3.4. Pharmacodynamic Statistical Inference

PD parameters may be transformed before statistical analyses, if deemed necessary. Actual values, as well as change from baseline, in each parameter will be analyzed using mixed effects models to evaluate treatment effects, as well as treatment comparisons. The model will include treatment, time point, and treatment-by-time point interaction as fixed effects and participant as a

random effect. Baseline values, as well as other influencing variables, may be used as covariates. Differences between each LY3502970-treated group and placebo group will be estimated. Participants who received placebo will be pooled across all cohorts. Least squares means and 90% CIs will be reported.

All PD parameters, including the change from baseline, will be summarized and tabulated by treatment group and time point. Summary statistics will be provided.

The individual observed and mean time profile of the postdose PD parameters will be plotted by treatment group.

9.3.4. Analysis of Columbia-Suicide Severity Rating Scale Data

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide .

9.4. Interim Analysis

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

9.5. Sample Size Determination

No formal statistical hypothesis testing will be performed.

The sample size is customary for Phase 1 studies evaluating safety and PK parameters. Approximately 24 Chinese participants who have obesity or are overweight with weight-related comorbidities may be enrolled so that 20 participants complete the study. The use of a 10:2 LY3502970:placebo ratio is intended to ensure that approximately 8 participants complete all planned LY3502970 doses in each cohort.

Participants who are randomized but discontinue before completing the study may be replaced to ensure that enough participants may complete the study.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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:

- providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC,
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures,
- providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations,
- reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity, and
- investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or the potential participant's legally authorized representative and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants or their legally authorized representatives 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 or the participant's legally authorized representative and is kept on file.

10.1.3. 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 sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the study due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone 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 Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

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

Data

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

10.1.5. 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.

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 or IEC review, and regulatory agency inspections and provide direct access to source documents.

Source data may include laboratory tests, medical records, and clinical notes.

Monitoring details describing strategy (for example, risk-based initiatives in operations, 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, contract research organizations).

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 Clinical Trial Agreement 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 EDC system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system(s) will be stored at third-parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive 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 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 PC 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 are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Section 10.1.5.

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 or 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, and
  - 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) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.8. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory, or by the local laboratory at screening, as detailed in the table below.

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.

Safety Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count	Bicarbonate or carbon dioxide
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium (ionized or total)
Mean cell hemoglobin concentration	Blood urea nitrogen or urea
Leukocytes (WBC)	Creatinine
Platelets	Total protein
Differential WBC – Absolute counts or % of:	Albumin
Neutrophils	Total bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Aspartate aminotransferase
Eosinophils	Alanine aminotransferase
Basophils	Calcitonin[e]
	Pancreatic amylase[e]
Urinalysis	Lipase[e]
Specific gravity	
pH	Ethanol testing[a,b]
Protein	Urine drug screen[a,b]
Glucose	Hepatitis B surface antigen[a]
Ketones	Hepatitis B core antibody[a]
Bilirubin	Hepatitis B virus DNA[a]
Urobilinogen	Hepatitis C antibody[a]
Leukocytes or urine leukocyte esterase	Human Immunodeficiency Virus[a]
Blood	Pregnancy test (females only)[d]
Nitrite	Follicle-stimulating hormone[a]
Microscopic examination of sediment[c]	Thyroid-stimulating hormone[a]
	Glycated hemoglobin (HbA1c)[a]
	Fasting plasma glucose[a]
	Fasting lipid panel[a]
	Total cholesterol
	Triglycerides
	Low density lipoprotein (LDL)
	Very low density lipoprotein cholesterol (VLDL)
	High density lipoprotein (HDL)

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

[a] Performed at screening only.

[b] Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit.

[c] Test only if dipstick result is abnormal.

[d] Serum pregnancy testing will be performed at screening and when urine test is positive. Urine pregnancy testing will be performed for women of childbearing potential at all other time points.

