

Protocol J2A-MC-GZGN(b)

A Multiple Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Tablet and Capsule Formulations of LY3502970 in Healthy Overweight and Obese Participants

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Title Page

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Protocol Title: A Multiple Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Tablet and Capsule Formulations of LY3502970 in Healthy Overweight and Obese Participants

Protocol Number: J2A-MC-GZGN

Amendment Number: b

Compound: LY3502970

Brief Title: A multiple dose study to assess tablet and capsule formulations of LY3502970 in healthy overweight and obese participants.

Study Phase: Phase 1

Sponsor Name: Eli Lilly and Company

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

Regulatory Agency Identifier Number: IND: 156143

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

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Amendment a	02-Mar-2023
Original Protocol	06-Feb-2023

Amendment (b)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The protocol is being amended to align with recommendations from the FDA and to provide clarifications on the protocol. The following table describes the changes made in this amendment.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added a 12-lead single ECG at 6 hours post dose on last day, Day 7 in Part A of Period 11.	To align with recommendations from the FDA, in order to assess any cardiovascular changes at previously unexplored plasma concentrations.
4.2 Scientific Rationale for Study Design	Included rationale for studying higher doses of LY3502970.	To align with recommendations by the FDA, and to provide a rationale for studying the higher doses of LY3502970.
4.3 Justification for Dose	Revised Margins of Safety table from a 1.2-fold factor to a 1.4-fold factor to account for higher exposure in tablet compared to capsule	To align with recommendations by the FDA. This change provides more conservative safety margins and the rationale for studying a potentially higher exposure with the tablet formulation relative to the capsule.
5.2 Exclusion Criteria	Modified the following criterion • #24 revised to include QTc threshold cutoff values Included the following criteria • #56 renal function (estimated glomerular filtration rate) eGFR cutoff limits	To align with requests by the FDA and to clarify some of the exclusion criteria for participating in Study J2A-MC-GZGN.

Section # and Name	Description of Change	Brief Rationale
	• #57 excluded medications that may cause weight gain.	
5.3.1 Meals and Dietary Restrictions	Revised from 8 hour to at least 10 hours overnight fast prior to dosing for fasting periods.	To align with request by the FDA and to meet the standard requirements for assessing pharmacokinetics under fasting conditions.
6.9 Prior and Concomitant Therapy	Specified that participants receiving oral medications with rapid gastrointestinal absorption, the dose of LY3502970 should be separated by 2 to 4 hours.	To align with the recommendation by the FDA, in order to ensure adequate separation between LY3502970 and oral medications that have rapid gastrointestinal absorption, as initial doses of LY3502970 may delay gastric emptying.
8.2.3 Electrocardiograms	Revised from ECG printed to output to be reviewed at the time of collection.	To align with site on how ECGs are reviewed by the investigator or qualified staff.
10.8. Appendix 8: Examples of Excluded Medications	Included a list of excluded GLP-1 analogs not permitted during the study.	To align with recommendation by the FDA and to provide additional information regarding the list of GLP-1 analogs that are not permitted during the study.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multiple Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Tablet and Capsule Formulations of LY3502970 in Healthy Overweight and Obese Participants

Brief Title: A multiple dose study to assess tablet and capsule formulations of LY3502970 in healthy overweight and obese participants.

Regulatory Agency Identifier Number: IND: 156143

Rationale: Study J2A-MC-GZGN (GZGN) is a Phase 1, 2-part, multiple-dose titration study designed to assess the pharmacokinetics (PK), safety, and tolerability of LY3502970 following oral administration of multiple once daily (QD) doses for 13 weeks in healthy overweight and obese participants.

PK data from previous Phase 1 clinical studies supported QD administration of LY3502970 and found LY3502970 to be safe and well tolerated. The current study is intended to obtain sufficient PK data to establish the dose-exposure relationship of LY3502970 in the tablet and capsule formulations in healthy overweight and obese participants. Additional objectives include assessment of the effect of a high-fat meal on the PK of LY3502970 tablets and capsules, and the assessment of the PK of high doses of LY3502970.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To characterize and compare the PK of multiple doses of LY3502970 in different formulations in healthy overweight and obese participants	AUC₍₀₋₂₄₎, C_{max}, and t_{max}
Secondary	
- To assess the effect of a high-fat meal on the PK of LY3502970 tablets and capsules in healthy overweight and obese participants - To assess the PK of high doses of LY3502970 in healthy overweight and obese participants	- AUC₍₀₋₂₄₎, C_{max}, and t_{max} - AUC₍₀₋₂₄₎, C_{max}, and t_{max}

To describe the safety and tolerability of different formulations of LY3502970 in healthy overweight and obese participants	Incidence of TEAEs and SAEs
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Abbreviations: AUC₍₀₋₂₄₎ = area under the concentration versus time curve from time 0 to 24 hour time point; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{max} = time of maximum observed drug concentration.

Overall Design

Study GZGN is a Phase 1, 2-part, multiple-dose titration study in healthy overweight and obese participants.

Brief Summary:

Screening

All participants will be screened between 28 to 3 days prior to Day 1.

Treatment and Assessment Period

Eligible participants will be admitted to the clinical research unit (CRU) on Day -2.

Participants will be enrolled in Parts A and B. Approximately 50 participants will be enrolled to ensure 32 completers of Parts A and B.

Part A (Periods 1 to 11)

Throughout Periods 1 to 11, participants will receive a QD oral dose of LY3502970 in the tablet or capsule formulation, depending on the period of the study. Participants will be in a fasted state in all periods, except for Period 10. On Days 1 to 5 of Period 10, that is, Study Days 64 to 68, participants will consume a standard meal prior to dosing. On Days 6 and 7 of Period 10, that is, Study Days 69 and 70, participants will consume a high-fat meal prior to dosing. In Period 10, participants will be randomized 1:1 to receive **CCl** mg LY3502970 capsule or **CCl** mg LY3502970 tablet. Following Period 11, all participants will continue to Part B of the study.

Progression of Doses through Part A of Study GZGN

During the treatment period of Part A, doses will be escalated in a stepwise manner for all participants on a weekly basis for 11 weeks, with the following dose levels and formulations administered QD for 7 days as shown:

- Period 1: **CCl** mg LY3502970 tablet
- Period 2: **CCl** mg LY3502970 capsule
- Period 3: **CCl** mg LY3502970 tablet
- Period 4: **CCl** mg LY3502970 tablet
- Period 5: **CCl** mg LY3502970 capsule
- Period 6: **CCl** mg LY3502970 tablet
- Period 7: **CCl** mg LY3502970 capsule
- Period 8: **CCl** mg LY3502970 tablet
- Period 9: **CCl** mg LY3502970 capsule

- Period 10: **CCl** mg LY3502970 capsule or **CCl** mg LY3502970 tablet, in fed state, and
- Period 11: **CCl** mg LY3502970 tablet.

Part B (Periods 12 and 13)

Throughout Periods 12 and 13, participants will receive a QD oral dose of LY3502970 in the tablet formulation. Participants will be randomized 3:1 to receive either LY3502970 dose titration tablets or **CCl** mg LY3502970 tablets based on a computer-generated allocation code.

Participants may be allowed to leave the CRU after completing the safety assessments on Period 13, Day 9, or later at the investigator's discretion.

Progression of Doses through Part B of Study GZGN

During the treatment period of Part B, participants randomized to receive dose titration LY3502970 tablets will receive a stepwise dose titration of LY3502970 on Day 1 of Periods 12 and 13, with each of the following dose levels and formulations administered QD for 7 days as shown:

- Period 12: **CCl** mg LY3502970 in tablet formulation, and
- Period 13: **CCl** mg LY3502970 in tablet formulation.

Participants randomized to the control group will receive **CCl** mg LY3502970 in tablet formulation QD for 7 days in both Periods 12 and 13.

Follow-Up Period

A follow-up visit will be performed approximately 7 to 14 days after discharge from the CRU.

Study Population:

Participants will be healthy obese and overweight males or females between 18 and 70 years of age, inclusive, at the time of signing the informed consent, with a body mass index of 27.0 kg/m² or more at screening, and have a stable body weight, with 5% or less body weight gain or loss, for 90 days prior to dosing.

Number of Participants:

Approximately 50 participants will be enrolled to ensure 32 evaluable participants complete the study.

Intervention Groups and Duration:

All participants will be screened within 28 to 3 days prior to Day 1. On Day 1 of each period in Part A, participants will be administered 1 LY3502970 capsule or tablet. On Day 1 of each period in Part B, participants will be administered 3 LY3502970 tablets to reach the required dose. Each dose of LY3502970 will be administered orally with approximately 240 mL of room temperature water in the morning of each dosing day in a sitting position. Participants will be followed through to approximately 7 to 14 days after discharge from the CRU. Total study duration is up to approximately 135 days.

