

J2A-MC-GZGJ Protocol (a)

A Phase 1 Multiple Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of LY3502970 in Fed and Fasted Healthy Participants

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Approval Date: 19-Oct-2021

Title Page

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Protocol Title: A Phase 1 Multiple Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of LY3502970 in Fed and Fasted Healthy Participants

Protocol Number: J2A-MC-GZGJ

Amendment Number: (a)

Compound: LY3502970

Brief Title: A Multiple Dose Study of LY3502970 in Fed and Fasted Healthy Participants

Study Phase: 1

Acronym: GZGJ

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
<i>Original Protocol</i>	<i>26-Jul-2021</i>

Amendment (a)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The protocol was amended to correct minor content and editorial errors.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Removed urine pregnancy test at screening	Editorial error
Section 1.3 Schedule of Activities	Changed the specified timing of safety follow-up for early discontinuation footnote a from approximately 120 hours to 7 to 14 days post-dose.	Clarifies follow-up procedures will occur 7 to 14 days after the final dose for participants that discontinue early
Section 1.3 Schedule of Activities	Changed Day 41 from 168 hours to 144 hours during the terminal PK period for PK sampling.	Day to hour conversion error
Section 1.3 Schedule of Activities	Changed footnote b from 120 hours to 144 hours after final dose on Day 41.	Day to hour conversion error
Section 4.2 Scientific Rationale for Study Design	Changed the meal used before the collection of steady-state PK to be on the day of collection and not the day before collection.	Editorial error
Section 5.2 Exclusion Criteria	Changed concomitant therapy use limit from 7 days to 14 days prior to dosing in exclusion criterion 12.	Editorial error
Section 5.2 Exclusion Criteria	Changed calcitonin exclusion criterion to Number 18.	Editorial error

Section # and Name	Description of Change	Brief Rationale
Section 5.3.1 Meals and Dietary Restrictions	Removed Days 28 and 35 from titration period specification on when collecting prolonged PK profiles	Days 28 and 35 are not part of the titration period
Section 5.3.1 Meals and Dietary Restrictions	Added restrictions on water consumption before and after dosing on Day 1 of the titration period	Clarifies when to regulate the participants' water consumption

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 1 Multiple Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of LY3502970 in Fed and Fasted Healthy Participants

Brief Title:

A Multiple Dose Study of LY3502970 in Fed and Fasted Healthy Participants

Rationale:

Study J2A-MC-GZGJ (GZGJ) will investigate the pharmacokinetics (PK), safety, and tolerability of multiple oral doses of LY3502970 in fed and fasted state in healthy participants.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To characterize and compare the PK of LY3502970 after multiple oral doses in the fasted and fed states in healthy participants 	<ul style="list-style-type: none"> C_{max}, AUC₀₋₂₄, and t_{max}
Secondary	
<ul style="list-style-type: none"> To assess the safety and tolerability of LY3502970 in healthy participants 	<ul style="list-style-type: none"> Incidence of TEAEs and SAEs

Abbreviations: AUC₀₋₂₄ = area under the concentration-time curve from 0 to 24 hour; C_{max} = maximum observed concentration; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{max} = time to maximum observed concentration.

Overall Design:

Study GZGJ is a Phase 1, single site, randomized, open label, crossover study that will be conducted to assess PK, safety, and tolerability of LY3502970 in healthy participants in fed and fasted state. The study consists of a screening period, a dose titration period, 2 test periods, a terminal PK period and safety follow-up visit.

Brief Summary:

The purpose of this study is to assess PK, safety, and tolerability with LY3502970 in healthy participants in fasted and fed state. Study details include:

- The study duration will be up to approximately 13 weeks.
- The treatment duration will be up to 5 weeks.
- The visit frequency will be weekly.

Number of Participants:

Approximately 30 participants will be randomly assigned to study intervention such that approximately 24 evaluable participants complete the study.

Intervention Groups and Duration:

Screening period: 42 days

Dose titration period: Day 1 to Day 22; 2 mg to 16 mg LY3502970 CCI once daily (QD)

Test period 1: Day 22 to Day 28; 16 mg LY3502970 CCI QD

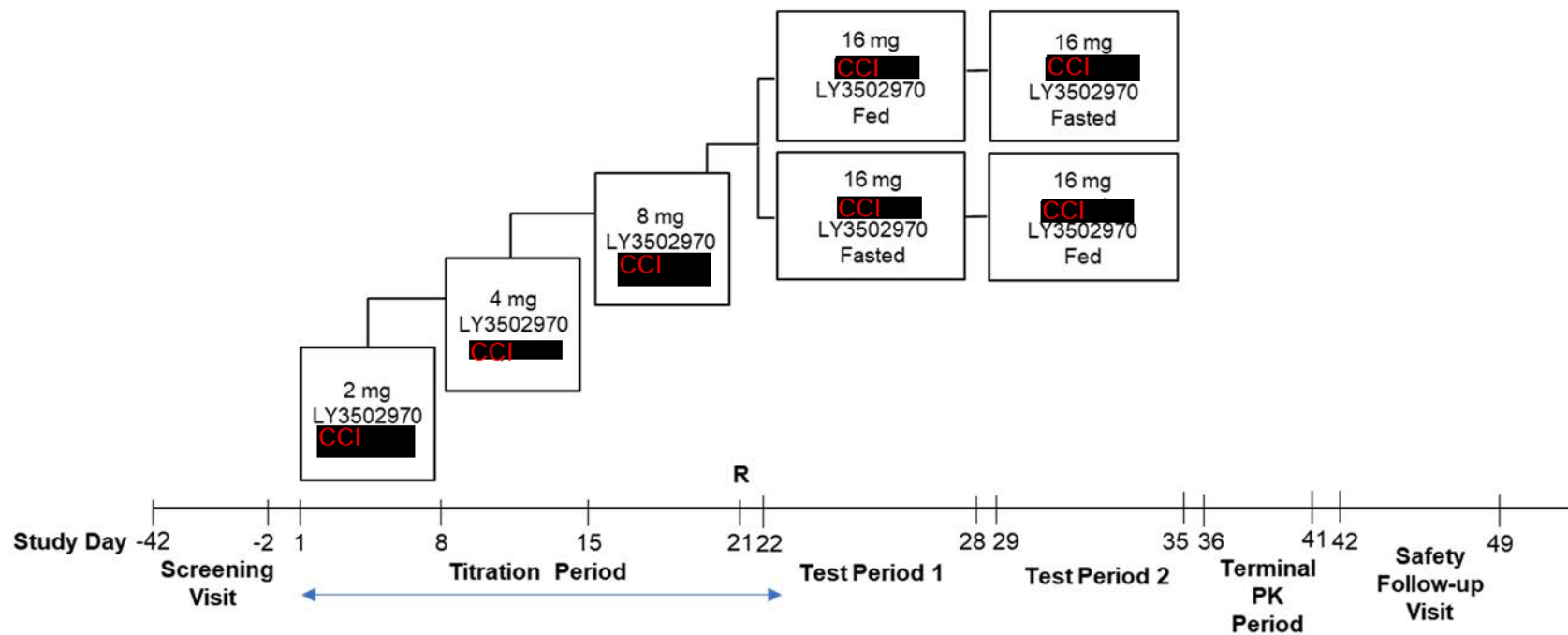
Test period 2: Day 29 to Day 35; 16 mg LY3502970 CCI QD

Terminal PK period: Day 36 to Day 41

Safety follow-up visit: Day 42 to Day 49

Data Monitoring Committee: No

1.2. Schema



Abbreviations: R = randomization.