[e] To be performed at screening, predose on Day 1 (excluding calcitonin), early discontinuation, and Day 113 for Cohort 1, or screening, predose on Day 1 (excluding calcitonin), early discontinuation, and Day 169 for Cohort 2 only.

10.2.1. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. The volume is an estimate and will vary depending on the local laboratory's testing guidance or requirements.

Protocol J2A-GH-GZGX Sampling Summary – Cohort 1

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	31	1	31
Local clinical laboratory tests[a]	8	11	88
Pregnancy tests (females only)	4	1	4
Calcitonin	4	1	4
Glycated hemoglobin (HbA1c)	2	3	6
Fasting plasma glucose	2	5	10
Insulin	2	5	10
Lipid panel	2.5	5	12.5
Pharmacokinetics	2	34[b]	68
Total			233.5
Total for clinical purposes			240

[a] Additional samples may be drawn if needed for safety purposes. FSH included, but only for females if needed.

[b] Includes additional 3 samples, if required.

Protocol J2A-GH-GZGX Sampling Summary – Cohort 2

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	31	1	31
Local clinical laboratory tests [a]	8	15	120
Calcitonin	4	1	4
Pregnancy tests (females only)	4	1	4
Glycated hemoglobin (HbA1c)	2	4	8
Fasting plasma glucose	2	7	14
Insulin	2	7	14
Lipid panel	2.5	7	17.5
Pharmacokinetics	2	52[b]	104
Total			316.5
Total for clinical purposes			320

[a] Additional samples may be drawn if needed for safety purposes. FSH included, but only for females if needed.

[b] Includes additional 3 samples, if required.

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 Events

AE Definition

- An 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 unfavourable 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, 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 study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, 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 or disorder being studied or expected progression, signs, or symptoms of the disease or 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 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 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, treatment, or both 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 or 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 or 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 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

- A PC 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 PCs:
  - 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 PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE or SAE, or both. In such cases, it should be reported as both a PC and as an AE or SAE.

10.3.4. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events and Product Complaints

AE, SAE, and Product Complaint Recording

- When an AE, SAE, or PC 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, or PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE and SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.
- Note: An event may meet the definition of both a PC and an AE or SAE. In such cases, it should be reported as both a PC and as an AE or 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 or SAE and the Product Complaint Form for PCs.
- There may be instances when copies of medical records for certain cases are requested by 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, other clinical information, or all of these. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

- Mild: 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 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE and 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 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 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements, evaluations, or both as medically indicated or as requested by sponsor or designee to elucidate the nature, causality, or both 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 Serious Adverse Events

SAE Reporting via SAE Report

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the medical monitor.
- 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

Word/Phrase	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. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, **and** with a follicle-stimulating hormone >40 mIU/mL; • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

Male Participants

No male contraception is required except in compliance with specific local government study requirements.

Female Participants

WOCBP and WNOCBP may participate in this trial.

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

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

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

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to treatment exposure. See the protocol SoA in Section 1.3 for subsequent pregnancy testing requirements.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective. These forms of contraception must be used for the duration of the study and for at least 30 days after the last day of study intervention.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (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 Note: Implantable contraceptives and injectable contraceptives are only permitted if started more than 18 months prior to screening. Participants should not start these methods of contraception after being enrolled in the study.
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

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

10.5. Appendix 5: Diet and Physical Activity Suggestions for Sites without Programs

10.5.1. Diet

Diet recommendations are based on the World Health Organization (WHO 2020) for everyone which is based on a Mediterranean eating pattern.

