Protocol J2A-MC-GZGC (c)

A Multiple-Dose Study in Participants with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970

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Approval Date: 28-Jan-2021

Title Page

Protocol Title: A Multiple-Dose Study in Participants with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970

Protocol Number: J2A-MC-GZGC

Amendment Number: (c)

Compound: LY3502970

Study Phase: Phase 1

Short Title: A Study of LY3502970 in Participants with Type 2 Diabetes Mellitus

Acronym: GZGC

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

EudraCT: 2020-000125-86

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Approval Date:

Protocol Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately.

Approval Date: 28-Jan-2021 GMT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment (b)	16-Sep-2020
Protocol amendment (a)	14-Aug-2020
Original Protocol	12-May-2020

The original protocol was amended as protocol amendment (a) to address the Food and Drug Administration (FDA) comments and to address the observations from the preceding Phase 1 Study J2A-MC-GZGA. Few minor typo errors were also corrected in this document.

Protocol amendment (a) was amended as protocol amendment (b) to address questions by the Federal Institute for Drugs and Medical Devices (BfArM) and the German Ethics Committee. This amendment also included certain changes proposed by Lilly.

Both protocol amendments (a) and (b) have been submitted and approved by the FDA. Details of the changes and the rationale for the changes are provided in Section 10.9.

Amendment (c)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The protocol was amended to add additional time points for weight measurement and clarify the replacement of discontinued participants.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities Study Schedule for Cohort A – Treatment Period Procedures Study Schedule for Cohort B through E – Treatment Period Procedures	Time point added for measurement of weight on Day 42. Time points added for measurement of weight on Days 36 and 42.	Participants could still be undergoing dose titration at these time points, and this data will contribute to the LY3502970 data analysis.
Section 9.2 Sample Size Determination	Updated verbiage on replacement of participants enrolled in the study.	To provide clarification on the criteria for the replacement of participants who have discontinued from the study for nonsafety reasons.
Section 9.3 Populations for Analysis	Deleted row on definition of randomized study participants	This is redundant as it was not used for statistical consideration.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multiple-Dose Study in Participants with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970

Short Title: A Study of LY3502970 in Participants with Type 2 Diabetes Mellitus

Rationale:

LY3502970 is a chemically synthesized, oral glucagon-like peptide-1 (GLP-1) receptor agonist that exhibits the antihyperglycemic actions of GLP-1. LY3502970 is being developed as a daily oral adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Study J2A-MC-GZGC will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple oral doses of LY3502970 in participants with T2DM.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of multiple oral doses of LY3502970 in participants with T2DM	• Incidence of TEAEs and SAE
Secondary	
• To characterize the PK of LY3502970 after multiple oral doses in participants with T2DM	• C_{max} and AUC
• To investigate the effects of LY3502970 on fasting plasma glucose and insulin following multiple oral doses administered to participants with T2DM	• Change in fasting plasma glucose, insulin, and C-peptide from baseline to Week 12

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event; T2DM = type 2 diabetes mellitus.

Overall Design

Study GZGC is a multicenter, randomized, participant- and investigator-blinded, placebo-controlled, multiple-dose, Phase 1 study with 3 study periods.

This 18-week study in participants with T2DM is designed to investigate the following:

- safety,
- tolerability,
- PK,
- PD, and
- efficacy of LY3502970.

Up to 5 cohorts, Cohort A through E, are planned. Each cohort comprises approximately 12 participants with T2DM with approximately 9 receiving LY3502970 and 3 receiving placebo.

The study will consist of 3 intervals:

- Study interval 1: screening and baseline,
- Study interval 2: treatment period, and
- Study interval 3: follow-up,

Disclosure Statement: This is a participant- and investigator-blinded, placebo-controlled study with up to 5 arms.

Number of Participants:

Approximately 72 participants may be randomly assigned to study intervention such that approximately 60 evaluable participants complete the study.

Intervention Groups and Duration:

Participants will be randomized in a 3:1 ratio to receive multiple daily doses of either LY3502970 or placebo. Doses of LY3502970 will escalate within each of the 5 cohorts over the first 4 to 8 weeks.

In Cohort A, 3, 6, 12, and 21 mg multiple daily doses of study intervention will be administered.

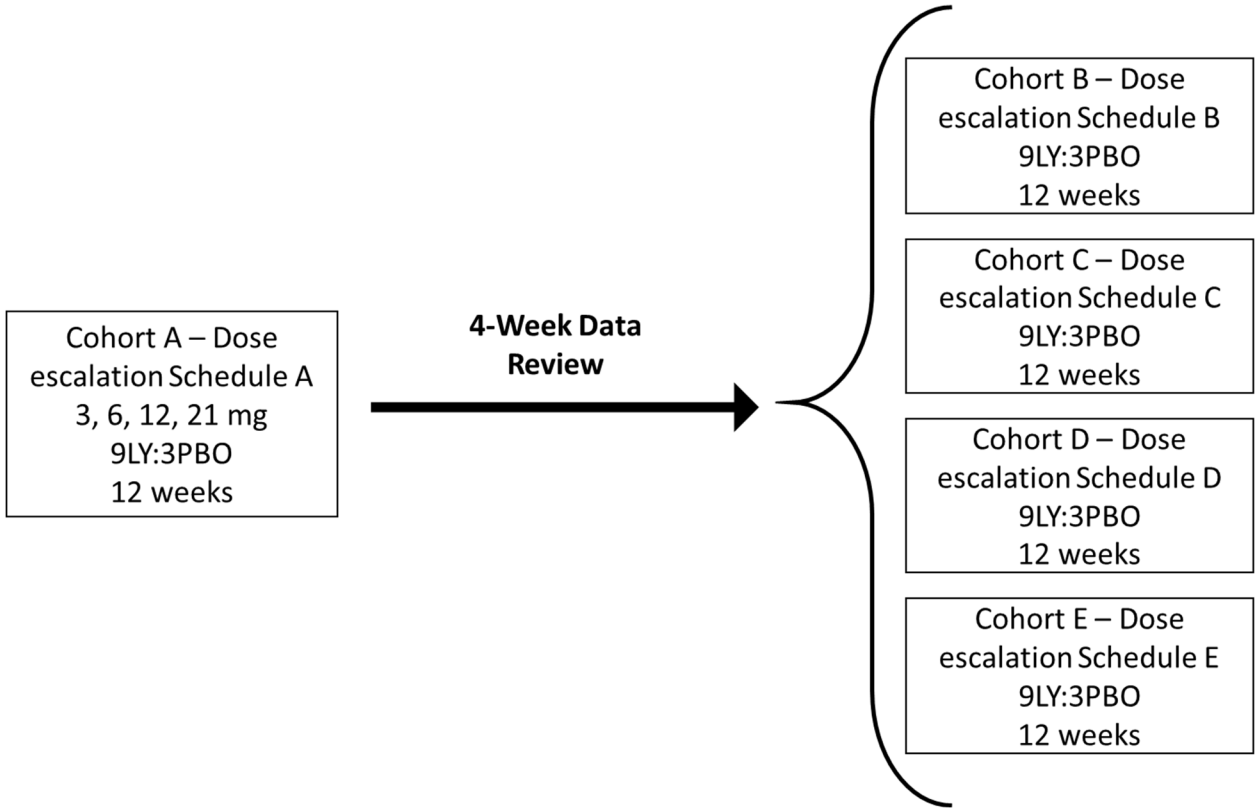
Cohorts B to E will run in parallel and the different maximum doses of LY3502970 and within dose-level escalation will be determined based on safety, tolerability, PK, and PD data from Cohort A.

The maximum total duration of study participation for each participant is up to 18 weeks, across the following study intervals:

- screening and baseline, approximately 4 weeks
- treatment period, 12 weeks
- follow-up, 1 to 2 weeks

Data Monitoring Committee: No

1.2. Schema



Abbreviations: LY = LY3502970; PBO = placebo.

1.3. Schedule of Activities (SoA)

Study Schedule for All Cohorts – Screening, Baseline, Early Termination, and Follow-up Procedures

Procedure	Screening	Baseline		Follow up/ET	Comments
	-28 to -3 days prior to Day 1	Day -2	Day -1	Day 91 to Day 105	
Informed Consent	X				
Admission to CRU		X			
Medical History	X				
Height	X				
Weight	X		X		Recorded on Day -1 for all cohorts.
Vital Signs	X			X	BP and PR (supine)
Body Temperature	X			X	
Clinical Laboratory Tests	X			X	See Appendix 2, Clinical Laboratory Tests, for details.
HbA1c	X				
6-point SMBG			X		Glucose measurements should be obtained before each meal (breakfast, lunch, and dinner) and approximately 2 hours after each meal
Serum Pregnancy Test	X				Females only.
Urine Pregnancy Test			X	X	Females only.
Physical Examination	X				Full physical examination at screening.
Medical Assessment			X	X	Medical review and targeted examination, as appropriate.
Urine Drug Screen and Ethanol Test	X		X		
Diary Handout			X		
Single 12-Lead ECG	X			X	
VAS for Appetite			Pre-meal		Administered at 30 min (±20 min) prior to the start of breakfast unless specific time points are shown.
Nonpharmacogenetics			X		

Procedure	Screening	Baseline		Follow up/ET	Comments
	-28 to -3 days prior to Day 1	Day -2	Day -1	Day 91 to Day 105	
Genetic Sample			X		
AE/Medication Review	X	X	X	X	
MMTT					The mixed meal should be given 24 h before the start of the meal on Day 1. Participants should consume the mixed meal within 15 or 20 min.
MMTT: insulin sample (h)			0, 0.25, 0.5, 1, 1.5, 2		Hours relative to the start of the MMTT meal.
MMTT: glucose sample (h)			0, 0.25, 0.5, 1, 1.5, 2		
MMTT: C-peptide sample (h)			0, 0.25, 0.5, 1, 1.5, 2		
Acetaminophen dose			X		Acetaminophen dose to assess gastric emptying will be administered 5 to 10 min after completion of the meal for MMTT. To be administered with 240 mL room temperature water
Acetaminophen PK samples			0, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12		Hour relative to acetaminophen dosing.