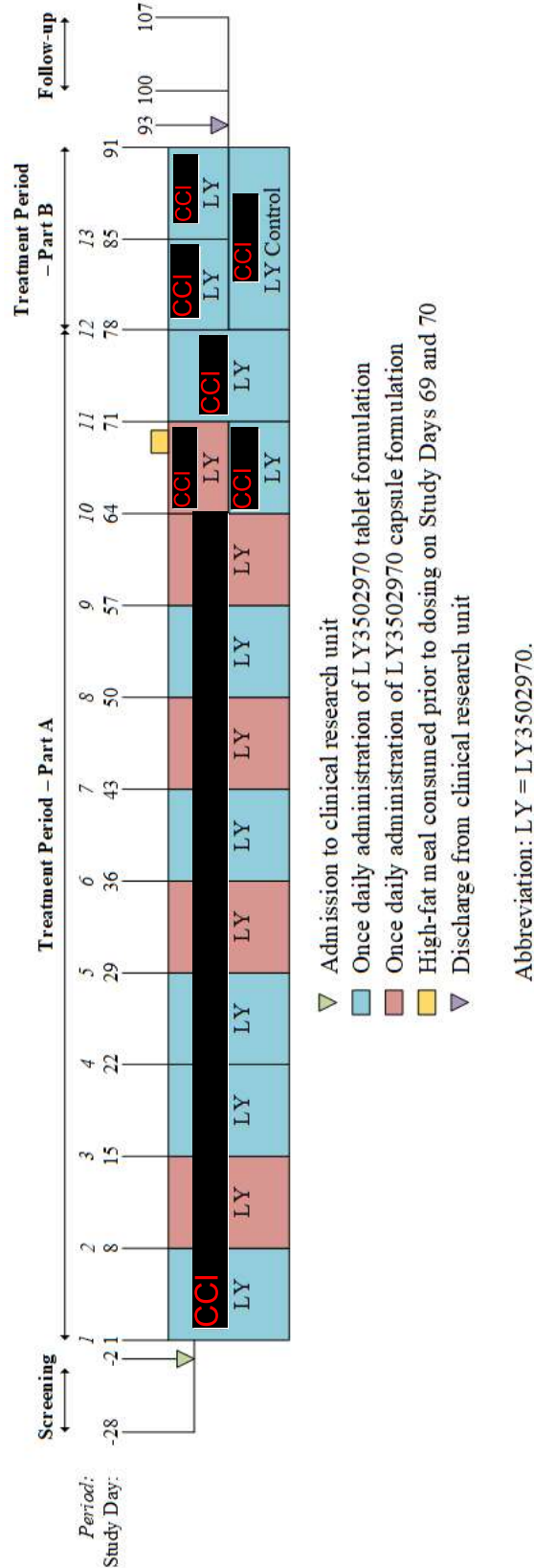
Ethical Considerations of Benefit/Risk:

No safety or tolerability concerns that preclude further investigation of LY3502970 have been identified in 268 healthy participants, 72 healthy overweight and obese participants, 222 participants with obesity or overweight with weight-related comorbidities, and 381 participants with type 2 diabetes mellitus to date, up to the highest administered single dose of █ mg and the highest administered multiple dose of █ mg.

Data from Phase 1 studies indicate that LY3502970 treatment may result in a decrease in body weight. These data support improved weight management in healthy overweight and obese participants.

Data Monitoring Committee: No.

1.2. Schema



1.3. Schedule of Activities

Schedule of Activities – Part A

Procedure	Screening 1	Baseline	Part A – Treatment Periods 1 to 11				E/T	Notes
Visits			2					
Days	-28 to -3	-2	-1	1	2 to 6	7		
Informed consent	X							Admit in advance if judged to be required by investigator.
Admission to CRU		X						
Outpatient visit	X							
Medical history	X							
Randomization				X				Period 10 only.
Height	X							
Weight	X					X	X	Day 7 weight must be taken in the fasted state.
Physical examination	X	X					X	Complete physical examination at either screening or check-in on Day -2. Symptom-directed physical examination at other visits.
Ethanol test and urine drug screen	X	X						Urine alcohol test at screening. Breath or urine test on Day -2.
Pregnancy test (females only)	X		X				X	Serum pregnancy testing at screening, and if a urine test is positive.
Pharmacogenetic sample			X					Urine pregnancy testing at other time points.
PK sampling				P		P, 0.5h, 1h, 2h, 4h, 6h, 8h, 12h		
Clinical laboratory tests	X	X				P	X	Day 7 P collection will only be performed in Periods 1, 5, 9, and 11. See Appendix 2 in Section 10.2 for details.
Vital signs	X	X		P			X	Day 1 P collection will only be performed in Periods 2, 4, 6, 8, and 10. Vital signs must be measured before any blood sample collection.
Fasting plasma glucose	X			P			X	Samples will be measured with a capillary glucose monitor.
Single 12-lead ECG	X			P		6h (Only Period 11)	X	ECG collection must occur before blood sample collection.
Triplicate 12-lead ECG				-45 min P, -30 min P, -15 min P				Period 1 only. Time points correspond to time prior to dosing.
C-SSRS baseline	X							
C-SSRS since last assessed			X			X	X	
Study intervention administration								Study intervention will be administered daily throughout Periods 1 to 11. Participants will be fasted, except for Period 10. In each period, participants will increase LY3502970 dose and formulation. See Section 1.2.
Pre-dose meal				X	X	X		For Period 10 only. Prior to dosing, participants will consume a standard meal on Days 1 to 5, and a high-fat meal on Days 6 and 7. See Section 5.3.1.
AE and SAE review							X	

Procedure	Screening	Baseline	Part A – Treatment Periods 1 to 11			ET	Notes
Visits	1		2				
Days	-28 to -3	-2	-1	1	2 to 6	7	
Concomitant medication review	← →		← →		← →		
						X	

Abbreviations: AE = adverse event; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; h = hour; min = minute; P = predose; PK = pharmacokinetic; SAE = serious adverse event.

Schedule of Activities – Part B

Procedure	Part B - Treatment Periods 12 and 13			Period 13	Follow- up Period	ET	Notes
Visits	2				3		
Days	1	2 to 6	7	8	9		
Participant discharge from CRU					X		
Outpatient visit						X	Extend if judged to be required by investigator.
Weight			X			X	Day 7 weight measurements must be taken in the fasted state.
Physical examination					X	X	Symptom-directed physical examination.
Pregnancy test (females only)						X	Urine pregnancy testing.
PK sampling	P		P, 0.5h, 1h, 2h, 4h, 6h, 8h, 12h	24h			
Clinical laboratory tests			P			X	Day 7 P collection will only be performed in Period 12. See Appendix 2 in Section 10.2 for details.
Vital signs	P				X	X	Vital signs must be measured before any blood sample collection.
Fasting plasma glucose	P					X	Samples will be measured with a capillary glucose monitor.
Single 12-lead ECG						X	ECG collection must occur before any blood sample collection.
Triplicate 12-lead ECG	P		P, 0.5h, 1h, 2h, 4h, 6h, 8h, 12h	24h			See Section 8.2.3 for details. ECG collection must occur before any blood sample collection.
C-SSRS since last assessed			X			X	
Study intervention administration							Study intervention will be administered daily throughout Periods 12 and 13. Participants will be fasted. Participants will increase LY3502970 dose or receive 80 mg LY3502970 as a control. See Section 1.2.
AE and SAE review	X	X	X			X	
Concomitant medication review						X	

Abbreviations: AE = adverse event; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; h = hour; P = predose; PK = pharmacokinetic; SAE = serious adverse event.

2. Introduction

LY3502970 is a chemically synthesized, oral GLP-1 RA being developed as a daily oral therapy as an adjunct to diet and exercise. In addition, it is being developed as a therapy for the indication of chronic weight management and T2DM.

2.1. Study Rationale

Study J2A-MC-GZGN (GZGN) is a Phase 1, 2-part, multiple-dose titration study designed to assess the PK, safety, and tolerability of LY3502970 following oral administration of multiple QD doses for 13 weeks in healthy overweight and obese participants.

PK data from previous Phase 1 clinical studies supported QD administration of LY3502970 and found LY3502970 to be safe and well tolerated. The current study is intended to obtain sufficient PK data to establish the dose-exposure relationship of LY3502970 in the tablet and capsule formulations in healthy overweight and obese participants. Additional objectives include assessment of the effect of a high-fat meal on the PK of LY3502970 tablets and capsules, and the assessment of the PK of high doses of LY3502970.

2.2. Background

LY3502970 is being investigated for its potential use as a therapy for chronic weight management and T2DM. LY3502970 is a chemically synthesized molecule that shows agonist activity for human GLP-1 receptor. To date, no off-target toxicity has been identified in the clinical studies.

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

With the prevalence of T2DM increasing worldwide, new antihyperglycemic agents offering significant improvements in glycemic control and additional weight loss as well as other health benefits, which would result in improved health outcomes, are highly desired. Obesity is a chronic disease, and its increasing prevalence is a public health concern associated with rising incidence of T2DM, increased risk for premature death, and increased risk for some cancers (American Medical Association 2013; Council on Science and Public Health 2013; Lauby-Secretan et al. 2016). There remains an unmet need in the pharmacologic treatment of obesity for drugs that are safe, efficacious, and well tolerated. There are currently only a few FDA-approved medications for long-term use for the treatment of obesity that yield a placebo-adjusted average weight loss between 3% and 7% (Srivastava and Apovian 2018). Although moderate weight loss of 5% to 10% in individuals with obesity or overweight has long been shown to yield significant metabolic benefits, including improvements in cholesterol, BP,

and glucose parameters (Goldstein 1992; Wing et al. 2011), greater weight loss can maximize these benefits and may be required to realize clinically meaningful improvements in other weight-related comorbidities, such as sleep apnea, nonalcoholic steatohepatitis, and cardiovascular disease (Ryan and Yockey 2017). In addition to moderate efficacy, some centrally acting weight loss agents to date have had adverse neurocognitive, psychiatric, or cardiovascular effects, further limiting their application in clinical practice (Srivastava and Apovian 2018). The development program for LY3502970 is to demonstrate that this oral non-peptide molecule has benefits on weight management and glucose control similar to that observed with injectable GLP-1 RAs with the convenience of an oral medication.