The Mediterranean eating pattern for a healthy diet consists of:

- legumes (for example, lentils and beans),
- nuts,
- whole grains (for example, unprocessed wheat, maize, millet, oats, and brown rice),
- at least 5 portions of fruit and vegetables per day (excluding potatoes, sweet potatoes, cassava, and other starchy roots),
- less than 10% of total energy intake from free sugars (equivalent to 50 g or 12 level teaspoons), but ideally less than 5% of total energy intake. Free sugars are sugars added to foods and drinks, as well as sugars present in honey, syrups, fruit juices, and fruit juice concentrates,
- less than 30% of total energy intake from fats. Unsaturated fats are preferred over saturated fats. Unsaturated fats are found in fish, avocado, nuts, sunflower, canola, and olive oils. Consumption of saturated fats, which are fats in fatty meat, butter, palm and coconut oil, cream cheese, ghee, and lard, should be reduced to less than 10% of total energy intake. Trans fats, which are found in industrially produced foods, should be avoided, and
- salt intake should not be more than 5 g (about 1 teaspoon) per day and should be iodized.

10.5.2. Physical Activity

Regular physical activity can improve a participant's health. Moving more and sitting less benefits everyone, regardless of age, sex, race, ethnicity, or current fitness level. Benefits accumulate with even small amounts and start immediately.

To safely engage in physical activity, types of physical activity appropriate for the participant's current fitness should be chosen. Furthermore, the amount and duration of physical activity should be gradually increased over time. Participants with chronic conditions and symptoms should be under the care of a health care provider about the types and amounts of physical activity that are appropriate for the participant.

Physical activity recommendations are based on WHO recommendations (WHO 2020) and with the US Health and Human Services (HHS 2020) recommendations.

- Any physical activity is better than none. Adults should move more and sit less.
- Adults should do 150 minutes (2 hours 30 minutes) to 300 minutes (5 hours) of moderate-intensity aerobic physical activity throughout the week or 75 minutes (1 hour 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and

vigorous-intensity aerobic activity. Preferably, aerobic activity should be spread throughout the week.

- Aerobic activity should be performed in bouts of at least 10 minutes duration.
- For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond the equivalent of 300 minutes (5 hours) of moderate-intensity physical activity a week.
- Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.
- Older adults, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week, as well as aerobic and muscle-strengthening activities. They should be as physically active as their abilities and conditions allow. When older adults cannot do 150 minutes of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow.

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

Hepatic Evaluation Testing

See Section 8.2.7.2 for guidance on appropriate test selection. See Appendix 11 in Section 10.11 for details of laboratories.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

In circumstances where required in accordance with local regulations, local laboratory testing may be performed in lieu of Lilly-designated central laboratory testing (in the table below).

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

The local laboratory must be qualified in accordance with applicable local regulations.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatitis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA [b]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA [b]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV IgG antibody
Total bilirubin	HDV IgM antibody
Direct bilirubin	**Hepatitis E virus (HEV) testing:**
Alkaline phosphatase (ALP)	HEV IgG antibody
Alanine aminotransferase (ALT)	HEV IgM antibody
Aspartate aminotransferase (AST)	HEV RNA [b]
Gamma-glutamyl transferase (GGT)	**Anti-nuclear antibody**
Creatine kinase (CK)	**Anti-smooth muscle antibody** [a]
Hepatic Coagulation Panel	**Anti-actin antibody** [c]
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgA (quantitative)**
Urine Chemistry	**Immunoglobulin IgG (quantitative)**
Drug screen	**Immunoglobulin IgM (quantitative)**
Haptoglobin	**Epstein-Barr virus (EBV) testing:**
	EBV antibody

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody [d]
Alkaline phosphatase isoenzymes	CMV DNA [b]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol	HSV (Type 1 and 2) DNA [b]
Phosphatidylethanol	Liver kidney microsomal type 1 antibody
Urine Chemistry	**Microbiology**
Ethyl glucuronide	Culture:
Epstein-Barr virus (EBV) testing:	Blood
EBV DNA [b]	Urine

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 If available.