1.3. Schedule of Activities

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

Procedure	Screening	Baseline	Safety Follow-up Visit ^a	Comments
Day	-42 to -2 days	-1	42 to 49	Screening visit and safety follow-up visit may occur anytime during the specified window.
Informed consent	X			
Admission to CRU		X		
Outpatient visit	X		X	
Medical history	X			
Physical examination	X			Full physical examination at screening. Symptom-directed examinations at all other timepoints.
Height/weight	X		X	Height at screening only. Body weight will be measured in a consistent manner as indicated in Section 8.2.3
Body temperature	X			
Vital signs (supine)	X		X	Blood pressure and pulse rate measurements will be taken after at least 5 minutes in the supine position.
Safety laboratory tests	X		X	Participants will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 (Section 10.2), Clinical Laboratory Tests, for details.
Pregnancy test	X		X	Females only. Serum pregnancy test at screening. Urine pregnancy test at all other times.
Follicle stimulating hormone	X			For females with a history of spontaneous amenorrhea for 6 to 12 months.
Serum calcitonin	X			
Serology tests	X			See Appendix 2 (Section 10.2), Clinical Laboratory Tests, for details.
Medical assessment			X	Symptom-directed physical examination
Single 12-lead ECG	X		X	ECGs must be recorded before collecting any vital signs or blood samples. Participants must be supine for approximately 5 minutes before ECG collection and remain supine but awake during ECG collection.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram.

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

^a Participants who discontinue early will undergo safety follow-up procedures 7 to 14 days after final dose.

Study Schedule for Treatment Period Procedures

Procedure	Titration Period ^a			Test Period 1 ^a	Test Period 2 ^a	Terminal PK Period (Day 36 to 41) ^b	Comments
Day	1 to 7	8 to 14	15 to 21	22 to 28	29 to 35	36 to 41	
Outpatient visit		Day 8	Day 15			Day 37, Day 39, Day 41	
Admission to CRU	Day -1		Day 21				
Discharge from CRU	Day 2					Day 36	
Weight	Day 1	Day 8	Day 15	Day 22	Day 29	Day 41	Body weight will be measured in a consistent manner as indicated in Section 8.2.3; Predose on Days 1 to 29
Vital signs ^c	Day 1	Day 8	Day 15	Day 22	Day 29	Day 41	≤2 hours predose; supine
Safety laboratory tests ^d	Day 1		Day 15		Day 29	Day 41	See Appendix 2 (Section 10.2), Clinical Laboratory Tests, for details; Predose
Point of care safety glucose samples ^e	Day 1	Day 8	Day 15	Day 22	Day 29	Day 41	Predose
Pharmacogenetic sample	Day 1						Predose; See Appendix 5 (Section 10.5 for details.
Medical assessment	Day 1	Day 8	Day 15	Day 22	Day 29	Day 41	Symptom-directed physical examination (predose on Day 22 and Day 29)
Single 12-lead ECG	Day 1	Day 8	Day 15	Day 22	Day 29	Day 41	≤2 hours predose; supine
Study intervention (QD)							
Randomization			Day 21				Predose

Procedure	Titration Period ^a			Test Period 1 ^a	Test Period 2 ^a	Terminal PK Period (Day 36 to 41) ^b	Comments
Day	1 to 7	8 to 14	15 to 21	22 to 28	29 to 35	36 to 41	
LY3502970 PK samples (hour) ^{d,f}	Day 1: Predose, 0.5, 1, 2, 4, 6, 8, 12, and 16 Day 2: Predose	Day 8: Predose	Day 15: Predose	Day 28: Predose, 0.5, 1, 2, 4, 6, 8, 12, and 16	Day 29: Predose Day 35: Predose, 0.5, 1, 2, 4, 6, 8, 12, and 16	Day 36 ^f : 24 Day 37 ^f : 48 Day 39 ^f : 96 Day 41 ^f : 144	Refer to Section 5.3.1 for timing of high-fat high-calorie meal on the last day of fed treatment period.

Abbreviations: COVID-19 = Coronavirus Disease 2019; CRU = clinical research unit; ECG = electrocardiogram; PCR = polymerase chain reaction; PK = pharmacokinetics; QD = once daily.

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

^a Participants who discontinue early will undergo safety follow-up procedures 7 to 14 days after final dose.

^b Day 41 procedures begin approximately 144 hours after final dose.

^c Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.

^d Sampling times are relative to the time of study intervention administration each day (0 hour). Sampling times may be adjusted after review of preliminary data.

^e Fasting samples will be taken with a capillary blood glucose monitor.

^f Sampling times in the terminal PK period are relative to the time of the final dose of study intervention received (0 hour) and may be adjusted after review of preliminary data.

2. Introduction

LY3502970 is a chemically synthesized, oral glucagon-like peptide-1 receptor agonist (GLP-1RA) that exhibits the antihyperglycemic actions of glucagon-like peptide-1 (GLP-1).

LY3502970 is being developed as a daily oral adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

2.1. Study Rationale

Study GZGJ will investigate the PK, safety, and tolerability of multiple oral doses of LY3502970 in fed and fasted state in healthy participants.

2.2. Background

Multiple GLP-1RA therapies are approved. These are most commonly administered QD or once weekly by subcutaneous injection. Even with several different GLP-1RAs approved for use in type 2 diabetes (T2D), the injection remains a barrier for many patients to initiate and to adhere to therapy long-term. The recently approved oral semaglutide (Rybelsus[®], Novo Nordisk) is expected to provide patients with a viable alternative to subcutaneous injection delivery.

However, its administration requires the patient to adhere to a number of steps to improve bioavailability including (Hedrington and Davis 2019; Rybelsus package insert, 2019)

- fasting for ≥ 6 hours
- no more than approximately 120 mL of water at administration, and
- no food or fluid for at least 30 minutes after taking the medication.

Therefore, development of additional oral GLP-1RA therapies remains an unmet need.

LY3502970 is an oral GLP-1RA that exhibits the antihyperglycemic actions of GLP-1. It acts as an insulin secretagogue and increases glucose-dependent insulin secretion after a glucose challenge.

A detailed description of the chemistry, pharmacology, efficacy, and safety of LY3502970 is provided in the investigator's brochure (IB).