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; HbA1c = hemoglobin A1c; h = hours; min = minutes; MMTT = mixed meal tolerance test; PK = pharmacokinetics; PR = pulse rate; VAS = visual analog scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

Study Schedule for Cohort A – Treatment Period Procedures

Procedure	**Treatment Period**																**Comments**
Visit	**1**		**2**	**3**	**4**	**5**			**6**	**7**		**8**			**9**	**10**	
Day	**1**	**2**	**8**	**15**	**22**	**27**	**28**	**29**	**42**	**55**	**56**	**83**	**84**	**85**	**86**	**88 ± 24h**	
Admit to CRU						X				X		X					
Discharge from CRU		X						X			X		X				
Outpatient Visit			X	X	X				X					X	X	X	
Dispensing of IP	X		X	X	X		X		X		X		X				
Drug collection/account			X	X	X		X		X		X		X				
Weight	X		X	X	X		X		X		X		X				Measure fasted with empty bladder
Vital Signs	P		X	X	X		X		X	X		X	X				Supine BP and PR
Clinical Laboratory Tests	P			X			X		X			X					See Section 10.2 for details.
HbA1c	P						X				X		X				
6-point SMBG	X					X	X	X		X	X	X	X				Glucose measurements should be obtained before each meal (breakfast, lunch, and dinner) and approximately 2 hours after each meal.
Fasting Plasma Glucose	P		X	X	X				X				X				
Fasting Insulin	P		X	X	X				X				X				
Medical Assessment						X				X		X	X				Medical review and targeted examination, as appropriate
Urine Drug Screen and Ethanol Test						X				X		X					
Single 12-Lead ECG			X	X	X				X								

Procedure	**Treatment Period**																**Comments**
Visit	**1**		**2**	**3**	**4**	**5**			**6**	**7**		**8**			**9**	**10**	
Day	**1**	**2**	**8**	**15**	**22**	**27**	**28**	**29**	**42**	**55**	**56**	**83**	**84**	**85**	**86**	**88 ± 24h**	
Triplicate 12-Lead ECG	P, 0.5, 1, 2, 4, 6, 8, 12	24					P, 0.5, 1, 2, 4, 6, 8, 12						P, 0.5, 1, 2, 4, 6, 8, 12				ECGs must be recorded before collecting any vital signs or blood samples, close to the time of the blood draw, and prior to eating.
VAS for appetite	P		P	P	P		P				P		P				30 min (±20 min) before start of breakfast unless specific time points are shown
PK Samples (h)	P, 0.5, 1, 2, 4, 6, 8, 12	24					P, 0.5, 1, 2, 4, 6, 8, 12	24			P		P, 0.5, 1, 2, 4, 6, 8, 12	24	48	96	Sampling times are relative to study treatment administration (0 min).
AE/Diary Check	X		X	X	X	X			X	X		X	X				Includes a medication review
Lipid Panel	P						X				X		X				
Nonpharmacogenetics							X				X		X				
MMTT: 2 hours postdose, participants should consume the mixed meal within a 15- or 20-min window.																	
MMTT insulin sample							X				X		X				Collected at 2 (premeal) 2.25, 2.5, 3, 3.5, and 4 h postdose.
MMTT glucose sample							X				X		X				Collected at 2 (premeal), 2.25, 2.5, 3, 3.5, and 4 h postdose
MMTT C-peptide sample							X				X		X				Collected at 2 (premeal), 2.25, 2.5, 3, 3.5, and 4 h post dose

Procedure	**Treatment Period**															**Comments**
Visit	**1**		**2**	**3**	**4**	**5**			**6**	**7**		**8**			**9**	**10**	
Day	**1**	**2**	**8**	**15**	**22**	**27**	**28**	**29**	**42**	**55**	**56**	**83**	**84**	**85**	**86**	**88 ± 24h**	
Gastric Emptying: Acetaminophen dose will be administered approximately 2 h postdose and 5 to 10 min after completion of the meal for MMTT																	
Acetaminophen dose	X[a]				X[a]		X						X				To be administered with 240 mL room temperature water
Acetaminophen PK samples	X				X		X						X				Collected at 0, 0.5, 0.75, 1, 2, 3, 4, 6, 9, and 12 h post acetaminophen dose.

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; h = hours; HbA1c = glycated hemoglobin; IP = investigational product; min = minutes; MMTT = mixed meal tolerance test; P = predose; PK = pharmacokinetics; PR = pulse rate; VAS = visual analog scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

a On Days 1, and 22, the participants will consume the MMTT meal without collecting MMTT samples.

Study Schedule for Cohorts B through E – Treatment Period Procedures

Procedure	**Treatment Period**																**Comments**
Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**			**8**		**9**			**10**	**11**	
Day	**1**	**2**	**8**	**15**	**22**	**28**	**36**	**41**	**42**	**43**	**55**	**56**	**83**	**84**	**85**	**86**	**88 ± 24h**	
Admit to CRU								X			X		X					
Discharge from CRU		X								X		X		X				
Outpatient Visit			X	X	X	X	X								X	X	X	
Dispensing of IP	X		X	X	X	X	X		X			X		X				
Drug Collection/Account			X	X	X	X		X				X		X				
Weight	X		X	X	X	X	X		X			X		X				Measure fasted with empty bladder.
Vital Signs	P		X	X	X	X	X		X		X		X	X				BP and PR (supine)
Clinical Laboratory Tests	P			X		X	X		X				X					See Section 10.2 for details.
HbA1c	P					X						X		X				
6-point SMBG	X							X	X	X	X	X	X	X				Glucose measurements should be obtained before each meal (breakfast, lunch, and dinner) and approximately 2 hours after each meal
Fasting Plasma Glucose	P		X	X	X	X								X				
Fasting Insulin	P		X	X	X	X								X				
Medical Assessment			X	X	X	X	X	X			X		X	X				Medical review and targeted examination, as appropriate.
Urine Drug Screen and Ethanol Test								X			X		X					
Single 12-Lead ECG			X	X	X	X			X									

Procedure	**Treatment Period**																	**Comments**
Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**			**8**		**9**			**10**	**11**	
Day	**1**	**2**	**8**	**15**	**22**	**28**	**36**	**41**	**42**	**43**	**55**	**56**	**83**	**84**	**85**	**86**	**88 ± 24h**	
Triplicate 12-Lead ECG	P, 0.5, 1, 2, 4, 6, 8, 12	24							P, 0.5, 1, 2, 4, 6, 8, 12					P, 0.5, 1, 2, 4, 6, 8, 12				ECGs must be recorded before collecting any vital signs or blood samples, close to the time of the blood draw, and prior to eating.
VAS for appetite	P		P	P	P	P			P			P		P				Administered at 30 min (±20 min) prior to the start of breakfast unless specific time points are shown
PK Samples (h)	P, 0.5, 1, 2, 4, 6, 8, 12	24							P, 0.5, 1, 2, 4, 6, 8, 12	24		P		P, 0.5, 1, 2, 4, 6, 8, 12	24	48	96	Sampling times are relative to the time of study treatment administration (0 min).
AE/Diary Check	X		X	X	X	X		X			X		X	X				Includes a medication review
Lipid Panel	P					X						X		X				
Nonpharmacogenetics						X						X		X				
MMTT: 2 h post dose, participants should consume the mixed meal within a 15- or 20-min window.																		
MMTT insulin sample									X			X		X				Collected at 2 (premeal), 2.25, 2.5, 3, 3.5, and 4 h postdose.
MMTT glucose sample									X			X		X				Collected at 2 (premeal), 2.25, 2.5, 3, 3.5, and 4 h postdose.
MMTT C-peptide sample									X			X		X				Collected at 2 (premeal), 2.25, 2.5, 3, 3.5, and 4 h postdose.

Procedure	Treatment Period																	Comments
Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**			**8**		**9**			**10**	**11**	
Day	**1**	**2**	**8**	**15**	**22**	**28**	**36**	**41**	**42**	**43**	**55**	**56**	**83**	**84**	**85**	**86**	**88 ± 24h**	
Gastric Emptying: Acetaminophen dose will be administered approximately 2 h postdose and 5 to 10 min after completion of the meal for MMTT.																		
Acetaminophen dose	X[a]				X[a]				X					X				To be administered with 240 mL room temperature water
Acetaminophen PK samples	X				X				X					X				Collected at 0, 0.5, 0.75, 1, 2, 3, 4, 6, 9, and 12 h post acetaminophen dose.

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; h = hours; HbA1c = glycated hemoglobin; IP = investigational product; min = minutes; MMTT = mixed meal tolerance test; P = predose; PK = pharmacokinetics; PR = pulse rate; VAS = visual analog scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

a On Days 1, and 22, the participants will consume the MMTT meal without collecting MMTT samples.

2. Introduction

2.1. Study Rationale

LY3502970 is a chemically synthesized, oral glucagon-like peptide-1 receptor agonist (GLP-1RA) that exhibits the antihyperglycemic actions of GLP-1. LY3502970 is being developed as a daily oral adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Study J2A-MC-GZGC (GZGC) will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple oral doses of LY3502970 in participants with T2DM.

2.2. Background

Multiple GLP-1RA therapies are approved, the most commonly prescribed being administered once daily or once weekly through subcutaneous injection. Even with several different GLP-1RAs approved for use in T2DM, the injection remains a barrier for many patients to initiate and to adhere to therapy long-term. The recently approved oral semaglutide (Rybelsus®; Novo Nordisk; Rybelsus package insert, 2019) is expected to provide patients with a viable alternative to subcutaneous injection delivery. However, its administration requires the patient to adhere to a number of steps to improve bioavailability including:

- fasting for ≥6 h,
- no more than approximately 120 mL of water at administration, and
- no food or fluid for at least 30 min after taking the medication (Hedrington and Davis 2019; Rybelsus package insert, 2019).

Therefore, providing additional oral GLP-1RA therapies remains an unmet need. LY3502970 is an oral GLP-1RA that exhibits the antihyperglycemic actions of GLP-1, acting as an insulin secretagogue and increasing glucose-dependent insulin secretion after a glucose challenge.

A detailed description of the chemistry, pharmacology, efficacy, and safety of LY3502970 is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

No safety or tolerability concerns that preclude further investigation of LY3502970 have been identified in 100 healthy participants to date, up to the highest single dose given (6 mg) and multiple dose given (24 mg).

To mitigate the well-known gastrointestinal (GI) tolerability issues of GLP-1 RA, participants will be assigned a treatment regimen that includes increasing or escalating doses of LY3502970. Before each dose escalation step, the investigator will 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 escalation steps will be approximately weekly, and escalation will occur in the early part of the study until the target final dose is achieved. Participants will continue on that final target dose for the remainder of the treatment period.

The nonclinical safety profile of LY3502970 included negative genetic toxicity and a range of target organ effects that were generally associated with pharmacologic and class-effect activity. These included

- increased PR interval
- decreased blood pressure
- decreased gastrointestinal motility
- vomiting
- decreased food consumption
- body weight loss

These effects were reversible and monitorable. CCI [redacted] Additionally, a potential off-target embryo-fetal developmental effect was identified in a pilot study in pregnant rabbits. Women of childbearing potential will not be included in the proposed clinical trial. No-observed-adverse-effect dose levels (NOAELs) have been identified in both rats and monkeys and are associated with the projected exposure multiples at the planned human doses (see Table 4.1). It is informative to examine the exposure multiples that correspond to the maximum tolerated doses (MTD) in these studies (see Table 4.2). For rats, these levels are the same but for monkeys the MTD was the highest dose given and was characterized by effects that were consistent with exaggerated pharmacology or class effects, and that are considered monitorable and reversible in clinical trial participants. An adequate margin of safety has been demonstrated for the rat and these data do not suggest any potential off-target toxicities. The observation of pharmacologically mediated toxicity in the monkey and the adequate margins observed in the rat for off-target toxicity are considered sufficient to enable further safe clinical investigation of LY3502970 in the proposed dose range.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of LY3502970 may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of multiple oral doses of LY3502970 in participants with T2DM	• Incidence of TEAEs and SAEs
Secondary	
• To characterize the PK of LY3502970 after multiple oral doses in participants with T2DM	• C_{max} and AUC
• To investigate the effects of LY3502970 on fasting plasma glucose and fasting insulin following multiple oral doses administered to participants with T2DM	• Change in fasting plasma glucose and fasting insulin from baseline to Week 12
Exploratory	
• To investigate the PD effects of LY3502970 following multiple oral doses administered to participants with T2DM	• The absolute change in body weight from baseline to Week 12 • The change in C-peptide, glucose, and insulin during MMTT from baseline to Week 12 • The change in lipid profile from baseline to Week 12 • The change in VAS for appetite from baseline to Week 12 • Gastric emptying using acetaminophen • Insulin sensitivity • Beta-cell function
• To evaluate the efficacy of multiple oral doses of LY3502970 in participants with T2DM	• The absolute change in HbA1c from baseline to Week 12

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; HbA1c = glycated hemoglobin A1c; MMTT = mixed meal tolerance test; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event; VAS = visual analog scale.