10.7. Appendix 7: Clinically Significant Adverse Events

The table below summarizes the type and severity of symptoms, clinical signs, and clinical laboratory findings that may qualify as a clinically significant event. These are intended as a guideline to the investigator(s), not as a set of absolute criteria. The underlying principle is to define a level of moderate-to-severe abnormality in safety findings that could cause harm to health and would preclude further dosing of a participant who experiences this effect. Safety parameters not included in this table may be interpreted in a similar fashion according to investigator judgment.

Parameter	CSE level
Symptoms	
Severe hypoglycemia	One episode of severe hypoglycemia defined as low blood glucose with mental status impairment severe enough to require third-party assistance.
Dizziness/hypotension	Orthostatic CNS symptoms (dizziness, confusion) that are not vasovagal responses to provocative stimuli (for example, phlebotomy, nausea, bowel, or bladder function), and are associated with orthostatic SBP decrease >20 mm Hg or DBP decrease >10 mm Hg or heart rate >105 bpm, for >3 hours
Sensorium	Disorientation to time, place, or identity. Any abnormal ideation.
Mood	Feelings of grief or loss that interfere with study procedures or activities of daily living. Any suicidal ideation.
Headache/pain	Any focal or generalized head pain that disrupts normal activities and is not responsive to medical therapies
Pruritus	Generalized itching over >24 hours unresponsive to oral antihistamine.
Hypersensitivity	Clinically significant systemic-hypersensitivity reaction occurs following administration of the IMP (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) that requires parenteral medication, does not respond to symptomatic medication, or results in clinical sequelae or an anaphylactic reaction.
Signs	
Systolic blood pressure	>30 mm Hg increase from baseline values and an absolute level >190 mm Hg
Diastolic blood pressure	>20 mm Hg increase from baseline values and an absolute level >115 mm Hg
Heart rate	Resting (sitting or recumbent) HR >120 bpm
Cardiac rhythm	Any rhythm other than sinus rhythm, mild sinus bradycardia, or mild sinus tachycardia
QTc	>500 msec or >60 msec increase from baseline value
QRS morphology	Significant prolongation of QRS interval or new onset of bundle branch block
Tremor	Readily visible tremor during normal movement deemed unrelated to hypoglycemia
Reflexes	New onset of clonic reflexes
Clinical Laboratory	(confirmed by repeat measurements within 48 hours)
Hemoglobin	Absolute value <10 g/dL and >2 g/dL reduction from baseline
Neutropenia	Absolute neutrophils <1,500/µL and >1,000 /µL decrease from baseline
Lymphopenia	Absolute lymphocyte count <800/µL and >500/µL decrease from baseline
Platelet count	<75,000/µL and >50,000/µL decrease from baseline
Creatinine	>2 mg/dL and >0.5 mg/dL increase from baseline value
Urea	>8 mmol/L and >3 mmol/L increase from baseline values
Alanine aminotransferase	>5-fold above laboratory reference upper limit value
Aspartate aminotransferase	>5-fold above laboratory reference upper limit value
Bilirubin (total)	>1.5-fold above laboratory reference upper limit value
Potassium	<2.5 or >5.5 mEq/L and >0.5 mEq/L change from baseline value
Sodium	<130 or >150 mEq/L and >10 mEq/L change from baseline value

Abbreviations: bpm = beats per minute; CNS = central nervous system; CSE = clinically significant effect; DBP = diastolic blood pressure; HR = heart rate; IMP = investigative medicinal product; QRS = 3 graphical deflections on a typical electrocardiogram; corresponds to the depolarization of the right and left ventricles of the human heart; QTc = corrected QT interval; SBP = systolic blood pressure.

10.8. Appendix 8: New York Heart Association Functional Classification of Heart Failure

Class	Symptomatology
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

10.9. Appendix 9: 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 Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent/assent from the participant will be obtained for the below items, as required by ERB's and local regulations.

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

- participation in remote visits, as defined in Section "Remote Visits,"
- a change in the method of study intervention administration,
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, 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

Types of 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, collection of AEs, self-monitored blood glucose values, concomitant medications, review of participant's diary, and IP inventory at participant's end.
>
> **Other alternative locations:** participants may visit a local hospital other than the study site, except for Visit 2, when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor.