Phase 1 Studies

The safety, tolerability, PK, and PD of LY3502970 have been evaluated in 4 completed Phase 1 clinical pharmacology studies, J2A-MC-GZGA (GZGA), J2A-MC-GZGC (GZGC), J2A-MC-GZGD (GZGD), and J2A-MC-GZGF (GZGF).

- Study GZGA was a single-ascending dose and a 4-week multiple-ascending dose study in healthy participants that evaluated the safety, tolerability, PK, and PD of LY3502970. The single-ascending dose part of the study evaluated single oral doses of [REDACTED], [REDACTED], and [REDACTED] mg. The multiple-ascending dose part of the study evaluated 28 daily LY3502970 doses of [REDACTED] mg and weekly dose escalation doses evaluating different dose escalation schemes that ranged from [REDACTED] mg through [REDACTED] mg with terminal doses of [REDACTED], [REDACTED], or [REDACTED] mg.
- Study GZGC was a multiple dose study in participants with T2DM, designed to evaluate the safety, tolerability, PK, and PD of LY3502970 following 12 weeks of treatment in participants with T2DM controlled with diet and physical activity with or without a stable dose of metformin. Dose escalations occurred weekly to the target dose and then were maintained at the target dose for the duration of the study. The following were the dosing cohorts:
 - Cohort A: [REDACTED], [REDACTED], [REDACTED], and [REDACTED] mg
 - Cohort B: [REDACTED], [REDACTED], and [REDACTED] mg
 - Cohort C: [REDACTED], [REDACTED], [REDACTED], and [REDACTED] mg
 - Cohort D: [REDACTED], [REDACTED], [REDACTED], [REDACTED], and [REDACTED] mg
 - Cohort E: [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], and [REDACTED] mg.
- Study GZGD was a multiple dose study in healthy participants, designed to evaluate the safety, tolerability, and PK of multiple oral LY3502970 dose prototype tablets.
- Study GZGF was an open-label study to determine the disposition of radioactivity and PK of LY3502970 and total radioactivity in healthy male participants following a single oral dose of [REDACTED] mg LY3502970 containing approximately [REDACTED] µCi of [¹⁴C]-LY3502970. .

The Phase 1 Study J2A-MC-GZGJ (GZGJ) was a randomized, open-label, crossover study that was conducted to assess the PK, safety, and tolerability of LY3502970 in Asian healthy participants in fed and fasted state. Study GZGJ consisted of a dose titration period and test period. Within-treatment dose escalation was applied following several intermediate dose levels and up to a final dose of [REDACTED] mg.

Adverse Events in Phase 1 Studies

In all completed Phase 1 studies, GI-related AEs were the most commonly reported AEs, consistent with GLP-1 agonist pharmacology (Nauck et al. 2009; Dungan et al. 2014; Giorgino et al. 2015; Jendle et al. 2016; Nauck 2016). All AEs were mild or moderate in severity and consistent with other GLP-1 RAs. In Studies GZGA and GZGC, the incidence of GI AEs decreased with continued dosing in the multiple-ascending dose, thus demonstrating tachyphylaxis to the GI AEs.

Other Safety Evaluations in Phase 1 Studies

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

Asymptomatic elevations in serum lipase and/or amylase have been observed in clinical studies. In Studies GZGC and GZGD, elevations in lipase serum concentrations have been observed in 5 participants. In Study GZGD, elevation in amylase concentrations was observed in 1 participant. There have been no clinically significant effects on ECG parameters, vital signs, or other laboratory parameters noted to date. In Study GZGD, 1 event of Increased alanine aminotransferase and 1 event of Increased aspartate aminotransferase were reported.

Pharmacodynamics in Phase 1 Studies

Studies GZGA and GZGC showed that LY3502970 initially delayed gastric emptying, an effect that was greatly diminished with continued exposure similar to marketed GLP-1 RA drugs. Furthermore, LY3502970 showed a decrease in glucose and body weight in Studies GZGA and GZGC. In Study GZGC, LY3502970 treatment demonstrated a decrease in HbA1c levels and fasted serum glucose. PR interval has been observed to generally increase with increasing LY3502970 dose.

Pharmacokinetics in Phase 1 Studies

LY3502970 PK was studied across a range of doses administered as single doses or multiple doses (28 doses) via a QD dosing regimen. LY3502970 PK appeared dose proportional over the dose range studied after single and multiple doses from **CC1** to **CC1** mg. Peak concentrations were observed at approximately 4 to 16 hours postdose, and the half-life was approximately 24.6 to 35.3 hours for single doses and 48.1 to 67.5 hours for multiple doses. Studies GZGA, GZGD, and GZGJ showed that the effect of food on the PK of LY3502970 was a slight decrease in the AUC, whereas median t_{max} was unaffected between the dietary states. The decrease in AUC is not expected to have clinically meaningful impact on efficacy.

In vitro results indicate that CYP2J2 and CYP3A4 are responsible for █% and █% of the hepatic CYP mediated clearance of LY3502970, respectively, in human liver microsomes and that LY3502970 is a substrate of P-gp, OATP1B1, and OATP1B3 transporters. In Study GZGF, which assessed the disposition of [¹⁴C]-LY3502970 following oral administration in healthy male participants, fecal excretion was found to be the principal route of elimination with a mean (± standard deviation) of 86.75% (± 2.78%) of administered radioactivity recovered in feces, whilst only 0.24% (± 0.02%) was excreted in urine.

Phase 2 Studies

The safety, tolerability, and PK of LY3502970 is being evaluated in 2 ongoing Phase 2 clinical pharmacology studies, J2A-MC-GZGE (GZGE) and J2A-MC-GZGI (GZGI).

The ongoing Study GZGE is a multiple dose study in participants with T2DM evaluating the efficacy, safety, tolerability, and PK of QD oral doses of LY3502970 compared with placebo and once weekly 1.5 mg dulaglutide. Participants received oral doses of █, █, █, █, and █ mg QD LY3502970, placebo, or dulaglutide 1.5 mg.

Of 383 participants in Study GZGE, 16 participants experienced SAEs, of whom 12 received LY3502970. No SAEs were considered related to treatment. There were 2 participants who experienced ischemic stroke; one received placebo and one received LY3502970. Neither were judged as being related to study treatment. Overall, there were 272 participants (71% of safety population) who experienced 1 or more TEAEs as a part of this study. The most frequently reported TEAEs were from the Gastrointestinal disorders system organ class followed by those from the Infections and infestations system organ class.

The ongoing Study GZGI is a multiple dose study in participants who are overweight with weight-related comorbidities or obese, designed to determine if at least 1 QD dose of LY3502970 is superior in percent body weight reduction relative to placebo. Participants received oral doses of █, █, █, █, █, █, █, and █ mg QD LY3502970 or placebo.

2.3. Benefit/Risk Assessment

No safety or tolerability concerns that preclude further investigation of LY3502970 have been identified in 268 healthy participants, 72 healthy overweight and obese participants, and 381 participants with T2DM to date, up to the highest administered single dose of █ mg and highest administered multiple dose of █ mg.

Data from Phase 1 studies indicate that LY3502970 treatment may result in a decrease in body weight. These data support improved weight management in healthy overweight and obese participants.

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To characterize and compare the PK of multiple doses of LY3502970 in different formulations in healthy overweight and obese participants	AUC₍₀₋₂₄₎, C_{max}, and t_{max}
Secondary	
- To assess the effect of a high-fat meal on the PK of LY3502970 tablets and capsules in healthy overweight and obese participants - To assess the PK of high doses of LY3502970 in healthy overweight and obese participants - To describe the safety and tolerability of different formulations of LY3502970 in healthy overweight and obese participants	- AUC₍₀₋₂₄₎, C_{max}, and t_{max} - AUC₍₀₋₂₄₎, C_{max}, and t_{max} - Incidence of TEAEs and SAEs

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

4. Study Design

4.1. Overall Design

Study GZGN is a Phase 1, 2-part, multiple-dose titration study in healthy overweight and obese participants.

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

Screening

All participants will be screened between 28 to 3 days prior to Day 1.

Treatment and Assessment Period

Eligible participants will be admitted to the CRU on Day -2.

Participants will be enrolled in Parts A and B. Approximately 50 participants will be enrolled to ensure 32 completers of Parts A and B.

Part A (Periods 1 to 11)

Throughout Periods 1 to 11, participants will receive a QD oral dose of LY3502970 in the tablet or capsule formulation, depending on the period of the study. Participants will be in a fasted state in all periods, except for Period 10. On Days 1 to 5 of Period 10, that is, Study Days 64 to 68, participants will consume a standard meal prior to dosing. On Days 6 and 7 of Period 10, that is, Study Days 69 and 70, participants will consume a high-fat meal prior to dosing. In Period 10, participants will be randomized 1:1 to receive [CCI] mg LY3502970 capsule or [CCI] mg LY3502970 tablet. Following Period 11, all participants will continue to Part B of the study.

See Section 6.1 for LY3502970 formulation and dosing details. See Section 6.3 for details of randomization.