4. Study Design

4.1. Overall Design

Study GZGC is a multicenter, randomized, participant- and investigator-blinded, placebo-controlled, multiple-dose, Phase 1 study with 3 study periods. The study is designed to investigate the safety, tolerability, PK, PD, and efficacy of LY3502970 in participants with T2DM for 12 weeks. Up to 5 cohorts, Cohorts A through E, are planned. Each cohort comprises approximately 12 participants with T2DM with approximately 9 receiving LY3502970. For all cohorts, LY3502970 administration by oral dosing will begin on Day 1 and continue through Day 84.

The study will consist of 3 intervals:

- screening and baseline, approximately 4 weeks
- treatment period, 12 weeks
- follow-up, 1 to 2 weeks

The study schema is presented in Section 1.2.

Study governance considerations are described in detail in Section 10.1.

4.1.1. Study Visits

Screening and Baseline

The purpose of procedures at screening is to establish eligibility for inclusion in the study (see Sections 5.1 and 5.2). After completing all screening assessments, eligible participants will be admitted to the clinical research unit (CRU) on Day -2 for baseline procedure performed during Visit 1. During this period, participants will receive a participant diary and undergo procedures specified in the Schedule of Activities (SoA) (Section 1.3). The participants should use the diaries to track the following:

- at-home dosing schedule,
- any missed doses,
- self-monitoring of blood glucose,
- any AEs, and
- any episodes of hypoglycemia.

Also, on Day -1, a baseline PD profile using a mixed meal tolerance test (MMTT) and a baseline gastric emptying measure will be collected.

Treatment Period

While inpatient at the CRU, participants will receive their first oral dose of study intervention on Day 1. Participants should complete the study assessments and procedures planned during this period as specified in Section 1.3. Participants may be discharged from the investigative site on Day 2.

For all cohorts, participants will return to the CRU for outpatient visits on Days 8, 15, and 22 for planned study assessments and procedures. Participants should be fasting for at least 8 h upon

arrival to the investigative site. The study assessments and procedures planned during these outpatient visits should be performed as specified in Section 1.3.

For Cohort A, participants will be admitted to the CRU for an inpatient stay on Days 27, 55, and 83. Participants should be fasted for at least 8 h prior to the assessments and procedures scheduled on Days 28, 56, and 84. Participants may be discharged on Days 29, 56, and 84 following completion of procedures specified in Section 1.3.

Participants in Cohort A will return to the CRU for an outpatient visit on Days 42, 85, 86, and 88. Participants should be fasting for at least 8 h upon arrival to the investigative site. The study assessments and procedures planned should be performed as specified in Section 1.3.

For Cohorts B through E, participants will return to the CRU for an outpatient visit on Days 28, 36, 85, 86, and 88. Participants should be fasting for at least 8 h upon arrival to the investigative site. The study assessments and procedures planned should be performed as specified in Section 1.3.

Participants in Cohorts B, C, D, and E will be admitted to the CRU for an inpatient stay on Days 41, 55, and 83. Participants should be fasted for at least 8 h prior to the assessments and procedures scheduled on Days 42, 56, and 84. Participants may be discharged on Days 43, 56, and 84 following completion of procedures specified in Section 1.3.

The dose-escalation schemes for Cohorts B through E will be determined only after safety and tolerability of LY3502970 have been observed in patients with T2DM in Cohort A (dose up-titration scheme 3 mg, 6 mg, 12 mg, and 21 mg). Assuming the patients in Cohort A tolerate LY3502970 through 21 mg, which is expected as the healthy subjects tolerated 24 mg, the planned dose-escalation steps for Cohorts B through E will be

- 3, 6, and 9 mg
- 3, 6, 12, and 15 mg
- 3, 6, 12, 21, and 27 mg
- 3, 6, 9, 21, 36, and 45 mg

Follow-up

A follow-up visit 7 to 21 days after the last dose will be performed according to the SoA (Section 1.3).

4.2. Scientific Rationale for Study Design

This study will evaluate up to 5 dosing regimens of LY3502970 in participants with T2DM, compared with a placebo control. Based on the safety, tolerability and PD response of participants after 4 weeks of dosing in Cohort A, the doses and titration steps will be decided for Cohorts B, C, D, and E. The intention will be to evaluate a range of final doses (after 4 to 8 weeks of within cohort dose escalation) that travers the potential estimated efficacious dose range.

The study will last 12 weeks to have an adequate duration of exposure necessary to assess safety, tolerability, and PK/PD of LY3502970.

CCI

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CCI

- It is known that patients with T2DM tend to tolerate higher doses of GLP-1RAs (Coskun et al. 2018) and CCI

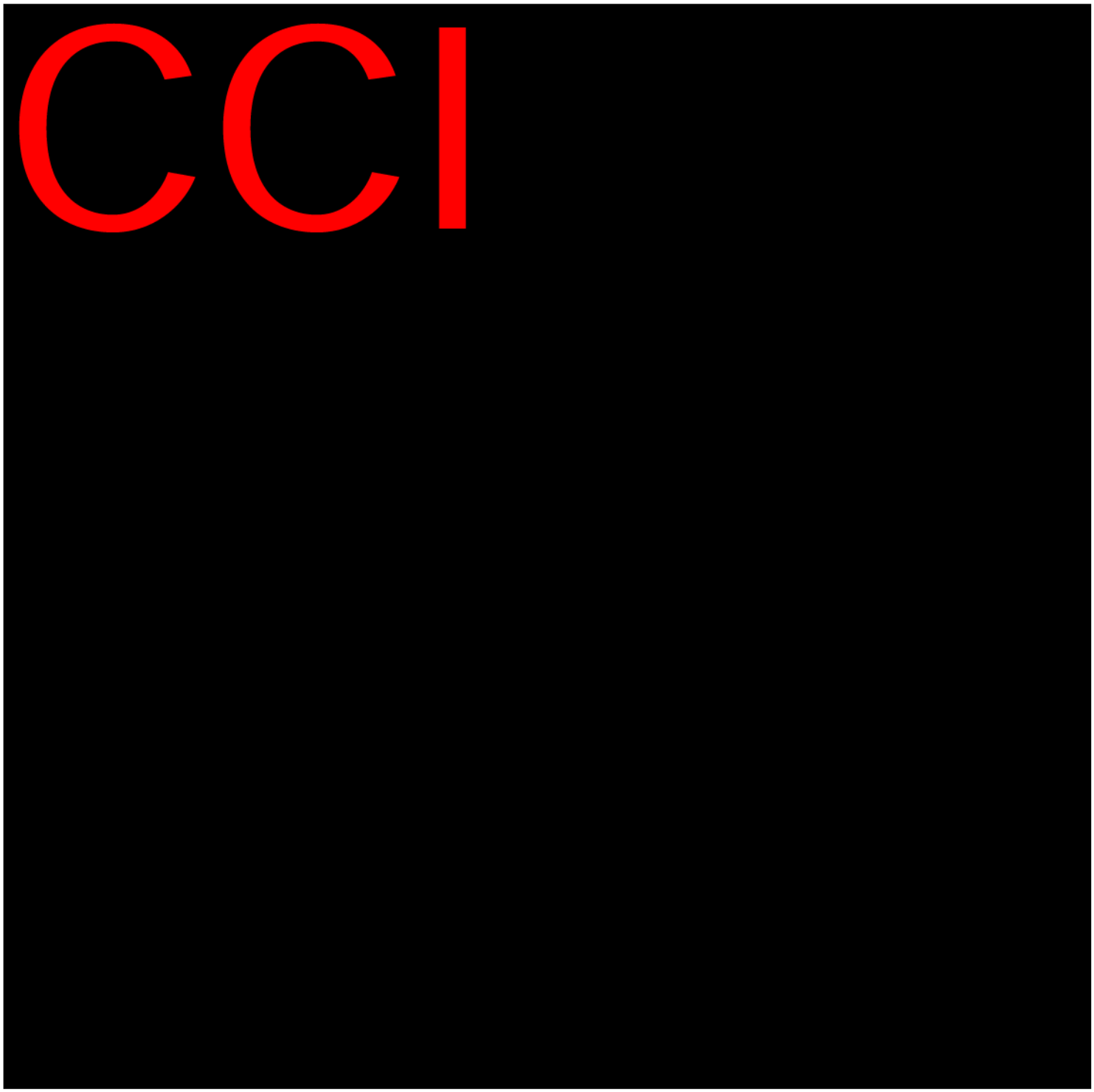
CCI

- The selected dose levels and dose range for the later Cohorts B to E will evaluate various titration schemes and support dose exposure-response analysis of multiple safety and efficacy measures to support selection of dose(s) of LY3502970 with optimal benefit-risk ratio for further clinical development.

CCI

Safety of study participants will be closely monitored during the early stages of dose escalation to determine whether adjustments to the initial dose and dose adjustment are needed. As additional data emerge, dose levels and titration schemes may be modified.

For more details of the tolerability profile of participants in Study GZGA, see the Investigator's Brochure for LY3502970.



4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3). A participant who has missing data for a small number of the study activities may still be considered to have completed the study after review by the sponsor team.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

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 electrocardiogram (ECG).

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only, and not continuously throughout the trial.

Screening may occur up to 28 days prior to enrollment. Participants who are not enrolled within 56 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. In such instances, repeat all the screening tests and procedures.

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 at screening:

Type of Participant and Disease Characteristics

1. Participants with T2DM for at least 6 months
2. have a glycated hemoglobin (HbA1c) value at screening of ≥7.0% and ≤10.5% and are treated with diet and exercise alone or a stable dose of metformin for at least 3 months prior to screening
3. have a body weight of ≥45 kg and have a body mass index of 18.5 to 45 kg/m^2, inclusive
4. have had a stable body weight for the 3 months prior to screening (<5% body weight change)
5. have clinical laboratory test results within normal reference range for the population or CRU, or results with acceptable deviations that are judged to be not clinically significant by the investigator
6. have venous access sufficient to allow for blood sampling as per the protocol
7. are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

Participant Characteristics

8. Males and females (not considered woman of childbearing potential) aged 18 to 70 years, inclusive, at the time of signing the informed consent. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For contraceptive guidance refer to Section 10.4.