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 PD laboratory assessment, except screening, as described in the SoA in Section 1.3. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies, and

- working with the sponsor to determine how study intervention that is typically administered on site will be administered to the participant.

These requirements must be met before action is taken:

- alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- when delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

If study intervention will be administered to the participant at an alternate location, these additional requirements must be met:

- only authorized study personnel may supply, prepare, or administer study intervention
- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies from site to participant.

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 30 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 30 days from screening visit to randomization visit: the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within 30 days from screening visit.
    - 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 30 days from screening visit 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. The screening procedures per the usual SoA should be followed, starting at 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.

This table describes the allowed adjustments to visit windows.

Visit Number	Protocol-Specified Visit Interval Tolerance	Mitigation Extension of Visit Interval Tolerance
Cohort 1: Visits 3, 5, 7, and 9 (Weeks 3, 7, 11, and 15)	±2 days	±5 days
Cohort 1: Visit 11 (Week 19)	±3 days	±7 days
Cohort 2: Visits 3, 5, 7, 9, 11, and 13 (Weeks 3, 7, 11, 15, 19, and 23)	±2 days	±5 days
Cohort 2: Visit 15 (Week 27)	±3 days	±7 days

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

Changes to study conduct will be documented

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.

10.10. Appendix 10: Protocol GZGX Recommendations for the Measurement of Height, Weight, and Waist Circumference

The following information has been adapted from standardized physical measurement protocols for the WHO's STEPwise approach to Surveillance (STEPS) (WHO 2017).

Measuring Height

Step 1. Ask the participant to remove their footwear and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the participant at every clinic visit when their height is measured).

Step 2. Ask the participant to stand on the calibrated height measuring board (stadiometer) or against a wall with their feet together and their knees straight with their heels against the backboard, the stadiometer, or the wall.

Step 3. Ask the participant to look straight ahead without tilting their head up.

Step 4. Ask the participant to breathe in and stand tall. Measure and record the participant's height in centimeters to 1 decimal place.

Measuring Weight

- Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms to 1 decimal place.
- All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.
- Body weight must be measured in fasting state. If the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting body weight measured.

Step 1. Ask the participant to empty their pockets, remove their footwear, outerwear (coat, jacket, etc.), and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the participant at every clinic visit when weight is measured).

Step 2. Make sure the scale is placed on a firm, flat, even surface (not on carpet, on a sloping surface, or a rough, uneven surface).

Step 3. Ask the participant to step onto the scale with 1 foot on each side of the scale.

Step 4. Ask the participant to stand still with arms by sides and then record weight in kilograms to the nearest one-tenth kilogram.

Measuring Waist Circumference

- Waist circumference should be measured in the horizontal plane and at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.
- Measurements should be taken at the end of a normal expiration using a non-stretchable measuring tape. The tape should lie flat against the skin without compressing the soft tissue.

- The waist circumference should be measured twice, rounded to the nearest 0.5 cm. The measuring tape should be removed between the 2 measurements. Both measurements will be recorded in the eCRF. If the difference between the 2 measurements exceeds 1 cm, this set of measurements should be discarded and the 2 measurements repeated.

Step 1: Ask the participant to wear little clothing (if available, garments could also be used).

Step 2: Ask the participant to stand with their feet close together, arms at their side, body weight evenly distributed.

Step 3: Ask the participant to relax and measure the participant's waist circumference.

10.11. Appendix 11: Clinical Laboratories and Specimen Disposal Units

The laboratories of pertinence that manage specimen tests are listed in the below table. Refer to Section 10.2 for the concrete laboratory assessment in details.