Progression of Doses through Part A of Study GZGN

During the treatment period of Part A, doses will be escalated in a stepwise manner for all participants on a weekly basis for 11 weeks, with the following dose levels and formulations administered QD for 7 days as shown:

- Period 1: [CCI] mg LY3502970 tablet
- Period 2: [CCI] mg LY3502970 capsule
- Period 3: [CCI] mg LY3502970 tablet
- Period 4: [CCI] mg LY3502970 tablet
- Period 5: [CCI] mg LY3502970 capsule
- Period 6: [CCI] mg LY3502970 tablet
- Period 7: [CCI] mg LY3502970 capsule
- Period 8: [CCI] mg LY3502970 tablet
- Period 9: [CCI] mg LY3502970 capsule
- Period 10: [CCI] mg LY3502970 capsule or [CCI] mg LY3502970 tablet, in fed state, and
- Period 11: [CCI] mg LY3502970 tablet.

Part B (Periods 12 and 13)

Throughout Periods 12 and 13, participants will receive a QD oral dose of LY3502970 in the tablet formulation. Participants will be randomized 3:1 to receive either LY3502970 dose titration tablets or [REDACTED] mg LY3502970 tablets based on a computer-generated allocation code, as detailed in Section 6.3.

Participants may be allowed to leave the CRU after completing the safety assessments on Period 13, Day 9, or later at the investigator's discretion.

Progression of Doses through Part B of Study GZGN

During the treatment period of Part B, participants randomized to receive dose titration LY3502970 tablets will receive a stepwise dose titration of LY3502970 on Day 1 of Periods 12 and 13, with each of the following dose levels and formulations administered QD for 7 days as shown:

- Period 12: [REDACTED] mg LY3502970 in tablet formulation, and
- Period 13: [REDACTED] mg LY3502970 in tablet formulation.

Participants randomized to the control group will receive [REDACTED] mg LY3502970 in tablet formulation QD for 7 days in both Periods 12 and 13.

Follow-Up Period

A follow-up visit will be performed approximately 7 to 14 days after discharge from the CRU.

4.2. Scientific Rationale for Study Design

This study will evaluate the dose-exposure relationship of LY3502970 in the tablet and capsule formulations, and the PK of high doses of LY3502970, in healthy overweight and obese participants.

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

This study will be conducted in 2 parts. Part A will be an 11-week open-label study and will include LY3502970 in the capsule and tablet formulations. The [REDACTED] mg LY3502970 capsule and the [REDACTED] mg LY3502970 tablet will be the highest doses administered for their respective formulations. Part B will be a 2-week double-blind study with LY3502970 tablets only, and no capsules. Based on the PKs of the tablet formulation from Study GZGD, it is possible that the tablet formulation might achieve higher exposures than the capsule formulation. This part of the study will therefore assess safety, tolerability, and PKs at small increments of previously-explored doses. If higher exposures than previously explored are achieved with the tablet formulation, data collected from this part of the study will provide a greater understanding of safety and risk considerations of LY3502970. Participants will be randomized to a dose titration LY3502970 group or a LY3502970 control group.

Each period of each part of the study will last 7 days to allow each participant to reach a PK steady state, based on half-life as discussed in Section 2.2. This steady state evaluation of PK

parameters is required because of the need for a titration period to dose high enough for the formulation to be expected to impact exposure, and to improve GI tolerability for GLP-1 RA class. This design also allows each individual participant to be used as their own control to limit the number of healthy participants needed for the assessment. Periods 10 and 11 will allow evaluation of the effect of a high-fat meal on PK compared to PK in a fed state.

Healthy overweight and obese participants will be enrolled, rather than healthy participants because the pharmacologic activity of LY3502970 includes weight loss and it is anticipated that the participants will experience some body weight loss during this study. Additionally, as chronic weight management is one of the intended indications of LY3502970, participants who are overweight or have obesity will be more representative of the target population than healthy participants. Participants without a history of alcohol or drug abuse or regular co-medication are proposed to avoid interaction on drug metabolism and to avoid non-compliance. The 11-week treatment duration will provide sufficient data to assess the PK, safety, and tolerability of LY3502970.

WOCBP are able to participate in this study based on review of developmental and reproductive toxicology studies.

4.3. Justification for Dose

LY3502970 doses of [REDACTED] to [REDACTED] mg administered orally QD were selected based on the following:

- In the single and a 4-week multiple dose study in healthy participants, GZGA, LY3502970 doses through [REDACTED] mg were safe and well tolerated following dose titration.
- In the 12-week study GZGC, in participants with T2DM, LY3502970 doses between [REDACTED] and [REDACTED] mg were safe and well tolerated following dose titration.
- The ongoing Phase 2b studies assessed safety, tolerability, PK, and PD in participants with T2DM (Study GZGE) and individuals who are overweight or have obesity (Study GZGI), at doses starting at [REDACTED] or [REDACTED] mg and titrating up to a maximum dose of [REDACTED] mg. In these studies, LY3502970 has been found to be safe and well tolerated in this dose range, with GI AEs being the most common AEs.
- LY3502970 in the tablet formulation has only been studied in study GZGD, at a single dose of [REDACTED] mg. In order to explore exposures up to and slightly beyond the highest dose of [REDACTED] mg that has been studied with the capsule formulation, tablet dose levels of [REDACTED] and [REDACTED] mg have been included in Part B of this study. The exposure multiples to predicted human AUC exposure at the [REDACTED] mg dose are given in Table GZGN.1. The values in the table correspond to the NOAEL for target organ toxicity in both animal toxicology species ([REDACTED]) in the 6-month rat toxicology study and 9-month monkey toxicology study. [REDACTED]

[REDACTED] The NOAEL in the monkey was characterized by effects that were consistent with exaggerated pharmacology or class effects, and that are considered monitorable and reversible in the participants of Study GZGN. Part A is an open-label study with no randomization, except for Period 10. As the Part B doses are likely to achieve previously unexplored exposures, a control arm at [REDACTED] mg tablet dose is also included. For this reason, Part B will be double-blind, with participants randomized to the dose titration arm or the control arm.

High acute doses of GLP-1 RAs, including LY3502970, are often poorly tolerated due to GI symptoms, whereas a more gradual dose titration scheme to reach a high dose has been shown to improve GLP-1 RA tolerability. Dosing algorithms starting at a low dose of **CCI** mg accompanied by dose titration every 7 days would permit adequate time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns. The selected dose and titration scheme would enable further evaluation of benefit and risk considerations of LY3502970.

Table GZGN.1.

CCI

4.4. End of Study Definition

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

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit shown in the SoA in Section 1.3.

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.

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination (screening or check-in on Day -2 assessment), vital signs, clinical laboratory tests, and ECG. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

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

Screening may occur up to 28 days prior to enrollment. Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment or clinical measurements to confirm their eligibility. In such instances, at minimum, the following screening tests and procedures will need to be repeated: weight, vital signs, ECG, clinical laboratory tests, and pregnancy test (females only).

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, unless otherwise specified:

Age

1. are 18 to 70 years of age, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history and physical examination.

Weight

3. have a BMI of 27.0 kg/m² or more.
4. have a stable body weight, with 5% or less body weight gain or loss, for 90 days prior to dosing.

Sex and Contraceptive/Barrier Requirements

5. are male or female. WOCBP and WNOCBP may participate in this study.

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the definition of WOCBP, WNOCBP, and the contraception requirements of this protocol, see Appendix 4 in Section [10.4](#).

Informed Consent

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

Other Inclusion Criteria

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

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply at screening, unless otherwise specified:

Medical Conditions

9. have any type of diabetes with:
 - a. a HbA1c level of 6.5% or greater, or
 - b. a fasting blood sugar level above 120 mg/dL.
10. have obesity induced by other endocrine disorders, such as Cushing's syndrome or Prader-Willi syndrome.
11. have:
 - a. a known clinically significant gastric emptying abnormality, such as severe gastroparesis or gastric outlet obstruction,
 - b. undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or
 - c. chronically take medications that directly affect GI motility, based on investigator review.
12. have a known self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or any form of thyroid cancer.
13. have an abnormal BP, PR, or both, including:
 - a. sitting systolic BP of 160 mmHg or greater,
 - b. sitting diastolic BP of 100 mmHg or greater.

Note: a repeat assessment may be conducted if necessary; if the second measurement shows values within the range, the participants can be included in the study.

14. have significant previous or current history of comorbidities capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data.

Note: a history of cholecystectomy or appendectomy is allowed.

15. regularly use known drugs of abuse or show positive findings on drug screening.
16. have a significant history of or current Major Depressive Disorder or psychiatric disorder within the last 2 years.

Note: Participants with Major Depressive Disorder or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.

17. are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
18. have a lifetime history of suicide attempt.
19. have answered “yes” to:
 - a. either Question 4 or Question 5 on the “Suicidal Ideation” portion of the C-SSRS, or
 - b. any of the suicide-related behaviors on the “Suicidal Behavior” portion of the C-SSRS, andthe ideation or behavior occurred within the past month.

20. have a history or presence of acute or chronic pancreatitis, or have an elevation in serum lipase or amylase greater than $3 \times$ ULN.

Note: a potential participant with a history of acute pancreatitis caused by gallstones may be included in the study if the participant has a cholecystectomy to resolve the problem.