Informed Consent

9. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

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

Medical Conditions

1. have type 1 diabetes mellitus, latent autoimmune diabetes in adults or have had an episode of ketoacidosis or hyperosmolar state requiring hospitalization in the 6 months prior to screening
2. have active proliferative diabetic retinopathy, diabetic maculopathy, or severe nonproliferative diabetic retinopathy that requires acute treatment as determined by an ophthalmologist
3. present with uncontrolled comorbid conditions commonly associated with diabetes (for example, hypertension, hypercholesterolemia) or have had changes to medication for those conditions within 1 month prior to screening
4. have had an episode of severe hypoglycemia, as defined by the occurrence of neuroglycopenic symptoms requiring the assistance of another person for recovery, within 6 months prior to screening visit, or have a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms. Any patient that the investigator feels will not be able to communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia should also be excluded
5. have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction), have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®)
6. have active or symptomatic gastric ulceration or chronic gastritis
7. have known definitive diagnosis of autonomic neuropathy as evidenced by neuropathic urinary retention, resting tachycardia, orthostatic hypotension, or diabetic diarrhea
8. have obesity induced by other endocrine disorders (such as Cushing's syndrome or Prader-Willi syndrome)
9. have had any of the following within the past 6 months prior to screening: myocardial infarction, unstable angina, coronary artery bypass graft, percutaneous coronary intervention (diagnostic angiograms are permitted), transient ischemic attack, cerebrovascular accident or decompensated congestive heart failure, or currently have New York Health Association Class III or IV heart failure
10. have an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, as determined by the local laboratory at screening or a level of eGFR that would contraindicate the use of metformin per the label in the respective country. Participants on metformin must meet local label requirements

11. have donated blood of more than 500 mL within the previous 3 months of study screening or have had a blood transfusion or severe blood loss within 3 months prior to screening or have any hematologic condition that may interfere with HbA1c measurement (e.g., hemoglobinopathy, hemolytic anemia, sickle-cell disease).
12. hemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with HbA1c methodology
13. have a history of atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis)
14. have known allergies to LY3502970 related compounds or any components of the formulation, acetaminophen, or history of significant atopy
15. have an abnormal blood pressure and/or pulse rate as determined by the investigator
16. have a history or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product [IP]; or of interfering with the interpretation of data
17. have an abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study or may confound ECG (QT) data analysis, such as a QT interval corrected using Fridericia's formula (QTcF) >450 msec for males and >470 msec for women, or PR interval >220 msec, second and third atrioventricular block, intraventricular conduction delay with QRS >120 msec, right bundle branch block, left bundle branch block, or Wolff-Parkinson-White syndrome
18. have evidence of hypothyroidism or hyperthyroidism based on clinical evaluation or an abnormal thyroid-stimulating hormone (for those with current or previous thyroid history) 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
19. have a history of acute or chronic pancreatitis or fasting serum triglyceride level of >500 mg/dL
20. amylase or lipase >2.5x ULN
21. have known liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or have elevations in aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) greater than 2X upper limit of normal (ULN)
22. have a history of Gilbert's syndrome or have total bilirubin level (TBL) above 1.5X ULN.
23. show evidence of current hepatitis C by testing positive for anti-hepatitis C antibody with confirmed presence of hepatitis C virus (HCV)

Note: Participants with a previous diagnosis of hepatitis C who have been treated with antiviral therapy and achieved a sustained virological response may be eligible for inclusion in the study, provided that they have no detectable HCV RNA on the screening HCV polymerase chain reaction test for this protocol. A sustained virological response is defined as an undetectable HCV RNA level 24 weeks after completion of a full, documented course of an approved antiviral therapy for HCV.

Participants who have spontaneously cleared HCV infection, defined as (1) a positive HCV antibody test and (2) a negative HCV RNA test, with no history of HCV antibody (anti-HCV) treatment, may be eligible for inclusion in the study, provided that they have no detectable HCV RNA at screening for this study.

24. show evidence of hepatitis B, and/or positive hepatitis B surface antigen
25. have active or untreated malignancy, or have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years (10 years for breast cancer), or are at increased risk for developing cancer or a recurrence of cancer in the opinion of the investigator
26. have a known self or family history (first-degree relative) of multiple endocrine neoplasia Type 2A or 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma
27. have a screening calcitonin >20 pg/mL as determined by the local laboratory
28. have known or ongoing psychiatric disorders considered clinically significant in the opinion of the investigator, including participants on medications that may affect food intake and/or body weight
29. regularly use known drugs of abuse or show positive findings on drug screening
30. show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies
31. have a history or presence of/significant history of or current conditions constituting a risk when taking the IP; or of interfering with the interpretation of data

Prior/Concomitant Therapy

32. any glucose-lowering medications other than metformin within 3 months prior to screening
33. have been treated or plan to be treated with prescription medications that promote weight loss (for example, Saxenda® [liraglutide 3.0 mg], Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Adipex® [phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], Contrave® [naltrexone/bupropion] or other similar body weight loss medication including over-the-counter [OTC] medications, for example, allī®]) within 3 months prior to screening
34. have received chronic systemic glucocorticoid therapy (>2 weeks) in the past year or within 4 weeks prior to screening (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations)
35. are currently taking a central nervous system stimulant (for example, Ritalin-SR) with the exception of caffeinated beverages

36. use of any drugs or substances that are known strong inducers or inhibitors of cytochrome P450 (CYP)3A and P-glycoprotein (P-gp) is specifically excluded within 14 days prior to the first administration of study drug and during the study

Prior/Concurrent Clinical Study Experience

37. are currently enrolled in any other clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study
38. have participated, within the last 30 days in a clinical trial involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed
39. have previously completed or withdrawn from this study or any other study investigating LY3502970

Other Exclusions

40. have an average weekly alcohol intake that exceeds 21 units per week (males ≤65 years) and 14 units per week (females and males above >65 years), or are unwilling to stop alcohol consumption from 24 h prior to dosing day, until the patient has been discharged from the CRU
41. smoke more than 10 cigarettes per day or are unable to abide by CRU smoking restrictions
42. are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
43. are employees of Eli Lilly and Company (Lilly) or the CRU
44. in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), qualified medical staff will provide diabetes management counseling, which will include instructions on diet and exercise and education about the signs, symptoms, and treatment of hypoglycemia, should it occur.

Prescription or OTC medications that promote weight loss are exclusionary if used within 3 months prior to screening or between screening and randomization. These medications are also not allowed at any time during the treatment period. If started after randomization, the medications should be immediately withdrawn.

Study participants should be instructed not to donate blood or blood products during the study or for 4 weeks following the study.

5.3.1. Meals and Dietary Restrictions

Participants will be provided with meals while resident at the CRU. The calorie intake and composition of these meals will not be pre-defined, except for the evening meal before an MMTT test Section 8.6.3.

A meal supplement will be provided on each day where there is an MMTT as described in Section 8.6.3, and during this test appetite will be assessed using visual analog scale (VAS) (Section 8.6.6).

If the participant is unable to consume the MMTT meal completely, the leftover amount (as percentage of total meal) will be recorded in the electronic case report form (eCRF). At all other times, participants should maintain their standard diet.

While in the CRU, participants will be administered study intervention with approximately 240 mL of room temperature water. Fluids will be restricted 1 h prior to and until 1 h after dosing, except for the water required for dose administration. Water may be consumed freely at all other times.

While in the CRU, participants will be required to fast overnight for at least 8 h before taking an oral dose of study intervention and for each study day when clinical safety laboratory, PK, and PD samples are taken and MMTTs are administered. Postdose ECG measurements should be taken prior to any food intake.

Participants should maintain adequate carbohydrate intake for the 3 days before the scheduled MMTT and will be fasted for at least 10 h before administration of the MMTT meal.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants will be allowed to maintain their regular caffeine consumption throughout the study period.

No alcohol will be allowed at least 24 h before each CRU admission and each outpatient visit and throughout the duration of each CRU visit. Between CRU visits, daily alcohol should not exceed 3 units for males and 2 units for females (a unit is defined in Exclusion Criterion [38], Section 5.2).

No nicotine use will be permitted while at the CRU. While not resident in the CRU, participants must consume no more than 10 cigarettes or equivalent per day.

5.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity/exercise during the study. When certain study procedures are in progress at the site, participants may be required to remain recumbent or sitting.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened twice. Rescreened participants should be assigned a new participant number. When rescreening, all screening tests and procedures should be repeated. The interval between

rescreenings should be at least 2 weeks. Each time rescreening is performed, the individual must sign a new ICF. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

This study involves a comparison of LY3502970 administered as oral daily dosing with placebo. Table 6.1 shows the treatment regimens.

6.1.1. Administration Details

Three capsules of either LY3502970 or placebo will be administered orally with 240 mL of room temperature water in the morning of each dosing day in a sitting position. The three capsules should be taken within 3 min. Participants will not be allowed to lie supine for 2 h after dosing, unless clinically indicated or for study procedures.

6.2. Preparation/Handling/Storage/Accountability

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

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply 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 site staff.

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an interactive web-response system (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 (Section 1.3).

Returned study interventions should not be re-dispensed to the participants.

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

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

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 clinical pharmacologist (CP) or clinical research physician (CRP) for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

In case of an emergency, the investigator has the sole responsibility of 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.

6.3.1. Package and Labeling

The drug product is supplied for clinical trial use as capsules for oral administration.[redacted] lacebo capsules look identical. The drug product should be stored according to instructions on the label.

The IP will be labeled according to the country's regulatory requirements.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the case report form (CRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by viewing participants; diaries during the site visits and documented in the source documents and CRF. It is preferred that participants take their dose before breakfast in the morning, but if they forget, it can be taken later that day.

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/or 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 the following:

- Information about study intervention administered at home by the participant via the participant's diary
- Information about the participant's adherence to the SoA
- Information about the participant's compliance with concomitant medications via the participant's diary
- Information about any other parameters the investigator considers necessary

6.5. Concomitant Therapy

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

Acetaminophen, at doses of ≤2 g/day, is permitted for use during the study and administered at the discretion of the investigator. In the case of mild intercurrent illness during the study, concomitant treatment with acetaminophen may be allowed at the discretion of the investigator. This will be recorded in the CRF. However, concomitant treatment with acetaminophen should not be allowed after midnight prior to the gastric-emptying test and throughout the day of the gastric-emptying test.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

The only concomitant antihyperglycemic medication permitted during this study is metformin. Metformin treatment must be stable for at least 3 months prior to screening.

Participants who enter the study on diet and exercise alone will not be allowed to initiate metformin therapy after study entry unless criteria for rescue therapy are met.

Participants who are being treated with metformin upon entering this study should remain on the same (or equivalent if switching to sustained release) metformin dose throughout the course of the study unless a change in dose is required to protect participants' safety. In case an adjustment is required due to recurrent/persistent hypoglycemia, refer to Section 7.1.4.

If a participant switches from the immediate-release formulation of metformin to the sustained-release formulation, the change will be on a milligram-per-milligram basis.

Doses of antihypertensive and lipid-lowering therapies must be stable for 30 days prior to screening. Doses of antihypertensive and lipid-lowering agents should not be changed during this study unless necessary to protect patient's safety on an emergency basis (for example, hypertensive crisis).

Doses of other prescription medications for treatment of concurrent medical conditions should remain constant during the study whenever possible.