Clinical Laboratory Tests	Laboratory Name	Disposal unit for remaining specimen
Hematology	Investigational Site Laboratory	Investigational Site Laboratory
Clinical chemistry		
Urinalysis		
Calcitonin		
Pancreatic amylase, Lipase		
Serum/urine pregnancy		
Follicle-stimulating hormone		
Thyroid-stimulating hormone		
Ethanol testing		
Urine drug screen		
Human Immunodeficiency Virus (HIV)		
Hepatitis B surface antigen		
Hepatitis B core antibody		
Hepatitis B virus DNA		
Hepatitis C antibody		
Glycated hemoglobin (HbA1c)- Screening		
Glycated hemoglobin (HbA1c)	CCI [redacted]	[redacted]
Fasting plasma glucose - screening	Investigational Site Laboratory	Investigational Site Laboratory
Fasting plasma glucose	CCI [redacted]	CCI [redacted]
Fasted insulin		
Fasting lipid panel - screening	Investigational Site Laboratory	Investigational Site Laboratory
Fasting lipid panel	CCI [redacted]	[redacted]
Pharmacokinetic samples		

Refer to the Section 10.6 for a detailed list of hepatic evaluation tests.

Tests assayed by Lilly-designated central laboratory	Laboratory name	Reference laboratory	Disposal unit for remaining specimen
Hepatic Hematology Panel	CCI [redacted]		CCI [redacted]
Hepatic Clinical Chemistry Panel			
Hepatic Coagulation Panel			
Urine Chemistry			

Haptoglobin			
Hepatitis A virus (HAV) testing:			
Hepatitis B virus (HBV) testing:			
Hepatitis C virus (HCV) testing:			
Hepatitis D virus (HDV) testing:			
HDV IgG antibody		CCI	CCI
HDV IgM antibody			
Hepatitis E virus (HEV) testing:			
HEV IgG antibody		CCI	CCI
HEV IgM antibody			
HEV RNA		MD BIOTECH CORP	CCI
Anti-nuclear antibody (ANA)			CCI
Anti-smooth muscle antibody (ASMA)		CCI	
Anti-actin antibody			
Immunoglobulin IgA (quantitative)			
Immunoglobulin IgG (quantitative)			CCI
Immunoglobulin IgM (quantitative)			
Epstein-Barr virus (EBV) testing			

Refer to the Section 8.2.7.1 for diagnostic tests of underlying acute pancreatitis.

Clinical Laboratory Tests	Laboratory Name	Disposal unit for remaining specimen
Pancreatic amylase, Lipase	Investigational Site Laboratory	Investigational Site Laboratory

10.12. Appendix 12: Examples of Excluded Medications

Participants cannot be taking strong CYP3A4 inhibitors or strong CYP3A inducers, drugs that are sensitive P-gp/BCRP substrates with a narrow therapeutic index, or strong OATP inhibitors. To be eligible for screening into this study, those drugs need to be washed out for at least 2 weeks and the participant should be on a stable dose of alternative medications for at least 2 weeks prior to screening. Medications that may be affected by an increase in gastric pH should be separated from study drug administration by at least 2 to 4 hours.

These lists are intended to be exhaustive, but with available information continually evolving, the status of every relevant drug cannot be guaranteed.

10.12.1. Strong CYP3A4 Inhibitors and Strong CYP3A inducers

- aminoglutethimide
- apalutamide
- atazanavir and cobicistat
- boceprevir
- carbamazepine (if daily dose exceeding 600 mg)
- ceritinib
- clarithromycin
- cobicistat
- conivaptan
- danoprevir and ritonavir
- elvitegravir and ritonavir
- enzalutamide
- forsamprenavir and ritonavir
- grapefruit juice
- idelalisib
- indinavir and ritonavir
- itraconazol
- ivosidenib
- josamycin
- ketoconazole
- lonafarnib
- lopinavir and ritonavir
- lumacaftor
- mitotane
- nefazodone
- nelfinavir

- nelfinavir
- nirmatrelvir and ritonavir
- paritaprevir and ritonavir and ombitasvir and/or dasabuvir
- phenobarbital
- phenytoin and fosphenytoin
- posaconazole
- ribociclib
- rifabutin
- rifampin
- rifapentine
- ritonavir
- saquinavir and ritonavir
- St. John's wort
- telithromycin
- tipranavir and ritonavir
- tucatinib
- voriconazole.