21. have known allergies to LY3502970, related compounds, or any components of the formulation, or a history of significant atopy.
22. have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
23. have evidence of hypothyroidism or hyperthyroidism based on clinical evaluation that, in the opinion of the investigator, would pose a risk to participant safety. Participants who are on a stable dose of thyroid replacement therapy for at least the prior 3 months and who are anticipated to remain on this dose throughout the study period may be included in the study.
24. have an ECG abnormality including a QT interval (calculated using Fridericia’s formula) greater than 450 milliseconds in males or greater than 470 milliseconds in females at the time of screening, that may represent a safety risk at the discretion of the investigator.
25. have a history of a transplanted organ. Corneal transplants (keratoplasty) are allowed.
26. have evidence of a significant, active autoimmune abnormality, for example, lupus or rheumatoid arthritis, that in the opinion of the investigator is likely to require concurrent treatment with systemic glucocorticoids in the next 6 months.
27. have evidence of a significant, active, uncontrolled medical condition or history of any medical problem capable of constituting a risk when taking the study medication or interfering with the interpretation of data, as judged by the investigator.
28. have had any of the following within the last 6 months:
 - a. myocardial infarction,
 - b. unstable angina,
 - c. coronary artery bypass graft,
 - d. percutaneous coronary intervention (diagnostic angiograms are permitted),
 - e. transient ischemic attack,
 - f. cerebrovascular accident (stroke) or decompensated congestive heart failure, or
 - g. have a history of heart failure.

Prior/Concomitant Therapy

29. have used or intend to use any prescription or over-the-counter medications within 30 days prior to screening and throughout the study, with the exception of vitamin or mineral supplements, vaccination, occasional acetaminophen, and prescription medications for the treatment of concurrent medical conditions such as thyroid replacement therapy, antihypertensive agents, antiplatelet drugs, or lipid-lowering agents with a stable dose for at least 1 months prior to enrollment.
30. have any exposure to dulaglutide, other GLP-1 analogs, or other related compounds within 3 months of screening.
31. have known or suspected hypersensitivity to study medication, to selective GLP-1 RAs or GIP/GLP-1 or GLP-1/Gcg dual RAs.

Note: Participants who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability should not be dosed.

32. have taken over-the counter, prescription, or alternative remedies, including herbal or nutritional supplements, intended to promote weight loss within 90 days prior to dosing of LY3502970, including but not limited to:
 - a. SAXENDA® (liraglutide 3.0 mg) or other GLP-1 RA
 - b. Xenical® (orlistat)
 - c. Meridia® (sibutramine)
 - d. Acutrim® (phenylpropanolamine)
 - e. Sanorex® (mazindol)
 - f. Adipex® (phentermine)
 - g. BELVIQ® (lorcaserin)
 - h. Qsymi™ (phentermine/topiramate combination)
 - i. Contrave® (naltrexone/bupropion)
 - j. WEGOVY™ (semaglutide 2.4 mg), and
 - k. other similar body weight loss medication, including over-the-counter premedications, for example, alli®.
33. are currently taking a central nervous system stimulant, for example, Ritalin-SR with the exception of caffeinated beverages.
34. are currently using metformin, or any other glucose-lowering medication, whether prescribed for polycystic ovarian syndrome or diabetes prevention.
35. are receiving or have received chronic (that is, more than 2 weeks) systemic glucocorticoid therapy, excluding topical, intraocular, intranasal, single intraarticular injection, or inhaled preparations within 3 months of screening, or have received any such therapy within 4 weeks immediately prior to screening.
36. are receiving, or have taken in 14 days prior to screening, strong or moderate CYP3A inhibitors or inducers, strong OATP inhibitors, and drugs that are P-gp or BCRP substrates with narrow therapeutic index. See Section 6.9 for detail.
37. have a history of use of marijuana or tetrahydrocannabinol-containing products within 90 days of enrolment or unwillingness to abstain from marijuana or tetrahydrocannabinol-containing products use during the study.

Prior/Concurrent Clinical Study Experience

- 38. have participated in a clinical study involving an IP, where they received the last dose of the IP within 90 days or 5 half-lives of the drug (whichever is longer).
- 39. have previously completed or withdrawn from this study or any other study investigating LY3502970.

Diagnostic Assessments

- 40. have a fasting serum triglyceride level of more than 500 mg/dL.
- 41. have a serum calcitonin level at screening of 20 ng/L or greater.
- 42. have a hemoglobin value of less than 11 g/dL for males or less than 10 g/dL for females.
- 43. have signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the local laboratory during screening:
 - a. ALT level greater than $3 \times$ ULN for the reference range (as determined by the local laboratory at study entry),
 - b. ALP level greater than $1.5 \times$ ULN for the reference range, or
 - c. TBL level greater than $1.5 \times$ ULN for the reference range, except for cases of suspected or known Gilbert's Syndrome.
- 44. show evidence of human immunodeficiency virus infection, positive human immunodeficiency virus antibodies, or both.
- 45. have a positive HCV antibody test. Those who have had treatment for HCV may enter the study if they have a negative HCV RNA test.
- 46. have a current infection with hepatitis B virus, that is, positive for hepatitis B surface antigen.

Other Exclusion Criteria

- 47. are women, who are currently pregnant or breastfeeding, or who intend to become pregnant or to breastfeed at any time during the study or within 20 weeks after receiving the last dose of study drug.
- 48. have any other conditions (including known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, may make the participant unsuitable for the study.
- 49. have donated more than 500 mL of blood within the 8 weeks, or a blood transfusion or severe blood loss within 90 days, prior to the first dose of the study drug.
- 50. have difficulty swallowing capsules or tablets.
- 51. have an average weekly alcohol intake that exceeds 21 units per week for males of 65 or less years, and 14 units per week for females and males of over 65 years.

Note: number of units = [total volume of drink (mL) x alcohol by volume (%)]/1000.

- 52. are unwilling to stop alcohol consumption 24 hours prior to CRU admission and for the duration of the study.
- 53. are unable or unwilling to abstain from smoking or consumption of any form of tobacco for 30 days prior to admission to the CRU, and to refrain from nicotine during CRU admission.

54. in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.
55. are employees of Eli Lilly and Company, are site personnel directly affiliated with this study or their immediate families, or are employees of a third-party organization involved in the study which requires exclusion of their employees.
56. have an estimated glomerular filtration rate (eGFR) less than 30 mL/minute/1.73 m² calculated by Chronic Kidney Disease-Epidemiology.
57. have taken over-the counter, prescription, or alternative remedies, including herbal or nutritional supplements, intended to promote weight gain within 90 days prior to dosing of LY3502970, including but not limited to:
 - tricyclic and tetracyclic antidepressants, such as imipramine, amitriptyline, and mirtazapine
 - typical anti-psychotics, such as chlorpromazine and thioridazine
 - atypical anti-psychotics, such as clozapine, olanzapine, and quetiapine
 - mood stabilizers, such as lithium, valproic acid and its derivatives
 - paroxetine, a selective serotonin reuptake inhibitor, or
 - phenelzine, a monoamine oxidase inhibitor.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

While resident at the CRU, participants will consume only food and beverages that are provided to them by the CRU staff. Standard meals (for example, breakfast, lunch, dinner, and snack) will be provided to the participants.

Participants will refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study intervention until discharge from the study.

On dosing days in Periods 1 to 9 and Period 11 of Part A and Periods 12 and 13 of Part B, participants need to be fasting for at least 10 hours prior to oral LY3502970 dosing. On Days 1 to 6 of these periods, participants may consume their meal 30 minutes after LY3502970 dosing. On Day 7 of these periods, no food will be allowed for at least 4 hours after LY3502970 dosing.

On Day 7 of each period in Parts A and B, fluids will be restricted from 1 hour prior to and until 1 hour after LY3502970 dosing, except for the water required for dose administration. Water may be consumed freely at all other times.

On Days 1 to 5 of Period 10, that is, Study Days 64 to 68, participants will consume a standard meal 30 minutes prior to LY3502970 dosing. On Days 6 and 7 of Period 10, that is, Study Days 69 and 70, participants will consume a high-fat meal 30 minutes prior to LY3502970 dosing. Participants should eat the meal in 30 minutes or less. On each dosing day of Period 10, no food will be allowed for at least 4 hours after LY3502970 dosing.

The standardized high-fat, high-calorie meal, where fat comprises approximately 50% of total caloric content of the meal, should consist of approximately 1000 calories. No additional food or substitute is allowed. A typical test meal consists of:

- 1 hash brown,
- 2 strips of bacon – grilled,
- 1 small (45 g) egg fried in 10 g butter,
- 2 slices of white medium sliced bread with 20 g of butter, and
- 240 mL of whole milk.

This test meal derives approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

Caffeine

Participants will be required to comply with the CRU's caffeine restrictions while they are in the CRU.

Alcohol

Participants will abstain from alcohol for 24 hours prior to CRU admission until discharge from the study.

Tobacco

Participants who use tobacco products will be instructed that use of nicotine-containing products, including nicotine patches, will not be permitted while they are in the CRU. Participants will abstain from smoking or other forms of tobacco use for 30 days prior to admission to the CRU.

5.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity and exercise during the study. Participants will abstain from strenuous exercise for 24 hours prior to PK sampling.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment/Administration of Study Intervention of a Participant

Not applicable.

6. Study Interventions and Concomitant Therapy

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

6.1. Study Interventions Administered

In Part A, participants will be administered 1 LY3502970 capsule or tablet. In Part B, participants will be administered 3 LY3502970 tablets to reach the required dose:

-  mg:  +  +  mg tablets,
-  mg:  +  +  mg tablets, or
-  mg control:  +  +  mg tablets.