Specifically excluded concomitant medications include the following:

- chronic use of medications that directly reduce GI motility including, but not limited to, anticholinergics, antiemetics, and opiates (for example, metoclopramide, promethazine, dicyclomine, and morphine)
- chronic use of medications that directly promote GI motility (for example, bethanechol and cisapride)
- prescription or OTC medications to promote weight loss
- have received chronic systemic glucocorticoid therapy (>2 weeks) in the past year or within 4 weeks prior to screening (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations)
- central nervous system stimulants (for example, Ritalin®-SR)
- strong inhibitors or inducers of CYP3A or P-glycoprotein (P-gp)

- any drug, other than those provided in this study, that has not received regulatory approval.

If the need for additional concomitant medication arises, the patient may be continued in the study on study medication if, in the investigator's opinion, the addition of the new medication does not pose a safety risk, and the sponsor agrees to the participants continuation in the study.

Nausea and/or vomiting during this study may be treated with antiemetics but these medications should not be used prophylactically. Nonsteroidal anti-inflammatory medications (including ibuprofen, aspirin), acetaminophen, 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. Any additional medication used during the study (including those not requiring sponsor notifications) must be documented on the appropriate eCRF.

6.6. Dose Modification

The participants should follow the planned dosing regimen. In the case of poor tolerability at any time during the study, dosing can be interrupted temporarily (Section 7.1).

6.6.1. Data Review during the Study

Interim access to data reviews is planned for this study.

Access to safety, tolerability, PD, and available PK data is scheduled after approximately 10 participants in Cohort A complete study procedures at 4 weeks. The purpose of this review is to guide dose selection for the subsequent part of the study (Cohorts B, C, D, and E).

Access to safety, tolerability, PD, and available PK data is scheduled to occur after 50% of participants in Cohort B through E complete 6 weeks of study procedures. The purpose of this review is to guide dose selection for subsequent development.

6.7. Intervention after the End of the Study

Study completion will occur following the final analysis of primary and secondary objectives, as determined by Lilly. Investigators will continue to follow SoA (Section 1.3) for all participants until notified by Lilly that study completion has occurred.

Investigational product will not be made available to participants after conclusion of the study. After study intervention is discontinued, an appropriate diabetes treatment regimen will be initiated by the investigator.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Participants discontinuing from study intervention prematurely for any reason should complete an Early Termination visit 7 to 21 days after the last dose of study drug and complete assessments of AEs and other follow-up procedures per Section 1.3 of this protocol.

Discontinuation of IP should be considered by the investigator if any of the following occur in a patient:

- an AE that is considered to be intolerable,
- an abnormal safety laboratory test result, determined to be clinically significant by the investigator, or
- the mean corrected QT interval (QTc) >500 msec or an increase from baseline in QTc >60 msec (if upon review the finding is confirmed by a cardiologist).

If a clinically significant cardiac 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 in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Early Termination of the Study

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

- One study participant develops an SAE considered possibly or probably related to study drug and is severe or medically significant
- Three study participants develop the same treatment-emergent adverse event (TEAE) or SAE considered possibly or probably related to study drug that is severe or medically significant, but not immediately life-threatening; or where hospitalization or prolongation of hospitalization is indicated; or is disabling; or limits self-care activities of daily living.
- Two study participants develop any TEAE or SAE regardless of attribution to study drug that has life-threatening consequences or requires urgent intervention.
- Death of any study participant at any time related to AE.

If either an SAE or 2 severe AEs considered possibly or probably related to study drug CCI [redacted] then dosing of patients receiving doses at and above

the level that the events occurred at will be interrupted. A restart of dosing at those dose levels can occur only with the agreement from the regulatory authorities.

7.1.2. Hepatic and Pancreatic Criteria for Discontinuation

Discontinuation of the study intervention for abnormal liver tests **should be considered** by the investigator when a participant meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

- ALT or AST >8X ULN
- ALT or AST >5X ULN sustained for more than 2 weeks or
- ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio (INR) >1.5 or
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- Lipase and/or amylase ≥3X ULN (Appendix 7 [Section 10.7] should be considered by the investigator)

Participants who discontinue from study intervention due to the abnormal liver tests will undergo monitoring as described in Sections 10.6 and 10.7.

7.1.3. Intolerable Gastrointestinal Events

In the presence of persistent GI events, participants who are unable to tolerate their assigned dose level for ≥1 week (have persistent vomiting or moderate to severe nausea) should be discontinued from using the study intervention.

7.1.4. Persistent Hyperglycemia/Hypoglycemia

Discontinuation of the IP should be considered by the investigator for participants with any persistent severe hyperglycemia, defined as a persistent fasting plasma glucose level above 240 mg/dL, without an identified cause (for example, intercurrent illness).

Discontinuation of the IP should be considered by the investigator for participants with severe hypoglycemia (Level 3 according to Section 8.2.6.4) or persistent hypoglycemic events (Levels 1 and 2).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant or the participant's partner becomes pregnant during the study

- if enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

Discontinuation is expected to be uncommon.

Participants will be discontinued under the following circumstances:

- Enrollment in any other clinical study involving a study intervention or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- Any TEAE or SAE considered possibly or probably related to study drug that is severe but not immediately life threatening; or where hospitalization or prolongation of hospitalization is indicated; or is disabling; or limits self-care activities of daily living.
- Any TEAE or SAE regardless of attribution to study drug that has life-threatening consequences or urgent intervention is indicated.
- Investigator Decision
    - the investigator decides that the patient should be discontinued from the study
    - if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

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

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. The replacement strategy for discontinued participants is described in Section 9.2. Participants discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per Section 1.3 of this protocol.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from using the study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the CP agree it is medically

appropriate to continue, the investigator must obtain documented approval from the Lilly CP to allow the inadvertently enrolled participant to continue in the study with or without treatment with IP. All inadvertently enrolled participants will complete safety follow up as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

The documented approval must contain the benefit/risk assessment and a robust clinical justification that continuing in the study will not jeopardize the participant's safety.

7.3. Lost to Follow up

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

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

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

8. Study Assessments and Procedures

Section 1.3 lists the SoA, detailing the study procedures and their timing (including tolerance limits for timing).

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time has to be correctly recorded in the CRF. Failure or being late (i.e., outside stipulated time allowances) to perform procedures or obtain samples due to legitimate clinical issues (e.g. equipment technical problems, venous access difficulty, or subject 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 10.2 lists the laboratory tests that will be performed for this study.

Appendix 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

8.1.1. Exploratory Efficacy Assessment

The exploratory efficacy measure is the absolute change in HbA1c from baseline to Week 12. The planned time points for HbA1c assessments are provided in the SoA (Section 1.3).

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded. Refer to Section 8.2.3 for further details on weight measurements.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, all vital sign measurements should be conducted according to the SoA (Section 1.3) and each measurement recorded in the CRF.

Vital sign measurements should be obtained before collection of blood samples.

Blood pressure and pulse rate should be measured twice after at least 5 min in a supine position.

If orthostatic measurements are required, participants should be supine for at least 5 min and stand for at least 2 min. If the participant feels unable to stand, only supine vital signs will be recorded. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

Body temperature will be measured according to the SoA (Section 1.3). All measurements will be recorded in the CRF.

8.2.3. Body Weight

Weight will be measured as indicated in the SoA (Section 1.3) and all measurements will be recorded in the CRF. Participants will be weighed in light clothing at approximately the same time in the morning before dosing and after an overnight fast and evacuation of bowel and the bladder, if possible.

During the treatment period, weight will be measured twice on each scheduled occasion, with the participant stepping off the scale between measurements. Both weight measurements will be recorded in the source document and the CRF. Wherever possible, the same scale will be used for all weight measurements throughout the study and the scale will not be moved or recalibrated.

8.2.4. Electrocardiograms

For each participant, both single and triplicate 12-lead digital ECGs will be collected according to the SoA (Section 1.3). Electrocardiograms must be recorded before collecting any vital signs or blood samples. Participants must be supine for approximately 5 to 10 min before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All single ECGs recorded should be stored at the investigational site.

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

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

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

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

8.2.5. Clinical Safety Laboratory Assessments

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

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

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

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

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.

8.2.6. 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 the following data:

- trends in safety data
- laboratory analytes including ALT, AST, TBL, amylase, and lipase
- adverse events, including AEs of special interest (AESIs; nausea, vomiting, and diarrhea), and
- reported and adjudicated pancreatitis.

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

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

8.2.6.1. Hepatic Safety

Close hepatic monitoring

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

If a participant with baseline results of	develops the following elevations:
ALT or AST <1.5X ULN	ALT or AST ≥3X ULN
ALP <1.5X ULN	ALP ≥2X ULN
TBL <1.5X ULN	TBL ≥2X ULN
ALT or AST ≥1.5X ULN	ALT or AST ≥2X baseline
ALP ≥1.5X ULN	ALP ≥2X baseline
TBL ≥1.5X ULN	TBL ≥2X baseline

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

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example,

heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including OTC), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

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

Comprehensive hepatic evaluation

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

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5X ULN	ALT or AST ≥3X ULN with hepatic signs/symptoms*, or ALT or AST ≥5X ULN
ALP <1.5X ULN	ALP ≥3X ULN
TBL <1.5X ULN	TBL ≥2X ULN
ALT or AST ≥1.5X ULN	ALT or AST ≥2X baseline with hepatic signs/symptoms*, or ALT or AST ≥3X baseline
ALP ≥1.5X ULN	ALP ≥2X baseline
TBL ≥1.5X ULN	TBL ≥1.5X baseline

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

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

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

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum 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 safety data collection in hepatic safety CRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests (if baseline ALT <1.5X ULN)

- In participants with baseline ALT ≥1.5X ULN, the threshold is ALT ≥3X baseline on 2 or more consecutive tests

2. Elevation of TBL to ≥2X ULN (if baseline TBL <1.5X ULN)
    - In participants with baseline TBL ≥1.5X ULN, the threshold should be TBL ≥2X baseline
3. Elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests (if baseline ALP <1.5X ULN)
    - In participants with baseline ALP ≥1.5X ULN, the threshold is ALP ≥2X baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study intervention due to a hepatic event

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

8.2.6.2. Pancreatic Safety

Serum amylase and lipase measurements will be collected as part of the clinical laboratory testing at time points specified in the SoA (Section 1.3). Additional measurements may be performed at the investigator's discretion.

Further diagnostic assessments will be recommended whenever lipase and/or amylase are confirmed to be ≥3X ULN at any visit posttreatment sequence allocation even if the participant is asymptomatic (as per the algorithm for the monitoring of pancreatic events in Section 10.7) and, if pancreatitis is suspected, the case will be further defined during an adjudication process.

To ensure participant safety and compliance with regulatory guidance, the investigator is to consult with the Lilly CP or CRP regarding collection of specific recommended clinical information and follow-up laboratory tests.

8.2.6.3. Glucose Monitoring

Participants will receive training on routine self-monitoring blood glucose and paper diary completion required during the study. When outpatient, participants should follow the investigator's instructions related to frequency of self-monitoring of blood glucose (BG). Participants should test their glucose while under fasted conditions, and at a minimum of 3 times per week; participants will be instructed to record their results in their diaries. When inpatient, 6-point glucose profiles consisting of glucose measurements should be obtained before each meal (breakfast, lunch, and dinner) and approximately 2 hours after each meal, as specified in the Schedule of Activities (Section 1.3).