2.3. Benefit/Risk Assessment

No unexpected safety or tolerability concerns have been identified to date in participants administered LY3502970 up to the highest single dose of 6 mg and multiple dose of 45 mg for up to 49 days.

The available safety data to date are from ongoing studies, which include

- first-in-human single-ascending dose (SAD) and multiple-ascending dose (MAD) study (J2A-MC-GZGA [GZGA])
- multiple-dose study (J2A-MC-GZGC [GZGC]) in patients with T2DM
- open-label study (J2A-MC-GZGF), and
- open-label 2-part drug-drug interaction study J2A-MC-GZGG (no dosing with LY3502970).

The most frequent adverse events (AEs) were gastrointestinal (GI) AEs. These included nausea, decreased appetite, vomiting, and constipation. These were mostly mild in severity and the majority resolved without treatment. The frequency of these AEs tended to increase with increasing LY3502970 dose.

A total of 2 participants dosed with LY3502970 in Study GZGA and 2 participants dosed with LY3502970 or placebo in Study GZGC discontinued from the study due to GI AEs, which were considered related to study treatment (Section 4.3).

To mitigate the well-known GI tolerability issues of GLP-1RA, participants will be assigned a treatment regimen that includes increasing or escalating doses of LY3502970. Before each dose-escalation step, the investigator will assess the safety and tolerability data of each participant and decide if they should continue with the assigned treatment regimen.

There is no anticipated therapeutic benefit for the participants in this study. However, participants may benefit from the screening procedures (through detection of unknown health issues) even if they receive no therapeutic benefit from the trial.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3502970 may be found in the IB.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To characterize and compare the PK of LY3502970 after multiple oral doses in the fasted and fed state in healthy participants 	<ul style="list-style-type: none"> C_{\max}, AUC_{0-24}, and t_{\max}
Secondary	
<ul style="list-style-type: none"> To assess the safety and tolerability of LY3502970 in healthy participants 	<ul style="list-style-type: none"> Incidence of TEAEs and SAEs

Abbreviations: AUC_{0-24} = area under the concentration-time curve from 0 to 24 hour; C_{\max} = maximum observed concentration; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{\max} = time to maximum observed concentration.

4. Study Design

4.1. Overall Design

Study GZGJ is a Phase 1, single site, randomized, open label, crossover study that will be conducted to assess PK, safety, and tolerability of LY3502970 in healthy participants in fed and fasted state.

Screening Period

Screening may occur up to 42 days prior to enrollment.

Participants who are not enrolled within 42 days of screening may be subjected to an additional medical assessment with or without clinical measurements to confirm their eligibility.

Dose Titration Period (Inpatient and Outpatient Visits)

There will be a dose titration period where participants will receive increasing doses of LY3502970 CCI for dose titration. Participants will be admitted in the CRU on Day -1 and will undergo assessments as mentioned in Section 1.3 until Day 2. Participants are planned to be discharged on Day 2 after receiving the study intervention. Within-treatment dose escalation will be every 7 days up to a dose of 16 mg QD on Day 22. Participants will be provided take-home CCI for the remaining dose titration period. They will be required to visit the clinical research unit (CRU) on an outpatient basis during this period as mentioned in Section 1.3.

Test Periods (Inpatient)

Participants will be admitted in the CRU on Day 21 and will undergo assessments as mentioned in Section 1.3.

Participants will be randomized to receive study intervention under 2 administration conditions (fed state or fasted state). In the fed part of test periods, participants will be administered a high-fat, high-calorie meal on the last day of dosing with LY3502970, and serial blood samples for PK will be collected as mentioned in schedule of activities (SoA) (Section 1.3). Refer to Section 6.1 for further details on administration conditions.

During the test period 1 (Days 22 to 28), participants will receive 16 mg LY3502970 CCI QD either in the fed or fasted state as per randomization. They will crossover on Day 29 and will then receive the study intervention under the other administration condition during test period 2 (Days 29 to 35).

Participants should follow local guidance and CRU precautions to minimize risk for coronavirus disease 2019 (COVID-19) infection. During this period, participants may be allowed to leave the CRU after completing the 4-hour fasting requirements post dosing. However, they would be required to return to the CRU for overnight fasting on all days of test periods.

Participants are planned to be discharged on Day 36. However, the duration of stay in the CRU may be extended at the discretion of the investigator for safety or operational reasons.

Terminal Pharmacokinetics Period and Safety Follow-up Visits

There will be a terminal PK period from Day 36 through the morning of Day 41 to collect additional PK samples following the final dose on Day 35.

Participants will complete the study after the safety follow-up visit, which will occur between 7 and 14 days after last dose. Participants will undergo PK and safety assessments during this period as mentioned in Section 1.3.

4.2. Scientific Rationale for Study Design

Developmental and reproductive toxicology studies have not been completed. Therefore, females of childbearing potential will not be allowed to participate in the study

This study will evaluate the PK of LY3502970 at steady state in healthy participants in fed and fasted state. Within cohort escalation is required for this oral incretin in order to assess the PK profile in fed and fasted states at the predicted efficacious dose.

In addition, delays in gastric emptying are observed after the first dose of LY3502970 and this was shown to resolve after 28 days when healthy participants were escalated from 2 mg to 24 mg in Study GZGA. Therefore, performing the fed and fasted assessments after a similar period and similar dose escalation will limit the potential impact of a gastric emptying delay on the PK profile.

Each dose level will last 7 days to allow the participant to reach a PK steady state (based on half-life [$t_{1/2}$] as discussed in Section 4.3) for the study intervention. This steady state evaluation of relative bioavailability is required because of the need for a titration period to dose high enough for the study intervention. This cross-over design also allows each participant to be used as their own control to limit the number of healthy volunteers needed for the assessment.

Pharmacokinetic profiles are also being collected on the first day of the titration period to better characterize PK. The study contains 2 test periods that commence on Days 22 and 29 to assess the effect of food on the study intervention. As the effect of food is unknown to date at dose of 16 mg, the fed and fasted status will be maintained for 7 days before the steady state PK in the fed or fasted states are collected to ensure that the baseline PK is also representative of fed or fasted status.

The meal used on the day of collection of steady-state PK for the fed state will be a high-fat high-calorie meal, which is in compliance with Food and Drug Administration (FDA) guidance for the fed and fasted assessment (FDA 2019, Bækdal et al. 2021).

4.3. Justification for Dose

The planned LY3502970 doses (2 mg to 16 mg) will allow characterization of PK in healthy participants, which will support selection of the best formulation for future clinical trials.

These planned doses were selected based on the following:

- The nonclinical safety profile of LY3502970 as detailed in the IB.
- Following weekly within-treatment dose escalation, doses up to and including 24 mg were tolerated in the multiple dose part of Study GZGA. The mean $t_{1/2}$ ranging from 24.6 to 67.5 hours supports a QD dosing regimen. Therefore, the proposed dosing regimen in this study (2 mg, 4 mg, 8 mg, and 16 mg QD dosing with within-treatment dose escalation every 7 days) is similar to the dosing regimens that have been previously administered and tolerated in the MAD study.