Each dose of LY3502970 will be administered orally with approximately 240 mL of room temperature water in the morning of each dosing day in a sitting position. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures. See Section 5.3.1 for details of dosing in the fed and fasted states. [Table GZGN.2](#) lists the interventions used in this clinical study.

Table GZGN.2. Study Interventions Administered

Intervention Name	LY3502970	LY3502970
Type	Drug	Drug
Dose Formulation	Capsule	Tablet
Unit Dose Strength(s)	 mg  mg  mg  mg	 mg  mg  mg  mg  mg  mg
Route of Administration	Oral	Oral
Use	Experimental	Experimental

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current good manufacturing practice. Study interventions will be labeled as appropriate for country requirements.

Participants will be able to see whether they are administered a capsule or tablet.

6.2. Preparation, Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

Further guidance and information for the final disposition of unused study interventions are provided separately.

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

6.3. Assignment to Study Intervention

On Day 1 of Period 10, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to administration of:

- █ mg LY3502970 capsule or █ mg LY3502970 tablet in Period 10 of Part A, and
- LY3502970 dose titration tablets or the control group that will receive █ mg LY3502970 tablets in Periods 12 and 13 of Part B.

Participants will be assigned according to the randomization schedule generated prior to the study by the Statistics Department at █. Each participant will be dispensed study intervention, labeled by the CRU unblinded personnel with the participant's unique randomization number, throughout Periods 12 and 13.

6.4. Blinding

Part A of this study is open-label.

Part B of this study is double-blind and randomized to reduce potential bias. For the blind Periods 12 and 13, the CRU personnel who will prepare the doses for each treatment period will not be blinded and will be separate and distinct from those who are involved in participant care. Blinding will be maintained throughout the conduct of Part B of the study.

Treatment assignment will be kept strictly confidential and accessible only to authorized persons until after the time of unblinding. Codes with treatment assignment will, however, be readily available to the blinded personnel in case of an emergency.

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

6.5. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

6.6. Dose Modification

Dose reductions or adjustments will not be allowed during this study.

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

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

6.8. Treatment of Overdose

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

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

In the event of an overdose, the investigator should:

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE or SAE and laboratory abnormalities until, for example, LY3502970 no longer has a clinical effect or can no longer be detected systemically (Day 105), and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.9. Prior and Concomitant Therapy

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

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

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

If acetaminophen treatment is needed for pain management, the maximal allowed dose will be 3 g per day, from all acetaminophen-containing medicinal products.

Participants must abstain from taking prescription or nonprescription drugs, including vitamins and dietary or herbal supplements, within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives, whichever is longer, before the start of study intervention until completion of the study, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study. Some concomitant medication, for example thyroid replacement therapy as described in Exclusion Criterion [23], may be allowed on a case-by-case basis by the investigator in consultation with the medical monitor if required, as long as they are at a stable dose.

Allowed concomitant medications should be taken according to label instructions. Specifically, medications that may be affected by an increase in gastric pH, such as levothyroxine, bisphosphonates, and ferrous sulfate, should be separated from study intervention administration by at least 2 to 4 hours.

Participants must abstain from taking strong or moderate CYP3A inhibitors, strong or moderate CYP3A inducers, strong OATP inhibitors, and drugs that are P-gp or BCRP substrates with a narrow therapeutic index. To be eligible for screening into this study, those drugs need to be washed out for at least 2 weeks and the participant should be on a stable dose of alternative medications for at least 2 weeks prior to screening. See Appendix 8 in Section 10.8 for examples of excluded medications.

To be eligible for screening into this study, participants taking the following anti-fungal agents should discontinue taking these medications for at least 2 weeks prior to screening:

- ketoconazole,
- itraconazole,
- voriconazole, and
- posaconazole.

However, if the participant is unable to wash out these drugs because of an underlying condition, then if appropriate, the participant could switch to:

- miconazole, or
- clotrimazole.

For participants taking clarithromycin or telithromycin, azithromycin may be substituted 2 weeks prior to screening.

Initial doses of LY3502970 may delay gastric emptying and have the potential to transiently impact the rate of absorption of concomitantly administered oral medicinal products. LY3502970 should be used with caution in participants receiving oral medicinal products that require rapid GI absorption following the initial doses of LY3502970, as exposure to oral medications may be increased. For participants receiving oral medications with rapid GI absorption, the dose of the study intervention should be separated by 2 to 4 hours.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

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

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

A participant should be permanently discontinued from study intervention if:

- the participant becomes pregnant during the study,
- they experience an AE that is considered to be intolerable,
- they experience more than 1 incidence of emesis in Periods 1 to 3,

Note: participants that are discontinued after experiencing more than 1 incidence of emesis in Periods 1 to 3 must be replaced.

- they experience the following circumstances:
 - diagnosis of cirrhosis after randomization,
 - pancreatitis or pancreatic cancer,
 - diagnosis of medullary thyroid cancer after randomization,
 - diagnosis of an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization, or
 - diagnosis of T1DM or latent autoimmune diabetes in adults.
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons,
- the participant answered "yes" to:
 - Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, or
 - any of the suicide-related behaviors on the "Suicidal Behavior" portion of the C-SSRS.

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

7.1.1. Liver Chemistry Stopping Criteria

The discontinuation values required below pertain to participants enrolled with normal or near normal hepatic biochemical tests including ALT equal to or less than $1.5 \times \text{ULN}$, TBL equal to or less than $1.5 \times \text{ULN}$, or ALP equal to or less than $1.5 \times \text{ULN}$. In participants with abnormal hepatic biochemical tests at baseline, the discontinuation values may need to be adjusted on a

case-by-case basis. For example, those enrolled with baseline ALT greater than $1.5 \times \text{ULN}$, for example nonalcoholic fatty liver disease, the discontinuation value may need to be ALT greater than $2 \times$ baseline plus symptoms instead of ALT greater than $3 \times \text{ULN}$ plus symptoms. Similarly, in those with elevated TBL (for example, Gilbert's syndrome) or elevated ALP (for example, underlying bone disease) at baseline, the discontinuation values will increase and will be based on direct bilirubin levels and hepatic ALP-isoenzyme levels, respectively.

Interrupting study drug based on liver test elevations in participants with normal or near-normal baseline liver tests

In study participants with normal or near normal baseline liver tests (ALT, AST, ALP less than $1.5 \times \text{ULN}$), the study drug should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.7.2) if one or more of these conditions occur:

Elevation	Exception
ALT or AST $>5 \times \text{ULN}$	
ALT or AST $>3 \times \text{ULN}$ and either TBL $>2 \times \text{ULN}$ or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is $>0.5 \text{ mg/dL}$, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL $>2 \times \text{ULN}$.
ALT or AST $>3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$)	
ALP $>3 \times \text{ULN}$, when the source of increased ALP is the liver	
ALP $>2.5 \times \text{ULN}$ and TBL $>2 \times \text{ULN}$	For participants with Gilbert's syndrome: If baseline direct bilirubin is $>0.5 \text{ mg/dL}$, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL $>2 \times \text{ULN}$.
ALP $>2.5 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications	

Interrupting study drug based on elevated liver tests in participants with abnormal baseline liver tests

In study participants with abnormal baseline liver tests (ALT, AST, ALP equal to or greater than $1.5 \times \text{ULN}$), the study drug should be **interrupted** if one or more of these conditions occur:

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

ALT or AST >2× baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >2.5× baseline, when the source of increased ALP is the liver	
ALP >2× baseline and TBL > 2× ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2× ULN.
ALP >2× baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications	

Resuming study drug after elevated liver tests

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

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request for any reason or without providing any reason,
- at the request of the participant's designee (for example, parents or legal guardian),
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons,
- if enrolled in any other clinical study involving an IP, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study,
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol.

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

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

7.3. Lost to Follow up

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

8. Study Assessments and Procedures

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

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

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

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

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based on emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.

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

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

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

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

A complete physical examination at screening or check-in on Day -2 will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded. Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

8.2.2. Vital Signs

For each participant, sitting vital signs measurements should be conducted according to the SoA in Section 1.3 and following the study-specific recommendations included in Appendix 7 in Section 10.7. BP and PR should be measured after at least 5 minutes in the sitting position.

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

8.2.3. Electrocardiograms

Single and triplicate 12-lead ECGs will be obtained according to the SoA in Section 1.3.

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

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

If a clinically significant finding is identified after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed, and must document his or her review of the ECG output at the time of collection.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of LY3502970 should be reported to Lilly or its designee as an AE via CRF.

All single 12-lead ECGs should be stored at the investigational site. 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.

8.2.4. Clinical Safety Laboratory Tests

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

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 in Section 10.2, must be conducted in accordance with the SoA in Section 1.3, standard collection requirements, and laboratory manual.

If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator, for example, SAE, AE, or dose modification, then the information will be reported as an AE.

8.2.5. Pregnancy Testing

Serum or urine pregnancy testing will be performed for all female participants at the time points detailed in the SoA in Section 1.3.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Overweight and obese participants are at increased risk for depression (Luppino et al. 2010). Depression can increase the risk for suicidal ideation and behavior. Therefore, study participants will be screened at study entry and monitored during the study for depression, suicidal ideation, and behavior.

Participants being treated with LY3502970 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of suicidal ideation and behavior should undergo a risk assessment. All factors contributing to suicidal ideation and behavior should be evaluated and consideration should be given to discontinuation of the study intervention.

One study partner is requested to be present on all days the C-SSRS is administered.

Timing of collection and AE monitoring

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

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

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

C-SSRS

C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events.