Note: To be eligible for screening into this study, participants taking ketoconazole, itraconazole, voriconazole, or posaconazole should discontinue taking these medications for at least 2 weeks prior to screening. However, if the participant is unable to wash out these drugs, then if appropriate, the participant could switch to:

- miconazole
- clotrimazole, or
- fluconazole.

For participants taking clarithromycin or telithromycin, azithromycin may be substituted 2 weeks prior to beginning screening. Participants who chronically use these drugs should be excluded.

10.12.2. Strong OATP inhibitors

- rifampin
- cyclosporine
- faldaprevir
- tipranavir/ritonavir
- glecaprevir/pibrentasvir
- telaprevir
- sofosbuvir/velpatasvir/voxilaprevir
- lopinavir/ritonavir
- darunavir/ritonavir

- elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

10.12.3. Sensitive P-gp substrates where small increases in exposure may result in serious toxicity

- colchicine
- cyclosporine
- dabigatran etexilate
- digoxin
- everolimus
- pimozide
- quinidine
- quinine
- sirolimus
- tacrolimus.

10.12.4. Sensitive BCRP substrates where small increases in exposure may result in serious toxicity

- prazosin.

10.12.5. Drugs affected by increase in gastric pH

Drugs that may be affected by an increase in gastric pH should be separated from study drug administration by at least 2 to 4 hours. Examples include:

- simvastatin
- levothyroxine
- ferrous sulfate
- bisphosphonates
- other narrow therapeutic index substrates with potential pH-dependent solubility or stability
- tyrosine kinase inhibitors
  - erlotinib
  - dasatinib
  - nilotinib
  - acalabrutinib
  - bosutinib
  - gefitinib
  - lapatinib
  - pazopanib
- antiretrovirals
  - rilpivirine

- atazanavir
- nelfinavir
- ledipasvir/sofosbuvir
- fosamprenavir
- delavirdine mesylate
- Emtricitabine+rilpivirine+tenofovir+ disoproxil fumarate (Complera®)
- Ledipasvir+sofosbuvir (Harvoni®)
- raltegravir, sofosbuvir+velpatasvir (Epclusa®).

10.13. Appendix 13: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{(0-24)}$	area under the concentration versus time curve from time 0 to 24 hour time point
BCRP	breast cancer resistance protein
blinding	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 the pariticpants are aware of the treatment received.
BMI	body mass index
C-SSRS	Columbia Suicide-Severity Rating Scale
CIOMS	Council for International Organizations of Medical Sciences
BP	blood pressure
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
C-SSRS	Columbia Suicide-Severity Rating Scale

CP	clinical physician
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.
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
CT	computerized tomography
CYP	cytochrome P450
Device deficiencies	Equivalent to product complaint
ECG	electrocardiogram
ED	early discontinuation
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
Hb1Ac	glycated hemoglobin
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
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.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB	Institutional Review Board
IWRS	interactive web-response system
MAD	multiple-ascending dose
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 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 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 either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MRI	magnetic resonance imaging
OATP	organic anion transporting polypeptide
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
PC	product complaint
P-gp	P-glycoprotein 1

PHQ-9	Patient Health Questionnaire-9
PK/PD	pharmacokinetics/pharmacodynamics
PR	pulse rate
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected for heart using Fridericia's formula
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time of maximum observed drug concentration
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

10.14. Appendix 14: Protocol Amendment History

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

Amendment (a): 26 July 2023

Overall Rationale for the Amendment:

Protocol J2A-GH-GZGX has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to the protocol are described in the following table. Note that minor edits may have been made throughout the protocol, which are not captured in the amendment summary table.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Study duration corrected from 133 to 157 days for Cohort 1 and from 189 to 213 days for Cohort 2.	To correct incorrect numbers.
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design	Discharge day changed from Day 115 of Cohort 1 to Day 114, and Day 171 of Cohort 2 to Day 170.	To allow participants to leave the CRU instead of staying when no activities are performed.
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design	Day 115 of Cohort 1 changed to Day 116, and Day 171 of Cohort 2 changed to Day 172.	To correct the visit day that correlates with the 96-hour postdose PK collection.
1.3 Schedule of Activities	Screening tests specified in Notes column for Cohorts 1 and 2.	To clarify screening processes.
1.3 Schedule of Activities	Fasting added for Days 2, 56, and 112 for Cohort 1, and for Days 2, 28, 84, 140, and 168 for Cohort 2.	To make consistent with Section 5.3.1 which states to fast 'for outpatient and residential visits.'
1.3 Schedule of Activities	A window of ±1 day added to Days 56 and 112 of Cohort 1 and Days 28, 84, 140, and 168 of Cohort 2.	To provide a time window for inpatient visits.
1.3 Schedule of Activities	Vital signs and single 12-lead ECG assessments added to Day 113 of Cohort 1, and moved	To correct the time point of safety data collection after treatment period in both cohorts

Section # and Name	Description of Change	Brief Rationale
	from predose of Day 168 of Cohort 2 to Day 169.	and to use the same time point as other related assessments.
1.3 Schedule of Activities	'C-SSRS since last visit' changed to 'C-SSRS since last assessed.'	To clarify the details of C-SSRS assessment requirements.
1.3 Schedule of Activities 8.4 Pharmacokinetics	Table added to specify time window allowances for individual PK sample collections. Note added to SoA.	To clarify requirements for PK collections.
5.2 Exclusion Criteria 6.9. Prior and Concomitant Therapy Appendix 12: Examples of Excluded Medications	Added list of examples of strong CYP3A4 inhibitors and strong CYP3A inducers, and other concomitant medicines that could lead to pharmacokinetic-based drug-drug interactions to Appendix 12. List of examples of OATP inhibitors moved from Section 6.9 to Appendix 12.	To clarify and provide lists of examples of prohibited concomitant therapies in advance.
5.3.1 Meals and Dietary Restrictions	'Postdose ECG measurements at 0.5- and 1 hour timepoints should be taken prior to any food intake' removed.	No postdose ECG procedures are planned.
6.6.3. Dose Up-titration Stopping Criteria	Follow-up period of 21 days changed to 14 days.	To correct error regarding overall design and SoA.
6.6.4 Dose Reduction	'CCI mg' changed to 'CCI mg'.	To make consistent with planned up-titrations dose levels.
6.6.4 Dose Reduction	'Highest received dose' added to text to definition of permitted dose reductions.	To further clarify the lower dose level definition during dose reduction.
8.2.6. Suicidal Ideation and Behavior Risk Monitoring	Clarification that the C-SSRS questionnaire will only have ideation and behavior categories assessed, and not intensity or lethality.	To clarify details of the C-SSRS questionnaire that was used during this compound development and will be used in this study.
8.4 Pharmacokinetics	Wording added to allow flexibility for PK collections.	To clarify requirements for PK collections.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests	Footnote 'a' added to follicle-stimulating hormone and thyroid-stimulating hormone tests.	To clarify that these tests are performed at screening only.
10.2 Appendix 2: Clinical Laboratory Tests	Footnote 'e' changed to clarify calcitonin is not assessed predose on Day 1 of Cohort 1 or 2.	To make consistent with the SoA.
10.11 Appendix 11: Clinical Laboratories and Specimen Disposal Units	Appendix added detailing laboratory responsibilities.	To clarify the laboratories responsible for clinical laboratory evaluation, hepatic evaluation, and pancreatitis testing.

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