- In the first-in-human Study GZGA, Part A (SAD) investigated single doses of 0.3, 1, 3, and 6 mg of LY3502970 or placebo and Part B (MAD) investigated multiple doses up to 24 mg QD. LY3502970 was well-tolerated and only 2 out of 108 participants dosed with LY3502970 were discontinued from the study due to nausea and decreased appetite, which were considered related to study treatment.
- In the 12-week, multiple-dose, ongoing Study GZGC investigating doses up to 45 mg in participants with T2DM, 2 out of 68 participants dosed with LY3502970 or placebo discontinued due to nausea and diarrhea, which were considered related to study treatment.
- CCI [REDACTED]

Safety of study participants will be closely monitored during the early stages of dose escalation, and participants that are unable to tolerate the dose regimen will be discontinued as described in Section 7.1.4. As additional data emerges, dose levels and escalation schemes may be modified but dose will not be increased.

More detailed information of the tolerability profile of participants in Study GZGA may be found in the IB.

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 or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial globally.

A participant is considered to have completed the study if the participant has completed all periods of the study including the safety follow-up visit. 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, vital signs, clinical laboratory tests, and electrocardiogram (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 and not continuously throughout the trial.

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 21 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, physical examination, clinical laboratory tests, vital signs, and 12-lead ECGs that are within normal reference range for the population or investigator site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
3. Participants who have a hemoglobin level of at least 11.4 g/dL for female participants and at least 12.5 g/dL for male participants.
4. Participants who are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures including dietary requirements.
5. Participants who have venous access sufficient to allow for blood sampling as per the protocol.

Weight

6. Participants with body weight of 45 kg or more and body mass index within the range 18.5 to 35.0 kg/m² (inclusive).

Sex and Contraceptive/Barrier Requirements

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

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

8. Women not of childbearing potential (WNOCBP) may participate in this study. Women of childbearing potential (WOCBP) will not be allowed to participate in the study.

See Section 10.4 for definitions on WOCBP and additional guidance related to contraception.

Informed Consent

9. Participants who are capable of giving signed informed consent as described in Section 10.1.2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Participants who have significant history of or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting risk when taking LY3502970; or of interfering with the interpretation of data.
2. Participants who have any abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study.
3. Participants who have an abnormal blood pressure and/or pulse rate, deemed to be clinically significant by the investigator at screening.
4. Participants who have a GI disorder (eg, relevant esophageal reflux or gall bladder disease) or any GI disease, which impacts gastric emptying (eg, gastric bypass surgery, pyloric stenosis [except for appendectomy]).
5. Participants who have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis), elevation in serum amylase or lipase (>1.5-fold upper limit of normal [ULN]) or GI disorder (eg, relevant esophageal reflux or gall bladder disease) or any GI disease, which impacts gastric emptying (eg, gastric bypass surgery, pyloric stenosis, with the exception of appendectomy) or could be aggravated by GLP-1 analogs.
6. Participants who currently have clinically significant atopy or have a history of clinically significant multiple or severe drug allergies or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).
7. Participants who have liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or have elevations in aminotransferase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) greater than 2x ULN at screening.
8. Participants who 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.
9. Participants who have a history of or current psychiatric disorders that in the opinion of the investigator would adversely affect patient safety or compliance.

10. Participants who regularly use known drugs of abuse.

Prior/Concomitant Therapy

11. Participants who have known allergies to LY3502970, related compounds, or any components of the formulation.
12. Participants who used or intend to use over-the-counter (OTC) or prescription medication and/or herbal/vitamin/traditional medicines or mineral supplements that may affect the safety or objectives of the study, as considered by the investigator after discussion with the sponsor, within 14 days (or 5 half-lives, whichever is longest) prior to dosing and for the duration of the study. Paracetamol and Covid-19 vaccinations are permitted.

Prior/Concurrent Clinical Study Experience

13. Participants who are currently enrolled in a clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study.
14. Participants who have participated, within the last 3 months, in a clinical study involving an IP. If the previous IP has a long $t_{1/2}$, 5 half-lives or 3 months (whichever is longer) should have passed since last dosing, prior to check-in.

Diagnostic Assessments

15. Participants who show evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies. A negative test within 6 months of screening would not need to be repeated.
16. Participants who show evidence of hepatitis C and/or positive hepatitis C antibody. A negative test within 6 months of screening would not need to be repeated.
17. Participants who show evidence of hepatitis B, positive hepatitis B surface antigen, and/or positive hepatitis B core antibody. A negative test within 6 months of screening would not need to be repeated.
18. Participants who have serum calcitonin level of
 - a) ≥ 20 ng/L at screening visit if estimated glomerular filtration rate ≥ 60 mL/min/1.73m²
 - b) ≥ 60 ng/L at screening visit, if estimated glomerular filtration rate < 60 mL/min/1.73m²

Other Exclusions

19. Women who are lactating.
20. Participants who are unwilling to comply with the dietary restrictions required for this study.
21. Participants who have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) or are unwilling to stop alcohol consumption 24 hours prior to dosing until discharged from the CRU (1 unit = 12 oz or 360 mL of beer, 5 oz or 150 mL of wine, and 1.5 oz or 45 mL of distilled spirits).
22. Participants who smoke more than 10 cigarettes or e-cigarettes, 3 cigars, or 3 pipes per day and are unable or unwilling to refrain from smoking while resident at the CRU.

23. Participants who have donated blood of 450 mL or more, or participated in a clinical study that required a blood volume of 400 mL or more since the last study visit within the past 3 calendar months.
24. Participants who are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
25. Participants who are employees of Eli Lilly and Company or the CRU.
26. Participants who, in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

Throughout the study, participants must adhere to lifestyle restrictions as outlined by the CRU and in the study procedures.

5.3.1. Meals and Dietary Restrictions

Refrain from consumption of grapefruit, pomelo, or grapefruit juice, from 7 days before the start of study intervention until after the final PK sample collection.

Titration Period

- On the days when PK samples will be collected, participants will be required to fast overnight for at least 10 hours.
- On Day 1 and when prolonged PK profiles are collected, participants must also fast for 4 hours post-dose and fluids will be restricted 1 hour prior to and until 1 hour after dosing, except for the water required for dose administration. Water may be consumed freely at all other times.

Test Periods

Fed Treatment Part

- Participants will fast overnight for at least 10 hours on the day prior to dosing.
- Participants will receive a pre-dose test meal. The pre-dose test meal will be a high-fat and high-calorie meal on the last day of dosing of fed part of test period.
- No additional food should be allowed for at least 4 hours post-dose.
- Meals will be provided at other times so that the participants have normally recommended daily calorie intake.
- Fluids will be restricted 1 hour prior to and until 1 hour after dosing, except for the water required for dose administration. Water may be consumed freely at all other times.