8.2.7. Safety Monitoring

The Lilly clinical pharmacologist or clinical research physician will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or clinical research physician will periodically review:

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

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

8.2.7.1. Pancreatic Monitoring

Diagnosis of acute pancreatitis

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

- abdominal pain, characteristic of acute pancreatitis (that is, epigastric pain radiating to the back, often associated with nausea and vomiting)
- serum amylase (total, pancreatic, or both) and/or lipase equal to or greater than 3× ULN
- characteristic findings of acute pancreatitis on computed tomography scan or magnetic resonance imaging.

If acute pancreatitis is suspected, the investigator should:

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

Discontinuation for acute pancreatitis

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

Asymptomatic elevation of serum amylase and/or lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck 2016; Steinberg et al. 2017a, 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes (lipase and/or p-amylase equal to or greater than $3 \times$ ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

8.2.7.2. Hepatic Monitoring

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

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

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

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

Comprehensive hepatic evaluation

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

If a participant with baseline results of...	develops the following elevations:
ALT or AST $<1.5 \times$ ULN	ALT or AST $\geq 3 \times$ ULN with hepatic signs/symptoms ^a , or ALT or AST $\geq 5 \times$ ULN
ALP $<1.5 \times$ ULN	ALP $\geq 3 \times$ ULN
TBL $<1.5 \times$ ULN	TBL $\geq 2 \times$ ULN (except for participants with Gilbert's syndrome)
ALT or AST $\geq 1.5 \times$ ULN	ALT or AST $\geq 2 \times$ baseline with hepatic signs/symptoms ^a , or ALT or AST $\geq 3 \times$ baseline
ALP $\geq 1.5 \times$ ULN	ALP $\geq 2 \times$ baseline
TBL $\geq 1.5 \times$ ULN	TBL $\geq 2 \times$ baseline (except for participants with Gilbert's syndrome)

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

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

- prothrombin time,
- international normalized ratio,
- viral hepatitis A, B, C, or E,
- autoimmune hepatitis, and
- an abdominal imaging study (for example, ultrasound or computed tomography scan).

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

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

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

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

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

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

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

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

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

8.2.7.3. Hypoglycemia Monitoring

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

Investigators should use the following classification of hypoglycemia:

Level 1 hypoglycemia:

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

Level 2 hypoglycemia:

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

Level 3 hypoglycemia:

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

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

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

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

8.2.7.4. Body Weight and Fasting Plasma Glucose

Body weight and fasting plasma glucose will be collected as specified in the SoA in Section 1.3.

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

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

- AEs,
- SAEs, and
- PCs.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue LY3502970 as described in Section 7.

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and AESIs as defined in Section 8.3.4 will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3. For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and or causality, or both. Further information on follow-up procedures is provided in Appendix 3 in Section 10.3.4.

8.3.1. Timing and Mechanism for Collecting Events

Table GZGN.3 describes the timing, deadlines, and mechanism for collecting events.

Table GZGN.3. Timing and Mechanism for Collecting Events

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	start of intervention	participation in study has ended	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE and SAE updates – prior to start of study intervention and deemed reasonably possibly related to study procedures	signing of the informed consent form	start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	start of intervention	participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – after participant’s study participation has ended and the investigator becomes aware	After participant’s study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	Up to Day 105, or upon ET	Within 24 hours (see Section 8.3.3)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; CRF = case report form; ET = early termination; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

* SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Adverse Event Monitoring with a Systematic Questionnaire

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

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

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

8.3.3. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LY3502970.

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

- obtain a consent to release information from the pregnant female partner directly, and
- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the

pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

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

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

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

A spontaneous abortion (occurring at less than 20 weeks gestational age) or still birth (occurring at 20 or more weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.4. Adverse Events of Special Interest

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 study treatment and protocol procedure will be captured. Other AESIs for this program include:

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

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

8.4. Pharmacokinetics

At the visits and times specified in the SoA in Section 1.3, venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of LY3502970. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed on between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

8.4.1. Bioanalysis

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

Concentrations of LY3502970 will be assayed using a validated liquid chromatography tandem mass spectrometry method.

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

During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as bioanalytical assay validation, additional metabolism, protein binding work, or all.

8.5. Pharmacodynamics

Not applicable.

8.6. Genetics

A blood sample for DNA isolation will be collected from participants.

See Appendix 5 in Section 10.5 for information regarding genetic research.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

This section is not applicable for this study.

9. Statistical Considerations

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

9.1. Statistical Hypothesis

The primary objective of this study is to characterize and compare the PK of multiple doses of LY3502970 in different formulations in healthy overweight and obese participants. There are no formal statistical hypotheses confirmed for this study.

9.2. Analyses Sets

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

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

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

9.2.1. Study Participant Disposition

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

9.2.2. Study Participant Characteristics

The participants' age, sex, weight, height, BMI, race, and other demographic characteristics will be recorded and summarized using descriptive statistics.

9.3. Statistical Analyses

9.3.1. General Considerations

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

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

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

9.3.2. Primary Endpoint Analysis

9.3.2.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3502970 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be $AUC_{(0-24)}$, C_{max} , and t_{max} of LY3502970. Other noncompartmental parameters, such as $t_{1/2}$, apparent clearance, and apparent volume of distribution may be reported.

9.3.2.2. Pharmacokinetic Statistical Inference

CCI [REDACTED]

9.3.3. Secondary Endpoints Analysis

9.3.3.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3502970 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be $AUC_{(0-24)}$, C_{max} , and t_{max} of LY3502970. Other noncompartmental parameters, such as $t_{1/2}$, apparent clearance, and apparent volume of distribution may be reported.

9.3.3.2. Pharmacokinetic Statistical Inference

CCI [REDACTED]

In addition, the relationship between the LY3502970 capsule and tablet formulations regarding $C_{\max}$ and AUC parameters will be explored using all data across Periods 1 to 11.

9.3.3.3. 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. AEs reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

The number of IP-related SAEs will be reported.

9.3.3.4. Statistical Evaluation of Safety

Safety parameters that will be assessed include vital signs and ECGs. The parameters and changes from baseline (Period 1, Day 1 predose), where appropriate, will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.3.4. Other Analyses

9.3.4.1. Analysis of C-SSRS Data

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

9.4. Interim Analysis

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

9.5. Sample Size Determination

CCI



10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for:

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

10.1.2. Informed Consent Process

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

Potential participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB, IEC, or study center.

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

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

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

10.1.3. Data Protection

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

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

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

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

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

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

Reports

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

Data

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

10.1.5. Data Quality Assurance

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

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

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

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

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

Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

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

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

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

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

In addition, 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.

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 for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

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

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

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

10.1.6. Source Documents

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

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

Definition of what constitutes source data can be found in Section [10.1.5](#).

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

- for study termination:
 - discontinuation of further study intervention development.
- for site termination:
 - failure of the investigator to comply with the protocol, the requirements of the IRB or IEC, or local health authorities, the sponsor's procedures, or GCP guidelines,
 - inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator, and
 - total number of participants included earlier than expected.

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

10.1.8. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

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

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

Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 5](#) of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

Safety Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count	Total calcium
Mean cell volume	Blood urea nitrogen
Mean cell hemoglobin	Fasting blood glucose
Mean cell hemoglobin concentration	Creatinine
Leukocytes (white blood cells [WBC])	Total protein
Platelets	Albumin
Differential WBC – Absolute counts and % of:	Total bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Aspartate aminotransferase
Monocytes	Alanine aminotransferase
Eosinophils	Calcitonin ^f
Basophils	Pancreatic amylase ^e
	Lipase ^e
Urinalysis	Hemoglobin A1c ^a
Specific gravity	Ethanol testing ^b
pH	Urine drug screen ^{a,b}
Protein	
Glucose	Fasting Lipid Panel ^a
Ketones	Total cholesterol ^a
Bilirubin	Triglycerides ^a
Urobilinogen	Low density lipoprotein (LDL) ^a
Leukocytes	High density lipoprotein (HDL) ^a
Blood	LDL/HDL ratio ^a
Nitrite	
Microscopic examination of sediment ^c	Hepatitis B surface antigen ^a
	Hepatitis C antibody ^a
	Human immunodeficiency virus (HIV) ^a
	Pregnancy test ^d
	Follicle-stimulating hormone ^a
	Thyroid stimulating hormone ^a

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

^a Performed at screening only.

^b Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit. Urine alcohol test will be used at screening, and breath or urine test will be used on Day -2.

^c Test only if dipstick result is abnormal.

^d Serum pregnancy test at screening and when urine test is positive. Urine pregnancy test at all other time points.

^e To be performed at screening, predose on Day 1, follow-up visit, and early termination if applicable.

^f To be performed at screening, follow-up visit, and early termination if applicable.

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-GZGN Sampling Summary – Parts A and B

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests ^a	45	1	45
Local clinical laboratory tests ^a	12	7	84
Pharmacogenetics	10	1	10
Pharmacokinetics	2	118 ^b	236
Total			375
Total for clinical purposes			380

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

^b Includes additional 3 samples, if required.