8.2.6.4. Hypoglycemia

Participants will collect information on episodes of hypoglycemia at each study visit according to the SoA (Section 1.3). Participants will be trained by site personnel about signs and symptoms of hypoglycemia, how to treat hypoglycemia, how to collect appropriate information for each episode of hypoglycemia and record the event in the patient diary. Site personnel will enter this information into the eCRF at each visit. Once a hypoglycemic event has started, it is advised that the investigator or participant performs further testing at regular intervals, for example, every 15 to 30 minutes, until normoglycemia (≥70 mg/dL) is documented. If symptoms are present during

the hypoglycemic event, then the end time of the hypoglycemic event should be either the time of resolution of symptoms or when normoglycemia is achieved, whichever is later.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the plasma glucose [PG] values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips) (ADA 2019).

Glucose Alert Value (Level 1):

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a PG level of <70 mg/dL.
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG <70 mg/dL.
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG <70 mg/dL.

Clinically Significant Hypoglycemia (Level 2):

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a PG level of <54 mg/dL.
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG <54 mg/dL.
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG <54 mg/dL.

Severe hypoglycemia (Level 3):

- **Severe hypoglycemia** is defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.

Other hypoglycemia categories:

- **Nocturnal hypoglycemia** is defined as any hypoglycemic event that occurs between bedtime and waking.

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

To avoid duplicate reporting, all consecutive BG values <70 mg/dL occurring within 1-h period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

In each case of suspected or confirmed hypoglycemia, it is important that the event be properly categorized, the effect of the intervention be assessed, and the frequency of hypoglycemia be evaluated. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established by the investigator. The participant should receive additional education, if deemed appropriate. If applicable, please refer to the protocol section regarding management of increased hypoglycemia risks.

Hypoglycemic events will be recorded in the hypoglycemia eCRF. All episodes of severe hypoglycemia must be reported as SAEs.

8.3. Adverse Events and Serious Adverse Events

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

For each event, assessment of severity, duration (start and stop dates and times), and investigator's opinion of relatedness to IP and protocol procedure will be captured.

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

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

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit OR participation in study has ended at the time points specified in the SoA (Section 1.3).

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

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to the sponsor begins after the patient has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving LY3502970, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 h, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AESIs (as defined in Section 8.3.6), will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

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

8.3.5. Pregnancy

Pregnancy (maternal or paternal exposure to study intervention) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Appendix 10.4 to collect data on the outcome for both mother and fetus.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 3 months after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 h of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

8.3.6.1. Nausea, Vomiting, and Diarrhea

Nausea, vomiting, and diarrhea events are considered AESIs and will be recorded as AEs in the eCRF. For each event assessment of severity, duration (start and stop dates and times), and investigator's opinion of relatedness to IP and protocol procedure will be captured.

Other AESIs (Section 8.2) for this program include

a. Cardiovascular events
b. Hypoglycemia
c. Hepatic events
d. Pancreatic events

8.3.7. Complaint Handling

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

Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the IP so that the situation can be assessed.

8.4. Treatment of Overdose

For the purposes of this study, an overdose of LY3502970 is considered any dose higher than the dose assigned through randomization. Treatment for overdose is supportive care.

Refer to the Investigator's Brochure for LY3502970.

8.5. Pharmacokinetics

At the visits and times specified in the SoA, venous blood samples will be collected to determine the plasma concentrations of LY3502970 and acetaminophen.

Blood samples of approximately 2 mL will be collected as specified in the SoA (Section 1.3).

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data to ensure appropriate monitoring.

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

Samples will be used to evaluate the PK of LY3502970.

Genetic analyses will not be performed on these blood samples. Participant confidentiality will be maintained. At visits during which blood samples for the determination of multiple aspects of study intervention will be taken, 1 sample of sufficient volume can be used.

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

8.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3502970 and acetaminophen will be assayed using a validated liquid chromatography tandem mass spectrometry method. Analyses of samples collected for LY3502970 concentrations from placebo-treated subjects are not planned. Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism and/or protein-binding work.

8.6. Pharmacodynamics

Preliminary assessment of LY3502970 PD will be evaluated based on

- glucose and insulin sampled at fasting;
- glucose, insulin, and C-peptide during the MMTT;
- body weight;
- lipids, including fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol;
- acetaminophen during gastric emptying; and
- appetite analysis.

Additional exploratory PD analysis may be analyzed as deemed appropriate.

At the visits and times specified in the SoA (Section 1.3), samples will be obtained for the measurement of PD previously listed. The timing of PD samples is intended to assess pharmacologic effects of LY3502970. The sampling times may be modified at the discretion of the sponsor, but the total number of the samples or total blood volume will not increase. The sample(s) will be stored for up to a maximum of 15 years after the last participant visit for the study at a facility selected by the sponsor.

Nonpharmacogenetic samples will be collected to enable potential exploratory biomarker analyses related to LY3502970 mechanism of action, diabetes, and diabetic complications, including obesity.

8.6.1. Fasting Plasma Glucose Samples

Plasma concentrations of glucose from the clinical laboratory samples and glucose-only samples, according to the SoA (Section 1.3), will be assayed using validated analytical methods. Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

8.6.2. Fasting Insulin Samples

Serum concentrations of insulin collected according to the SoA (Section 1.3) will be assayed using validated analytical methods. Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

8.6.3. Mixed Meal Tolerance Test

In Cohort A, participants are required to consume a mixed meal on

- Days -1, 28, and 84 for the MMTT and the gastric emptying procedures,
- Day 56 for the MMTT procedure only, and
- Days 1 and 22 for the gastric emptying procedure only.

In Cohorts B, C, D, and E, participants are required to consume a mixed meal on

- Days -1, 42, and 84 for the MMTT and the gastric emptying procedures,
- Day 56 for the MMTT procedure only, and
- Days 1 and 22 for the gastric emptying procedure only.

The test meal consists of a solid nutrition bar and a liquid nutrition shake that has a total caloric content of approximately 500 kcal. The macronutrient composition of the meals should be targeted to provide approximately 50% of the calories from carbohydrate, 30% of the calories from fat, and 20% of the calories from protein.

Participants will be fasted (except for water) for at least 10 h before each test meal and consume each meal within approximately 15 min. Test meals for each participant will be kept consistent with regard to calorie and nutrient content across all study periods. The participant will not be allowed to consume water for 2 h after dosing apart from fluid provided with the meal; however, water may be consumed freely after 2 h after dose. On days of acetaminophen administration, acetaminophen will be administered with 240 mL of room temperature water, 5 to 10 minutes after completion of the test meal. Participants should consume the mixed meal within 15 or 20 min, and must remain fasted until after the MMTT is complete (4 hours after LY3502970 dose).

Glucose, insulin, and C-peptide will be measured in an MMTT to assess effects of LY3502970 on glycemic control, disposition index, and insulin sensitivity. The schedule for MMTTs is indicated in the SoA (Section 1.3).

Participants shall maintain their regular carbohydrate intake 3 days before the scheduled MMTT, and on the evening before the MMTT a pre-defined meal will be administered to ensure the food intake in this period is comparable.

Otherwise, no specific caloric and macronutrient content will be required for other meals for each participant. If a participant develops symptoms of hypoglycemia, bedside blood glucose concentration may be measured, and the participant will be treated per investigator discretion.

Blood samples will be drawn for assessment of glucose, insulin, and c-peptide at times indicated in the SoA (Section 1.3). Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

8.6.4. Lipid Panel Samples

Samples for lipid panel tests collected according to the SoA (Section 1.3) will be assayed using validated analytical methods. Refer to Section 10.2 for details regarding the lipid panel tests. Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

8.6.5. Gastric Emptying

Acetaminophen is a well-established marker for the rate and extent of gastric emptying (Young 2005). It is rapidly absorbed from the duodenum upon release from the stomach. A delay in gastric emptying is reflected in the alterations to the concentration-time profile of acetaminophen, specifically, decreasing its maximum observed drug concentration (C_{max}) and time of C_{max} (t_{max}) without altering the extent (total drug amount) absorbed. A dose of approximately 1 g acetaminophen is considered to be sufficient for bioanalytical detection.

Acetaminophen to assess gastric emptying will be administered as indicated in the SoA (Section 1.3). The acetaminophen test and sampling test may be adjusted based on actual dosing schemes during the study. The acetaminophen dose should be given 5 to 10 min after completion of the meal for MMTT procedure.

Blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of acetaminophen.

8.6.6. Appetite Analysis

To explore the effects of LY3502970 on meal intake and appetite sensation, participants will be asked to rate their appetite sensations using a 100-mm VAS for parameters of hunger, fullness, satiety, and prospective food consumption. These measurements shall be performed according to the SoA (Section 1.3).

The VAS is a validated tool to assess appetite sensation parameters (Flint et al. 2000). The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually “extremely” and “not at all.” Participants are required to rate their subjective sensations on four 100-mm scales combined with questions similar to the following:

1. “How hungry do you feel?”

2. “How satisfied do you feel?”

3. “How full do you feel?”

4. “How much do you think you could eat?”

A staff member will use a caliper to measure the distance from 0 to the mark that the subject placed on the VAS and record the measurement in the source document. Overall appetite score is calculated as the average of the 4 individual scores: satiety + fullness + (100-prospective food consumption) + (100-hunger) / 4 (van Can et al. 2014). The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

8.7. Genetics

A blood sample for genetic analyses will be collected from participants according to SoA.

See Appendix 10.5 for information regarding genetic research and Appendix 10.1.11 for details about sample retention and custody.

8.8. Biomarkers

This section in not applicable.

8.9. Immunogenicity Assessments

This section is not applicable.

8.10. Health Economics

This section is not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The study will compare LY3502970 with placebo in adults with T2DM. The primary study objective is to determine the safety and tolerability of LY3502970.

Additional hypotheses will include the comparison of study intervention with placebo for the prespecified objectives and endpoints defined in Section 3.

9.2. Sample Size Determination

The sample size is customary for Phase 1 studies evaluating safety, PK, and/or PD parameters, and is considered sufficient to evaluate the primary objective of this study.

A maximum of 72 participants will be randomly assigned to study intervention such that approximately 60 evaluable participants complete the study.

Participants who are randomized but not administered treatment may be replaced to ensure that enough participants may complete the study. Participants withdrawn from the study due to safety reasons deemed related to LY352970 will not be replaced. If a participant does not complete all the treatment periods of the study, they may be replaced by another participant if decided by the sponsor. This replacement participant will go through the same treatment sequence as the discontinued participant.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis	All randomized participants who received at least 1 dose of LY3502970 and have at least 1 evaluable PK sample.

9.3.1. Study Participant Disposition

All participants who discontinue from the study will be identified and the extent of their participation in the study will be reported. A detailed description of participant disposition will be provided at the end of the study.

9.3.2. Study Participant Characteristics

The participant's age, sex, weight, height, or other demographic characteristics will be recorded and maybe used in the PK, PD, and safety analyses as quantitative or classification variables.

9.3.3. Treatment Compliance

At inpatient visits, the study intervention will be administered and documented at the clinical site. At all other times, the study intervention will be administered by the participant and documented in the participant's diary.

9.4. Statistical Analyses

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

Pharmacokinetic and PD analyses will be conducted on the Pharmacokinetic Analysis Set.