Participants should start this test meal 30 minutes prior to administration of the study intervention. They should eat this meal in 30 minutes or less. It is acknowledged that some participants will take less time to eat, but dosing should still occur 30 minutes after the start of meal. The start and stop times and percentage of the meal consumed must be recorded in the source documents.

The acceptable deviation for the predose meal from the nominal time point is:

- Participants will be dosed with LY3502970 30 minutes \pm 5 minutes after the start of meal.

The standardized high-fat (approximately 50% of total caloric content of the meal), high-calorie meal should consist of approximately 800 to 1000 calories. An example test meal consists of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz of hash brown potatoes, and 8 oz of whole milk. This test meal derives approximately 150, 250, and 500 to 600 calories from protein, carbohydrates, and fat, respectively.

Fasted Treatment Part

- Participants in the fasted treatment part of the study will receive the dose after fasting overnight for at least 10 hours and without a predose test meal.
- No food should be allowed for at least 4 hours post-dose.
- Meals will be provided at other times so that the participants have normally recommended daily calorie intake.
- Fluids will be restricted 1 hour prior to and until 1 hour after dosing, except for the water required for dose administration. Water may be consumed freely at all other times.

Refer to Section 6.1.1 for administration details.

5.3.2. Caffeine, Alcohol, and Tobacco

The participants should not consume alcohol for at least 24 hours before CRU admission and throughout the duration of the stay in the CRU. No nicotine use will be permitted while at the CRU.

5.3.3. Activity

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

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Vital signs and laboratory values may be repeated up to 2 times as part of the screening assessment at the discretion of the investigator.

Admission or pre-dose safety procedures, such as safety blood, ECGs, vital signs, and urinalysis, can be repeated as clinically indicated under the discretion of investigator or sub-investigator if there is a concern regarding a participant's safety or eligibility to participate in the study.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

Intervention Name	LY3502970
Type	Drug
Dose Formulation	CCI
Unit Dose Strength(s)	2, 4, 8, 16-mg
Dosage Level(s)	2, 4, and 8, 16-mg QD (CCI)
Route of Administration	Oral
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.

Abbreviations: IMP = investigational medicinal product; QD = once daily.

All investigational medicinal products will be reconciled and destroyed in accordance with the study-specific quality agreement and technical addendum.

6.1.1. Administration Details

During the titration period, LY3502970 has to be taken orally with approximately 240 mL of room temperature water in the morning of each dosing day, preferably at the same time, and in a sitting position. See Section 5.3.1 for details on fasting requirements on days when PK samples will be collected.

The fasting requirements during the test periods are described in Section 5.3.1. LY3502970 will be administered orally with 240 mL of room temperature water in the fed and fasted treatment parts of the study. In the fed treatment part, it will be administered 30 minutes after the start of the meal. They should eat this meal in 30 minutes or less. It is acknowledged that some participants will take less time to eat, but dosing should still occur 30 minutes after the start of meal.

While inpatient, dosing will be performed within ± 1 hour of the nominal timepoint, where nominal time is the time of dosing from Day 22. Should the window be utilized (eg, for logistical reasons) then dosing will revert back to nominal time at the next dosing occasion.

6.1.2. Package and Labeling

The study intervention is supplied for clinical trial use as CCI for oral administration. Each dosage unit contains LY3502970 CCI equivalent to 2 mg to 16 mg of the LY3502970 drug substance. The study intervention should be stored according to instructions on the label. All study interventions will be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

6.2. Preparation, Handling, Storage, and Accountability

1. 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.
2. 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.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the study reference manual.

Note: In some cases, sites may destroy the clinical trial materials 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 trial materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

On Day 21, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the 2 arms (fed or fasting) of the study, according to the randomization schedule generated prior to the study by the statistics department at sponsor.

This is an open-label study.

6.4. Study Intervention Compliance

Test Periods

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 in the case report form (CRF).

Titration Period

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned CCI [REDACTED] and reviewing participant diaries, and will be documented in the source documents and CRF.

A record of the number of LY3502970 CCI [REDACTED] dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

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

- information about the participant's adherence to the SoA
- information about the participant's compliance with concomitant medications, and
- Information about any other parameters the investigator considers necessary.

6.5. Dose Modification

The participants should follow the planned dosing regimen. In the case of poor tolerability up to Day 14 during the study, dosing may be interrupted temporarily (Section 7.1.4).

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

Study intervention will not be made available to participants after completion of the study.

6.7. Treatment of Overdose

For this study, any dose of study intervention greater than the planned dose as per the titration schedule will be considered an overdose.

Treatment for overdose is supportive care.

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/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 7 days)
- obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis), and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.8. Concomitant Therapy

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

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

The Lilly clinical pharmacologist (CP) or clinical research physician (CRP) or clinical research scientist should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 14 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

CCI



Acetaminophen, at doses of ≤ 3 g/day, is permitted for use during the study at the discretion of the investigator. This will be recorded in the electronic case report form (eCRF).

Nausea and/or vomiting during this study may be treated with antiemetics but these medications should not be used prophylactically. Nonsteroidal anti-inflammatory medications (including ibuprofen and aspirin), acetaminophen, cough suppressants, antihistamines, vitamin/mineral supplements, antibiotics, and topical ointments may be used on an as-needed basis. These and other concomitant medication may be considered on a case-by-case basis by the investigator preferably in consultation with the medical monitor.

Any additional medication used during the study (including those not requiring sponsor notifications) must be documented on the appropriate eCRF.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (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 as per early termination visit (Section 1.3).

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

- an AE that is considered to be intolerable
- an abnormal safety laboratory test result, determined to be clinically significant by the investigator, or
- QT interval corrected using Fridericia's formula (QTcF) >500 msec and an increase from baseline in QTcF >60 msec, from at least 2 consecutive readings.

A participant should be permanently discontinued from study intervention if the participant becomes pregnant during the study.

7.1.1. Early Termination of the Study

The investigator will thoroughly review the tolerability of the study intervention for each participant prior to each dose titration and decide whether they should continue with the assigned treatment regimen. No formal dose escalation is planned for this study. A safety investigation will be triggered to determine whether the study intervention should be terminated early based on the following criteria:

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

7.1.2. Liver Chemistry Stopping Criteria

The study intervention should be interrupted or discontinued if 1 or more of these conditions occur:

Elevation	Exception
ALT or AST >5x ULN	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN (when the source of increased ALP is the liver)	
ALP >2.5x ULN and TBL > 2x ULN	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL >2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

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

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

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

Participants who discontinue from study intervention will undergo monitoring as described in Appendix 6 (Section 10.6).

7.1.3. Discontinuation for Acute Pancreatitis

If acute pancreatitis is diagnosed, the participant must discontinue use of the study intervention. Please refer to Appendix 7 (Section 10.7) for further details.