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

10.3.1. Definition of Adverse Event

AE Definition

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

Events Meeting the AE Definition

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

Events 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 or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of Serious Adverse Event

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

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

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

10.3.3. Definition of Product Complaints

Product Complaint

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

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

AE, SAE, and Product Complaint Recording

- When an AE, SAE, or product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE, SAE, or product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE and SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.
- Note: An event may meet the definition of both a product complaint and an AE or SAE. In such cases, it should be reported as both a product complaint and as an AE or SAE.
- 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 CRF page for AE or SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, other clinical information, or all of these. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

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

An event is defined as ‘serious’ when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

Follow-up of AEs and SAEs

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

10.3.5. Reporting of Serious Adverse Events

SAE Reporting via SAE Report

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

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

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

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they: • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy^a, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone ≥ 40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. ^a Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

10.4.2.1. Male Participants

Males may participate in this study. No male contraception is required except in compliance with specific local government study requirements.

10.4.2.2. Female Participants

WOCBP and WNOCBP may participate in this study.

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

Must...	Must not...
agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods ○ calendar ○ ovulation ○ symptothermal, or ○ post-ovulation • declare abstinence just for the duration of a trial, or • use the withdrawal method

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

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

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide ○ male condom with spermicide ○ diaphragm with spermicide, or

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

10.5. Appendix 5: 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 or IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to LY3502970 or T2DM, chronic weight management, and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3502970, T2DM, chronic weight management, and related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3502970 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 DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on LY3502970 continues but no longer than 15 years or other period as per local requirements.

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

Hepatic Evaluation Testing

See Section 8.2.7.2 for guidance on appropriate test selection.

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

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

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

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

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	Cytomegalovirus (CMV) testing:
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA ^b
Ceruloplasmin	Herpes simplex virus (HSV) testing:
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA ^b

Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	Microbiology
Ethyl glucuronide (EtG)	Culture:
Epstein-Barr virus (EBV) testing:	Blood
EBV DNA ^b	Urine

- a Not required if anti-actin antibody is tested.
- b Reflex/confirmation dependent on regulatory requirements, testing availability, or both.
- c Not required if ASMA is tested.

10.7. Appendix 7: Standardized Protocols for the Measurement of Height, Weight, and Vital Signs

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

Measuring Height

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

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

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

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

Measuring Weight

Body weight measurements should be done in a consistent manner using a calibrated electronic scale that measures in kg up to 1 decimal place, with a capacity to accommodate participants with overweight or obesity.

All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.

Body weight must be measured in a fasting state. If the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting body weight measured.

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

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

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

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

Sitting Vital Sign Measurements

Vital sign measurements (BP and heart rate, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing.

The participant should sit quietly for at least 5 minutes before vital sign measurements are taken.

BP must be taken with an automated BP instrument, with full range of cuff sizes up to extra-large.

If BP and pulse measurements are taken separately, pulse should be taken prior to BP.

Note: In the event the pulse measurement cannot be taken via an automated BP instrument, the preferred location for measurement of pulse is the radial artery.

Unscheduled orthostatic vital sign measurements

Unscheduled orthostatic vital sign measurements (BP and heart rate, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing. They should be done after completing the triplicate measures in the sitting position.

The participant should be comfortably lying flat without legs crossed, in a calm, quiet area for at least 5 minutes before vital sign measurements are taken.

For measurement of vital signs in the supine position, the arm should be supported by a pillow, so it is at the level of the right atrium (approximately halfway between the bed and the level of the sternum).

Incorrect arm positioning results in erroneous BP values.

Upper arm below the level of the right atrium (for example, arm hanging down) results in readings that are too high.

Upper arm above the heart level results in readings that are too low.

Measure BP and PR once in the supine position.

After the BP and PR are determined in the supine position, the participant should immediately move to the standing position, bend the arm used for BP determination at the elbow, and rest the arm on an adjustable table or stand, so the upper arm is supported at the heart level.

Determine the standing BP and PR in the supported arm immediately after standing for 3 minutes. Only 1 measurement is needed.

Record all symptoms (AEs) that the participant may experience, such as lightheadedness, syncope, or dizziness as AEs.

10.8. Appendix 8: Examples of Excluded Medications

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

The FDA has provided a list of strong CYP3A4 inhibitors and CYP3A inducers, which are listed below:

- boceprevir,
- cobicistat,
- danoprevir and ritonavir,
- elvitegravir and ritonavir,
- grapefruit juice,
- indinavir and ritonavir,
- itraconazole,
- ketoconazole,
- lopinavir and ritonavir,
- paritaprevir and ritonavir and ombitasvir and/or dasabuvir,
- posaconazole,
- ritonavir,
- saquinavir and ritonavir,
- telaprevir,
- tipranavir and ritonavir,
- telithromycin,
- troleandomycin,
- voriconazole,
- clarithromycin,
- nefazodone,
- nelfinavir,
- apalutamide,
- carbamazepine,
- enzalutamide,
- mitotane,
- phenytoin,
- rifampin, and
- St John's wort.

Examples of moderate CYP3A4 inhibitors and CYP3A inducers include, but are not limited to:

- amprenavir,
- aprepitant,
- atazanavir,
- atazanavir and ritonavir,
- berotralstat,
- cimetidine,

- ciprofloxacin,
- clotrimazole,
- crizotinib,
- cyclosporine,
- darunavir,
- diltiazem,
- dronedarone,
- duvelisib,
- erythromycin,
- fedratinib,
- fluconazole,
- fluvoxamine,
- fosnetupitant and palonosetron,
- imatinib,
- indinavir,
- isavuconazole,
- istradefylline,
- ledipasvir/sofosbuvir,
- lefamulin,
- letermovir,
- magnolia vine (*Schisandra sphenanthera*),
- netupitant,
- nilotinib,
- tofisopam,
- verapamil, and
- voxelotor.

Participants should not take strong OATP inhibitors. Examples of strong OATP inhibitors include, but are not limited to:

- rifampin,
- cyclosporine,
- faldaprevir,
- tipranavir/ritonavir,
- glecaprevir/pibrentasvir,
- telaprevir,
- sofosbuvir/velpatasvir/voxilaprevir,
- lopinavir/ritonavir,
- darunavir/ritonavir, and
- elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

Participants taking P-gp substrates with narrow therapeutic index are excluded from being screened for this study. Examples of sensitive P-gp substrates are:

- colchicine,
- cyclosporine,

- dabigatran etexilate,
- digoxin,
- everolimus,
- pimozide,
- quinidine,
- quinine,
- sirolimus, and
- tacrolimus.

Participants taking BCRP substrates with narrow therapeutic index are excluded from being screened for this study. Examples of sensitive BCRP substrates are:

- coumestrol,
- daidzein,
- genistein,
- prazosin, and
- sulphasalazine.

For, participants with a confirmed diagnosis of T2DM during the study, GLP-1 receptor agonists, GIP/GLP-1 receptor agonists, and DPP-4 inhibitor are prohibited throughout the study. The following medications are examples:

- dulaglutide
- liraglutide
- semaglutide
- exenatide
- tirzepatide
- sitagliptin
- saxagliptin
- linagliptin
- alogliptin

10.9. Appendix 9: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment, but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BP	blood pressure
BRCP	breast cancer resistant protein
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
C-SSRS	Columbia Suicide Severity Rating Scale

CYP	cytochrome P450
Device deficiencies	Equivalent to product complaint
ECG	Electrocardiogram
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.
FDA	Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HCV	hepatitis C virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product (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. See also "IMP."
IRB	institutional review board

medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
CCI	
OATP	organic anion transporting polypeptide
P-gp	P-glycoprotein
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PD	pharmacodynamics
PK	pharmacokinetics
PR	Pulse rate
QD	once daily
QT	QT interval
RA	receptor agonist
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
t_{1/2}	half-life associated with the terminal rate constant

T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time to maximum observed drug concentration
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

10.10. Appendix 10: Protocol Amendment History

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

Amendment [a]: (02-Mar-23)

Overall Rationale for the Amendment:

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

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

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema	‘Day 92’ changed to ‘Day 91’.	Update made to clarify that participants receive the last dose on Day 91.
Section 1.3 Schedule of Activities Section 6.3 Assignment to Study Intervention	Scheduled randomization removed from Day 1 of Period 12, so that randomization for Periods 10, 12, and 13 only occurs on Day 1 of Period 10.	Randomization will now only occur on 1 day in order to ease logistics for multiple sites. After 10 weeks of QD exposure to LY3502970, participant withdrawal due to safety and tolerability concerns is less likely to be an issue.
Section 1.3 Schedule of Activities Section 8.2.3 Electrocardiograms	Triplicate 12-lead ECG collection time points added at 45, 30, and 15 minutes predose in Period 1 of Part A.	ECG collections added to provide predose baseline values.
Section 1.3 Schedule of Activities	Clinical laboratory test collections moved from: - Part A: Day 1, predose, of Periods 2, 6, and 10 to Day 7 of Periods 1, 5, and 9 - Part B: Day 1, predose of Periods 12 and 13 to Day 7 of Period 11 in Part A and Period 12.	Clinical laboratory test collections were moved a day earlier to allow sites sufficient time to receive and review results against the stopping criteria, prior to escalation to the next dose level on Day 1 of each period.
Section 6.8 Treatment of Overdose	The time at which LY3502970 no longer has a clinical effect or can no longer be detected	As participants receive the final dose on Day 91 and the 5× half-life of LY3502970 is approximately 14 days, this value was corrected to ‘Day 105’.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.1 Timing and Mechanism for Collecting Events	systemically changed from 'Day 106' to 'Day 105'.	
Section 10.2 Appendix 2: Clinical Laboratory Tests	Reference to central laboratory testing removed.	As only local laboratories will be used for clinical laboratory tests, reference to the use of 'local laboratory testing in lieu of central laboratory testing' was removed.

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