Safety analyses will be conducted based on the safety analysis set.

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.

9.4.1. General considerations

9.4.1.1. Clinical Evaluation of Safety

All IP 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 will be presented by severity and by association with IP as perceived by the investigator. Adverse events reported to occur prior to the first study dose 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 Dictionary for Regulatory Activities.

The number of IP-related SAEs will be reported. Details regarding the analysis of AESIs will be described in the statistical analysis plan (SAP).

9.4.1.2. 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.

Laboratory measurements will be summarized with regard to observed values and change from baseline by treatment group, at each time point, using descriptive statistics. In addition, all clinical chemistry, hematology, and urinalysis data outside the reference ranges will be tabulated by parameter and treatment group.

Vital signs will be summarized with regard to observed values and change from baseline (Day 1, predose) values by treatment at each time point using descriptive statistics. For change from baseline values, a mixed-model repeated-measure model with treatment, time (of measurement), and treatment-by-time interaction as fixed effects, participant as random effect, and baseline as covariate will be used to determine the effects of LY3502970. Least squares means as well as 90% confidence intervals (CIs) will be reported.

The ECG parameters and changes from baseline, including the PR, QT, RR, and QTcF intervals, QRS duration, and heart rate, will be summarized. The number and percentage of participants with a maximum increase from baseline in QTcF interval will be summarized for each treatment group according to the following categories: >30 msec and >60 msec. In addition, the number and percentage of participants with QTcF postdose values will be summarized by treatment group according to the following categories: >450 msec; >480 msec; and >500 msec. Analyses may be performed to determine the effects of PK parameters on QTcF. A concentration-response analysis will be performed according to International Council for Harmonisation (ICH)-E14 (the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs) guidelines.

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

9.4.2. Pharmacokinetic Analysis

9.4.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3502970 and acetaminophen will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will include C_{max}, area under the concentration versus time curve (AUC), and t_{max}. Other parameters, such as half-life, apparent clearance, renal clearance, and apparent volume of distribution, may be reported. If deemed necessary, additional model-based analysis may be performed.

All PK parameters will be listed and summarized using descriptive statistics.

9.4.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters for LY3502970 will be evaluated to estimate dose proportionality. Log-transformed C_{max} and AUC parameters will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and the corresponding 90% CI.

The t_{max} will be analyzed using a nonparametric method (Kruskal-Wallis test).

9.4.3. Pharmacodynamic Analysis

Inferences will be sought regarding the ability of LY3502970 over a range of doses to reduce fasting or dynamic glucose together with the effects on insulin. The effect of LY3502970 on body weight change and gastric emptying delay will also be assessed.

9.4.3.1. Pharmacodynamic Parameter Estimation

Fasting glucose and insulin concentrations and AUC for glucose and insulin during an MMTT will be presented. The AUC for glucose and insulin during an MMTT will be calculated using the trapezoidal rule. The AUC as well as derived parameters or observed concentration at specific time points for each subject on the study day will also be baseline adjusted. The concentrations on Day -1 will be used as baseline.

Body weight and change from baseline body weight will be summarized by visits.

The parameter estimates for acetaminophen will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be the C_{max}, the AUC, and the tmax

of acetaminophen. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

Insulin sensitivity and beta-cell function index may be estimated from glucose and insulin concentration profiles during the MMTT.

9.4.3.2. Pharmacodynamic Statistical Inference

The PD parameters from each cohort of the study will be analyzed separately. The PD parameters from placebo-treated participant within each part of the study will be pooled for the final analysis. The PD parameters may be transformed before statistical analyses, if deemed necessary. Absolute values and change from baseline in each parameter will be analyzed using mixed-effects models to evaluate treatment effects as well as treatment comparisons. The main comparisons will be between each LY3502970-treated group and placebo group.

Least squares means as well as 90% CIs will be reported. All PD parameters, including the baseline-corrected parameters, will be summarized and tabulated by treatment group and day. Summary statistics will be provided. The individual observed and mean time profile of the postdose PD parameters will be plotted by treatment group.

Baseline-adjusted C_{max} and AUC of acetaminophen (ratio to Day -1 value) will be calculated and log-transformed to evaluate the gastric-emptying effect of LY3502970. An MMRM with treatment, day, and treatment-by-day interaction as fixed effects, participant as random effect, and baseline (Day -1) as covariate will be used to perform the analysis for each parameter. Least-squares means as well as 90% CIs will be reported. The parameter t_{max} of acetaminophen will be analyzed using a nonparametric method.

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

9.4.4. Exploratory endpoint(s)

Refer to the SAP for analyses related to exploratory endpoints.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

9.4.5.1. Pharmacokinetic/Pharmacodynamic Parameter Estimation

Exploratory PK/PD modeling may be used to characterize exposure-response relationships between LY3502970 concentrations and various PD endpoints (i.e., HbA1c, glucose, body weight, and gastric emptying), provided data are sufficient.

9.4.6. Other Analyses

9.4.6.1. Appetite Analyses

The study assessment will be the overall appetite score as measured according to the 0- to 100-mm VAS. Descriptive statistics will be used to summarize the baseline, postdose time points, and absolute change from baseline in overall appetite score by treatment group. Details will be provided in the SAP.

9.5. Interim Analyses

Interim analyses are not planned for this study.

9.6. Data Monitoring Committee (DMC)

For further details refer to Section 10.1.5.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

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

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, through phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by 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.

10.1.6. Data Quality Assurance

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This might include laboratory tests, medical records, and clinical notes.

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

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

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

The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

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

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

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

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

- provide instructional material to the study sites, as appropriate.

- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel through mail, telephone, or fax.

Data Capture System

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

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

10.1.7. Source Documents

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

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

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

10.1.8. Study and Site Start and Closure

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

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

The sponsor 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:

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

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

10.1.9. Publication Policy

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

10.1.10. Investigator Information

Physicians working in teaching or nonteaching hospitals or outpatient setting will participate as investigators in this clinical trial.

10.1.11. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3502970 or after LY3502970 become(s) commercially available.

Sample Type	**Custodian**	**Retention Period After Last Patient Visit***
Long-term storage samples	Sponsor or Designee	15 years
Biomarkers	Sponsor or Designee	15 years
PK	Sponsor or Designee	2 years
Genetics/PD	Sponsor or Designee	15 years

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics.

The sponsor has a right to retain a portion of submitted biopsy tissue. Archival blocks will be returned to the study site. Slides and tissue samples collected on study will not be returned.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the following table will be performed by the local laboratory at screening only and by the central laboratory during the treatment period and follow up.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing (local laboratory
- Investigators must document their review of each laboratory safety report.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Safety Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium (total)
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	
Differential WBC Absolute counts of:	Glucose fasting
Neutrophils	Blood urea nitrogen (BUN)
Lymphocytes	
Monocytes	Albumin
Eosinophils	Total protein
Basophils	Amylase
Platelets	Lipase
	Creatinine
Urinalysis	
Specific gravity	Lipid Panel[a]
pH	Total cholesterol
Protein	Triglycerides
Glucose	Low-density lipoprotein cholesterol
Ketones	High-density lipoprotein cholesterol
Bilirubin	
Urobilinogen	Liver Panel
Blood	Total bilirubin
Nitrite	Alkaline phosphatase (ALP)
Microscopic examination of sediment[b]	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Serology	
Hepatitis B surface antigen[a]	
Hepatitis C antibody[a]	Ethanol testing[c]
HIV[a]	Urine drug screen[c]
Hemoglobin A1c[a]	Pregnancy test
Calcitonin[a]	FSH[a,d]
	Thyroid stimulating hormone[a,e]

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

[a] Performed at screening only

[b] Test only if dipstick result is abnormal

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

[d] For confirmation of postmenopausal, as needed

[e] Only for those on thyroid medications or those with previous thyroid history.

Note: Results of these assays will be validated by the local laboratory at the time of testing at screening. 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.

10.2.1. Blood Sampling Summary

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

Protocol J2A-MC-GZGC Sampling Summary for Cohort A

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	29.5	1	29.5
Clinical laboratory tests[a]	10.5	5	52.5
Pharmacokinetics	2	30	60
Pharmacokinetics: Acetaminophen	2	40	80
Lipid panel	2.5	4	10
MMTT			
Glucose	2	24	48
Insulin and C-peptide	2.5	24	60
HbA1c	2	4	8
Fasting plasma glucose	2	6	12
Fasting insulin	2	6	12
Genetic sample	10	1	10
Nonpharmacogenetics			
Plasma	2	4	8
Serum	2.5	4	10
P800 plasma	2	4	8
Total			408
Total for clinical purposes [rounded up to the nearest 10 mL]			410

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

Protocol J2A-MC-GZGC Sampling Summary for Cohorts B, C, D, and E

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	29.5	1	29.5
Clinical laboratory tests[a]	10.5	6	63
Pharmacokinetics	2	30	60
Pharmacokinetics: Acetaminophen	2	40	80
Lipid panel	2.5	4	10
MMTT			
Glucose	2	24	48
Insulin and C-peptide	2.5	24	60
HbA1c	2	4	8
Fasting plasma glucose	2	7	14
Fasting insulin	2	7	14
Genetic sample	10	1	10
Nonpharmacogenetics			
Plasma	2	4	8
Serum	2.5	4	10
P800 plasma	2	4	8
Total			422.5
Total for clinical purposes [rounded up to the nearest 10 mL]			430

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

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

10.3.1. Definition of AE

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of 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 TEAEs

TEAE Definition

- A TEAE is an AE that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.
- In this trial, AEs occurring from the first dosing until the follow-up visit will be considered as treatment emergent.

10.3.3. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with 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 occurrence of each AE/SAE.
- The investigator will consider any AEs, SAEs, and clinically important laboratory abnormalities as related to the study intervention unless there is clear evidence that the event is not related.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send 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 and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 h of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting

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

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

Definitions:

Woman of Childbearing Potential

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

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

Women in the following categories are not considered woman of childbearing potential

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy, tubal ligation
   - Documented bilateral oophorectomy

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

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

3. Postmenopausal female is defined as, women with:
   i. A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL; or
   ii. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
   iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Contraception Guidance for men

Men, regardless of their fertility status, with nonpregnant women of childbearing potential partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or effective method of contraception (such as diaphragms with spermicide or cervical sponge) for the duration of the study and for 3 months following the last dose of IP (i.e., until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus).

Men and their partners may choose to use a double-barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a

spermicide. It should be noted, however, that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.)

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Men with pregnant partners should use condoms during intercourse for the duration of the study and for 3 months following the last dose of IP (i.e., until the end of estimated relevant potential exposure in women of childbearing potential).

Men should refrain from sperm donation for the duration of the study and for 3 months following the last dose of IP (i.e., until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus).

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

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 study intervention.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 h of learning of the partner's pregnancy. The female partner will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 h of learning of a participant's pregnancy.

The participant will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

DNA samples will be used for research related to study intervention or T2DM and related diseases. They may also be used to develop tests/assays including diagnostic tests related to study intervention and/or interventions of this drug class and T2DM. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

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

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

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

The samples will be retained as described in Section 10.1.11.