7.1.4. Intolerable Gastrointestinal Events

In the presence of persistent GI events, participants who are unable to tolerate their assigned dose level for ≥ 3 days (have persistent vomiting or moderate to severe nausea) should be discontinued from using the study intervention. A participant may skip up to 2 doses up to Day 14 due to intolerable GI events.

7.1.5. Hypoglycemia

Discontinuation of the study intervention should be considered by the investigator for participants with severe hypoglycemia (Level 3 according to Section 8.2.7.3) or persistent hypoglycemic events (Level 2).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

- at any time at the participant's own request
- at the request of the participant's designee (eg, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrollment in any other clinical study involving a study intervention or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, and
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

Participants will be discontinued under the following circumstances:

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

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from both the study intervention and the study at that time.

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

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.
- 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.
- Section 1.3 lists the SOA, detailing the study procedures and their timing (including tolerance limits for timing). The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.
- Appendix 2 (Section 10.2) lists the laboratory tests that will be performed for this study.
- Appendix 2 (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

No efficacy data are planned to be collected for this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination 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.

Medical assessments are a symptom-directed physical examination and will be conducted according to the SoA (Section 1.3) and as clinically indicated.

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the SOA (Section 1.3) and each measurement recorded in the eCRF.
- Vital sign measurements should be obtained before collection of blood samples.
- Additional vital signs may be measured during each study period if warranted.
- Blood pressure and pulse rate should be measured after resting for at least 5 minutes in a supine position.
- Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participant should be supine for approximately 5 minutes and stand for at least 3 minutes. If the participant feels unable to stand, supine vital signs only will be recorded.
- Body temperature will be measured, as specified in the SoA, and as clinically indicated.

8.2.3. Body Weight

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

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

8.2.4. Electrocardiograms

For each participant, ECGs should be collected according to the SoA (Section 1.3) and the study specific recommendations included in the manual of operations for the study.

Single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1 for QTc stopping criteria.

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

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

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant

visit(s) and for immediate participant management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the participant for symptoms (eg, palpitations, near syncope, and syncope) to determine whether 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/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

8.2.5. Clinical Safety Laboratory Tests

Participants will be required to fast for at least 8 hours before each blood sample is drawn. Clinical laboratory tests include hematology, clinical chemistry, and urinalysis.

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA 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 7 days 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/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
 - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), report the information as an AE.

8.2.6. Pregnancy Testing

In this study, WOCBP will be excluded. In WNOCBP, serum/urine pregnancy test will be conducted at screening and safety follow-up (Section 1.3).

8.2.7. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), amylase, and lipase
- AEs, including adverse events of special interest (AESI) (nausea, vomiting, and diarrhea), and
- reported pancreatitis.

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

8.2.7.1. Hepatic Monitoring

Close Hepatic Monitoring

Laboratory tests (Appendix 6 [Section 10.6]), including ALT, AST, alkaline phosphatase (ALP), TBL, Direct Bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine whether it is increasing or decreasing, if 1 or more of these conditions occur:

If a Participant with Baseline Results of	Develops the Following Elevations
ALT or AST <1.5x ULN	ALT or AST ≥ 3 x ULN
ALP <1.5x ULN	ALP ≥ 2 x ULN
TBL <1.5x ULN	TBL ≥ 2 x ULN (except for patients with Gilbert's syndrome)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = triple bottom line; ULN = upper limit of normal.

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

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

Comprehensive Hepatic Evaluation

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

If a Participant with Baseline Results of	Develops the Following Elevations:
ALT or AST <1.5x ULN	ALT or AST $\geq 3x$ ULN with hepatic signs/symptoms* or ALT or AST $\geq 5x$ ULN
ALP <1.5x ULN	ALP $\geq 3x$ ULN
TBL <1.5x ULN	TBL $\geq 2x$ ULN (except for patients with Gilbert's syndrome)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = triple bottom line; ULN = upper limit of normal.

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

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

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and 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 Case Report Form) in Study Participants Who Have Abnormal Liver Tests during the Study

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

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

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

8.2.7.2. Pancreatic Monitoring

Please refer to Section 10.7.

8.2.7.3. Hypoglycemia

Blood glucose will be monitored for safety throughout the study according to the SoA (Section 1.3; point of care safety glucose samples) using a capillary blood glucose monitor. Participants will be trained by site personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia. Investigators should use the following classification of hypoglycemia:

- Level 1 hypoglycemia (glucose <70 mg/dL [3.9 mmol/L] and \geq 54 mg/dL [3.0 mmol/L]) - It 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 <54 mg/dL [3.0 mmol/L]) - This is also referred to as documented or blood glucose confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence of 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 eCRF and report it to Lilly as an SAE.

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

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

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

- AEs
- SAEs, and
- product complaints (PCs).

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.3.3) 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. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the informed consent form (ICF)	Participation in study has ended	As soon as possible upon site awareness	AE eCRF	NA
Serious Adverse Event					
SAE and SAE updates - prior to start of study intervention and deemed reasonably possibly related with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	LSS SAE reporting	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	LSS SAE reporting	SAE paper form
SAE* - after participant's study participation has ended and the investigator becomes aware	After participant's study participation has ended	NA	Promptly	SAE paper form	NA
Pregnancy					

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy in female participants and female partners of male participants	After the start of study intervention	90 days or 3 months after the last dose of study intervention	Within 24 hours (Section 8.3.2)	LSS SAE reporting	Pregnancy paper form
Product Complaints					
Product complaint 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	NA
Product complaint not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product complaint form	NA
Updated product complaint information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	NA
Product complaint (if investigator becomes aware)	Participation in study has ended	NA	Promptly	Product complaint form	

Abbreviations: AE = adverse event; eCRF = electronic case report form; ICF = informed consent form; LSS = Lilly Safety System; NA = Not Applicable; PC = product complaint; SAE = serious adverse event.

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

8.3.2. Pregnancy

Collection of Pregnancy Information

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After learning of a pregnancy in the female partner of a study participant, the investigator will
 - obtain a consent to release information from the pregnant female partner directly and

- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study 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.

8.3.3. Adverse Events of Special Interest

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

Other AESIs (Section 8.2) for this program include

- cardiovascular events

- hypoglycemia
- hepatic events, and
- pancreatic events.

8.4. Pharmacokinetics

- At the visits and times specified in the SoA (Section 1.3), venous blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of LY3502970.
- A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of LY3502970. Samples collected for analyses of LY3502970 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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 investigational product concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism and/or protein-binding work.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A blood sample for deoxyribonucleic acid (DNA) isolation will be collected from participants.

See Appendix 5 (Section 10.5) for information regarding genetic research and Appendix 1 (Section 10.1.9) for details about sample retention and custody.

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

Health economics or medical resource utilization and health economics parameters are not evaluated in this study

9. Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to 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 Hypotheses

The primary study objective is to characterize and compare the PK of LY3502970 after multiple oral doses in the fasted and fed state in healthy participants.

The secondary study objective is to assess the safety and tolerability of LY3502970 in healthy participants.

9.1.1. Multiplicity Adjustment

Treatment comparisons will be performed for the primary objective at the full significance level of 0.1. No multiplicity adjustments will be made for the analysis of secondary and exploratory objectives.

9.2. Analyses Sets

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

Participant Analysis Set	Description
Entered	All participants who sign the ICF.
Enrolled	All participants assigned to treatment.
Safety analysis set	All participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic analysis set	All enrolled participants who received LY3502970 and have evaluable PK samples.

Abbreviations: ICF = informed consent form; PK = pharmacokinetics.

9.3. Statistical Analyses

9.3.1. General Considerations

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.1, unless otherwise stated, and all confidence intervals (CIs) will be given at a 2-sided 90% level.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data may be conducted as deemed appropriate.

Pharmacokinetic analyses will be conducted on the PK analysis set. Safety analyses will be conducted on the safety analysis set. Additional exploratory analyses of the data may 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. Analyses will be fully detailed in the SAP.

9.3.2. Primary Endpoint(s) Analysis

Pharmacokinetic parameter estimates for LY3502970 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis of LY3502970 will be area under the plasma concentration-time curve from 0 to 24 hour (AUC_{0-24}), maximum observed concentration, and time to maximum observed concentration. Other parameters, such as $t_{1/2}$, apparent clearance, and apparent volume of distribution may be calculated as appropriate. All PK parameters will be listed and summarized using descriptive statistics.

The data for these PK parameters from test period 1 and 2 will be log-transformed. The log-transformed data will be analyzed using a linear mixed-effects model with treatment period (16 mg CCI LY3502970 fasted, 16 mg CCI LY3502970 fed) and sequence as fixed effects, and participant as a random effect. The ratios of the geometric least squares means and the 90% CIs for the ratios will be derived between the following comparison between treatments.

9.3.3. Safety Analyses

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

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

Vital signs will be summarized with respect to observed values and change from baseline values by treatment at each time point using descriptive statistics.

All 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 study intervention or study procedure as perceived by the investigator. Adverse events reported to occur prior to the first study dose will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities. The number of SAEs will be reported.

9.3.4. Other Analyses

Details for other analyses may be documented in the SAP.

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

This study is a pilot PK study to assess PK LY3502970 in healthy participants in fed and fasted state. The sample size is based on a calculation of precision of the estimated ratio of AUC_{0-24} between 16 mg CCI LY3502970 fasted and 16 mg CCI LY3502970 fed. Assuming a standard deviation of treatment difference of 0.444 in the log-scale in AUC_{0-24} (according to a preliminary analysis of the food effect data in Study GZGA), a sample size of 24 completed participants will provide approximately 80% coverage probability to get a 90% CI for the ratio R of geometric mean AUC_{0-24} between treatments within $[0.767 \cdot R, 1.303 \cdot R]$.

Approximately 30 participants will be randomly assigned to study intervention such that approximately 24 evaluable participants complete the study. If a participant does not complete all the treatment periods of the study, they may be replaced by another participant if decided by the sponsor. This replacement participant will go through the complete treatment sequence as the discontinued participant.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
 - applicable International Council for Harmonisation (ICH) GCP guidelines, and
 - applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
 - providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
 - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, and
 - providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement (CTA).

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information, which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, appropriate IRB/IEC members, and 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 trial due to safety findings, this decision will be communicated by Lilly to all investigators (eg, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by 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 (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source data may include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, 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 (eg, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

This study uses a web-based data collection system for CRF data collection. The investigator will have continuous access to the EDC system during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive 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 electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

Serious adverse events and PC reconciliation will follow current Lilly procedures. Data will be encoded and stored in the global safety and 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 the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section [10.1.5](#).

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

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator.

- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) 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.

10.1.9. Long-Term Sample Retention

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

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

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

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

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

Sample Retention Period

Sample Type	Custodian	Retention Period After Last Patient Visit^a
PK	Sponsor or designee	1 year

Abbreviation: PK = pharmacokinetics.

^a Retention periods may differ locally

10.2. Appendix 2: Clinical Laboratory Tests

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

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphate
Leukocytes (WBC)	Glucose, fasting
Differential WBC absolute counts of:	Urea
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Amylase
Eosinophils	Lipase
Basophils	Creatinine
Platelets	
	Lipid panel ^a
Urinalysis	Total cholesterol
Specific gravity	Triglycerides
pH	Low-density lipoprotein cholesterol
Protein	High-density lipoprotein cholesterol
Glucose	
Ketones	
Bilirubin	Liver panel
Urobilinogen	Total bilirubin
Blood	Direct bilirubin
Nitrite	Indirect bilirubin
Microscopic examination of sediment ^b	Alkaline phosphatase
Leukocytes	Aspartate aminotransferase
Serology ^{a,c}	Alanine aminotransferase
Hepatitis B surface antigen	
Hepatitis B core antibody	
Hepatitis C antibody	
HIV	Pregnancy test ^d
	Follicle-stimulating hormone ^{a,c}
Calcitonin ^a	

Abbreviations: HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

Note: 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. Inclusion or omission of calculated values will not be considered as a protocol deviation.

^a Performed at screening only.

^b Test only if dipstick result is abnormal and are further definable by microscopy. Microscopy to be performed at the local safety laboratory, if clinically indicated, at investigator's discretion.

^c Not required if test results within 6 months of screening are available.

^d For females only: Serum pregnancy tests will be performed at screening with urine pregnancy testing at all other times indicated in the Schedule of Activities (Section [1.3](#)).

^e For females with spontaneous amenorrhea for 6 to 12 months, if needed, to confirm postmenopausal status.

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-GZGJ Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests ^a including serum calcitonin	26	1	26
Safety laboratory tests ^a	17	5	85
Pharmacokinetics	2	38	76
Blood discard for cannula patency	0.3	27	8.1
Pharmacogenetics	10	1	10
Total			205.1
Total for clinical purposes (rounded up to nearest 10 mL)			210

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

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

Adverse Event Definition
<ul style="list-style-type: none"> • 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. • An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

Events Meeting the Adverse Event Definition
<ul style="list-style-type: none"> • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting 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. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the Adverse Event Definition
<ul style="list-style-type: none"> Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. Medical or surgical procedure (eg, 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 preexisting 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

A serious adverse event is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:
a. Results in death
b. Is life-threatening <p>The term <i>life-threatening</i> in the definition of <i>serious</i> 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.</p>
c. Requires inpatient hospitalization or prolongation of existing hospitalization <ul style="list-style-type: none"> In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity <ul style="list-style-type: none"> 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 (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
<p>e. Is a congenital anomaly/birth defect</p> <ul style="list-style-type: none"> Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
<p>f. Other situations</p> <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs: <ul style="list-style-type: none"> deficiencies in labeling information and use errors for device or drug-device combination products due to ergonomic design elements of the product. Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements. Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed. An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

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

Adverse Event, Serious Adverse Event, and Product Complaint Recording
<ul style="list-style-type: none"> When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. Adverse event or SAE information is reported on the appropriate eCRF page and PC information is reported on the PC Form. <p>Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.</p> <ul style="list-style-type: none"> It is not acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the eCRF page for AE/SAE and the PC Form for PCs. There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
<p>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:</p> <ul style="list-style-type: none"> 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. <p>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.</p>

Assessment of Causality
<ul style="list-style-type: none"> • The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. • A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of Adverse Events and Serious Adverse Events
<ul style="list-style-type: none"> • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any postmortem findings, including histopathology.