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

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

Hepatic Monitoring Tests

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

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

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

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

10.7. Appendix 7: Pancreatic Monitoring

Glucagon-like peptide 1 agonists have been associated with a possible risk of acute pancreatitis. In 2006, the US prescribing information for exenatide was revised to include the event of pancreatitis. In 2007, the US prescribing information for this medication was amended to include pancreatitis under "Precautions." Epidemiologic studies have indicated that there is an increased incidence and prevalence of pancreatitis in persons with T2DM.

To enhance understanding of the natural variability of pancreatic enzymes in the T2DM population, and to assess for any potential effects of LY3502970 on the exocrine pancreas, amylase and lipase values will be monitored in all current and future clinical trials with LY3502970.

Additional monitoring will be requested for amylase or lipase values ≥3X ULN at any visit after randomization, even in asymptomatic patients (see the following figure). Lipase and amylase may also be obtained at any time during the clinical trials for any patient suspected of having symptoms suggestive of pancreatitis (such as severe GI signs and/or symptoms), at the investigator's discretion.

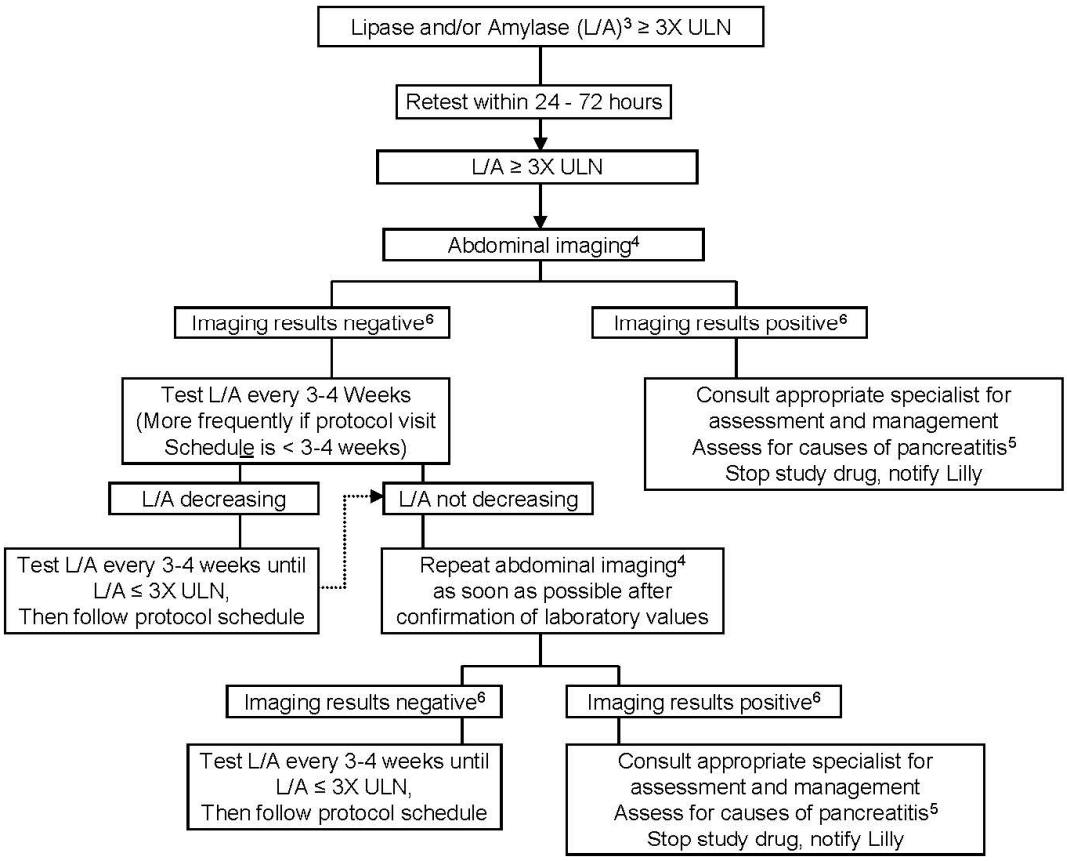
Acute pancreatitis is an AE defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase >3X ULN, and
- characteristic findings of acute pancreatitis on computed tomography scan or magnetic resonance imaging

Most patients with acute pancreatitis experience abdominal pain that is located generally in the epigastrium and radiates to the back in approximately one-half of the cases. The pain is often associated with nausea and vomiting. However, experience with GLP-1 agonists has demonstrated that some patients asymptomatic for classic pancreatitis may demonstrate significant elevations of lipase and/or amylase levels. For patients considered by investigators to be asymptomatic for pancreatitis, but whose value(s) for lipase and/or amylase are ≥3X ULN, an algorithm is in place to follow these patients safely and to quickly reach (or not reach) a diagnosis of pancreatitis.

Pancreatic Enzymes: Safety Monitoring Algorithm for Subjects/Patients without Symptoms of Pancreatitis[1,2]

Follow this algorithm when the value(s) for serum lipase and/or amylase are ≥ 3X ULN.



1. Symptomatic – related primarily to abdominal pain consistent with pancreatitis; however, severe nausea, vomiting and other symptoms may be considered by the investigator as symptomatic as well.

2. If, at any time, in the opinion of the investigator, patient/subject has symptoms of acute pancreatitis irrespective of L/A results:
   (a) Consult appropriate specialist for assessment and management
   (b) Assess for causes of pancreatitis
   (c) Stop study drug
   (d) Notify Lilly

3. L/A = Lipase and/or amylase. Either or both enzymes can be measured and either or both can be used to meet the algorithm criteria.

4. Abdominal imaging is most valuable when performed at the time of elevated enzyme values. If in the opinion of the radiologist or investigator, it is safe for the patient/subject to receive contrast, an enhanced abdominal CT is preferred. MRI is also an acceptable imaging modality.

5. As minimum, test hepatic analytes, triglycerides, and calcium, and record all concomitant medications

6. Imaging results positive or negative for signs of acute pancreatitis

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; SAE = serious adverse event; ULN = upper limit of normal.

10.8. Appendix 8: Abbreviations

Term	Definition
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BG	blood glucose
blinding/masking	A double-blind study is 1 in which neither the participant nor any of the investigator or sponsor personal who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed drug concentration
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
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.
CP	clinical pharmacologist
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
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.
FSH	follicle-stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycated hemoglobin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
investigational product (IP)	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.
IRB	Institutional Review Board
IWRS	interactive web-response system
MMTT	mixed meal tolerance test
MRI	magnetic resonance imaging
CCI	
OTC	over the counter

participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PG	plasma glucose
PK/PD	pharmacokinetics/pharmacodynamics
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
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
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.
ULN	upper limit of normal
VAS	visual analog scale

10.9. Appendix 9: Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment (b)	16-Sep-2020
Protocol amendment (a)	14-Aug-2020
Original Protocol	12-May-2020

Amendment (a)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The protocol was amended to

- address FDA advice.
- address a recent learning from the preceding Phase 1 Study J2A-MC-GZGA (GZGA)
- correct minor typo errors that are not reflected in the following table

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities Section 8.6.3 Mixed Meal Tolerance Test	Added acetaminophen dose to Day -1 and specified administration of the dose with 240 mL of room temperature water	Response to FDA comment to improve clarity of administration requirements for acetaminophen.
Section 1.3 Schedule of Activities	Added dispensing of IP on Day 36 for Cohorts B through E	Correct a typo.
Section 1.3 Schedule of Activities Section 8.2.6.3 Glucose Monitoring	Added details of 6-point SMBG	Added clarity for investigators on timing of SMBG during in-patient stays.
Section 1.3 Schedule of Activities	Change in VAS for appetite, • For Cohort A, moved from Day 27 to Day 28 • Cohorts B through E, moved from Day 41 to 42 and Day 83 to 84	Corrected VAS to days with breakfast or MMTT at CRU.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Added weight measurements, at Days 8, 15, and 22	Added to better define any potential weight loss throughout the study.
Section 6.5 Concomitant Therapy	Added the list of compounds that could exhibit clinically relevant changes in exposure with increased gastric pH. Added recommendation that compounds for which clinically relevant changes in exposure may occur be staggered from LY3502970 administration by at least 4 hours	Sodium bicarbonate contained in the current LY3502970 formulation transiently increases gastric pH.
Section 6.5 Concomitant Therapy Section 5.2 Exclusion criteria	Added P-glycoprotein (P-gp)	In vitro transporter results indicate that LY3502970 could be affected by inhibitors of P-gp.
Section 8.2.6.4 Hypoglycemia	Clarified testing of hypoglycemia events to better define end of event	To better describe the length of any hypoglycemic event.
Section 8.2.6.4 Hypoglycemia	Removed reference to plasma glucose level in mmol/L	70 mg/dL does not translate exactly to 3.9 mmol/L. Removed 3.9 mmol/L to avoid confusion.
Section 8.2.6.4 Hypoglycemia	Removed reference to plasma glucose level 3.0 mmol/L	To be consistent throughout the protocol.

Amendment (b)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The protocol was amended to

- address Federal Institute for Drugs and Medical Devices (BfArM) comments
- address German Ethics Committee comments
- address a few Lilly-proposed changes

Section # and Name	Description of Change	Brief Rationale
Changes made due to BfArM Questions		
Section 4.1.1 Study visits, Treatment period	Added planned dose escalation scheme for Cohorts B through E	Response to Federal Institute for Drugs and Medical Devices question
Section 7.1 Discontinuation of Study Intervention	Amended discontinuation criteria of IP if QTc >500 msec or an increase from baseline in QTc >60 msec	Response to Federal Institute for Drugs and Medical Devices question
Section 7.1.1 Early Termination of the study	Amended the trial dosing interruption and termination criteria	Response to Federal Institute for Drugs and Medical Devices question
Section 8.3 Adverse Events and Serious Adverse Events	Clarified that all AEs will be captured, not just those of special interest	Response to Federal Institute for Drugs and Medical Devices question
Changes made due to German Ethics Committee Questions		
Section 4.1.1 Study visits, Treatment period	Added planned dose escalation scheme for Cohorts B through E	Response to German Ethics Committee question
Section 4.3 Justification for Dose	Added NOAEL dose	Response to German Ethics Committee question
Changes proposed by Lilly		
Section 1.3 Schedule of Activities	Change in VAS for appetite, • For Cohort A, moved from Day 55 to Day 56 and Day 83 to 84 • Cohorts B through E, moved from 55 to Day 56	Corrected VAS to days with breakfast or MMTT at CRU
Section 1.3 Schedule of Activities	Removed fasting plasma glucose and fasting insulin assessment on Day 42 for Cohorts B to E	Corrected to avoid duplication of samples
Section 2.3 Benefit/Risk Assessment	Added decreased blood pressure	Changes in blood pressure were noted in the 3-month toxicology studies but had not been reported in earlier studies

Section # and Name	Description of Change	Brief Rationale
Section 8.2.4 Electrocardiograms	Clarified baseline ECG measurements	Clarification requested by investigator
Section 8.7 Genetics Section 10.5 Appendix 5: Genetics	Deleted the statements about analysis of entire genome	Feedback from clinical research unit
Section 10.2 Appendix 2: Clinical Laboratory Tests	Clarified FSH test done for confirmation of postmenopausal status	Clarification requested by investigator

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