10.3.5. Reporting of Serious Adverse Events

Serious Adverse Event Reporting via Serious Adverse Event Report
<ul style="list-style-type: none"> • Facsimile transmission of the SAE report is the preferred method to transmit this information to the sponsor or designee. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Report within the designated reporting time frames. • Contacts for SAE reporting can be found in SAE report.

10.3.6. Regulatory Reporting Requirements**Serious Adverse Event Regulatory Reporting**

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, 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	<p>Females are considered a woman of childbearing potential if they have</p> <ul style="list-style-type: none"> • had at least 1 cycle of menses or • Tanner 4 breast development. <p>Any amount of spotting should be considered menarche. If Tanner staging of breasts is performed as part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical Trial regarding Tanner staging.</p>
Women not of childbearing potential	<p>Females are considered women not of childbearing potential if they</p> <ul style="list-style-type: none"> • have a congenital anomaly, such as Mullerian agenesis • are infertile due to surgical sterilization, or • are post-menopausal <p>Examples of surgical sterilization, include hysterectomy, bilateral oophorectomy, and tubal ligation.</p>
Postmenopausal state	<p>The postmenopausal state should be defined as</p> <ol style="list-style-type: none"> 1. a woman at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note or 2. a woman at least 40 years old and up to 55 years old with an intact uterus, not on hormone therapy*, 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 3. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea or 4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy <p>*Women should not be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.</p>
Reproductive toxicology studies	<p>Embryo-fetal studies are toxicity studies in pregnant animals designed to identify abnormalities in the development of fetuses, which could indicate potential for teratogenicity in humans. The relevant dosing period is during organogenesis.</p>

10.4.2. Contraception Guidance

Topic	Guidance
For all men	Should refrain from sperm donation for the duration of the study and for 90 days or 3 months following last participant visit.
Contraception for men with partners of childbearing potential	<ul style="list-style-type: none"> • either remain abstinent (if this is their preferred and usual lifestyle) or • must use condoms during intercourse for the duration of the study and for 90 days or 3 months following last participant visit.
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception.

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

Methods	Examples
Highly effective contraception	<ul style="list-style-type: none"> • Combination oral contraceptive pill and minipill • Implanted contraceptives • Injectable contraceptives • Contraceptive patch (only women <198 lbs or 90 kg) • Total abstinence • Vasectomy (if only sexual partner) • Fallopian tube implants (if confirmed by hysterosalpingogram) • Combined contraceptive vaginal ring • Intrauterine devices
Effective contraception	<ul style="list-style-type: none"> • Male or female condoms with spermicide • Diaphragms with spermicide or cervical sponges • Barrier method with use of a spermicide <ul style="list-style-type: none"> ○ condom with spermicide ○ diaphragm with spermicide, or ○ female condom with spermicide <p>Note: The barrier method must include use of a spermicide (ie, condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.</p>

Ineffective forms of contraception	<ul style="list-style-type: none">• Spermicide alone• Immunocontraceptives• Periodic abstinence• Fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, and symptothermal)• withdrawal• Postcoital douche• Lactational amenorrhea
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10.5. Appendix 5: Genetics

Use/Analysis of Deoxyribonucleic Acid

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- Deoxyribonucleic acid samples will be used for research related to LY3502970 or T2D and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3502970 and/or interventions of this drug class and T2D. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- The samples may be analyzed as part of a 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 (CSR) 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 8.2.7.1 for guidance on appropriate test selection.

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

Hematology	Clinical Chemistry
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	Other Chemistry
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatitis B virus (HBV) testing:	Urine Chemistry
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	Other Serology
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) ^a
HBV DNA ^d	Anti-actin antibody ^b
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody

Hematology	Clinical Chemistry
HCV RNA ^d	EBV DNA ^d
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA ^d
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA ^d	HSV (Type 1 and 2) DNA ^d
Microbiology^c	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

Abbreviations: DNA = deoxyribonucleic acid; RBC = red blood cell; RNA = ribonucleic acid; WBC = white blood cell.

^a Not required if anti-actin antibody is tested.

^b Not required if anti-smooth muscle antibody (ASMA) is tested.

^c Assayed ONLY by investigator-designated local laboratory; no central testing available.

^d Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.7. Appendix 7: Pancreatic Monitoring Tests for Treatment-Emergent Abnormality

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 et al. 2006, Koizumi 2006):

- abdominal pain, characteristic of acute pancreatitis (ie, epigastric pain radiating to the back, often associated with nausea and vomiting)
- serum amylase (total, pancreatic, or both), and/or lipase ≥ 3 x ULN
- characteristic findings of acute pancreatitis on CT scan or magnetic resonance imaging (MRI).

If acute pancreatitis is suspected, the investigator should

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

Discontinuation for Acute Pancreatitis

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

Asymptomatic Elevation of Serum Amylase and/or Lipase

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

10.8. Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this Appendix

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

Exceptional Circumstances

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

Implementing Changes under Exceptional Circumstances

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

After approval by local Ethical Review Boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstances changes will not typically require additional notification to these groups, unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

In the event written approval is granted by the sponsor for changes in study conduct, an additional written guidance, if needed, will be provided by the sponsor.

Considerations for Making a Change

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

Informed Consent

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

- participation in remote visits, as defined in Section "Remote Visits"
- a change in the method, location, or both of study intervention administration
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct during Exceptional Circumstances

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

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

Remote Visits

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

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include but are not limited to those described in the safety follow-up only.

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include but are not limited to those described in the safety follow-up visit only.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and PCs remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible while ensuring the safety of both the participants and the site staff.

Documentation

Changes to study conduct will be documented.

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

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

10.9. Appendix 9: Abbreviations and Definitions

Term	Definition
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC₍₀₋₂₄₎	area under the plasma concentration-time curve from 0 to 24 hour
CFR	Code of Federal Regulations
CI	confidence interval
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.
COVID-19	coronavirus disease 2019
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
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal

GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IP	Investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
MAD	multiple-ascending dose
MRI	magnetic resonance imaging
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
PK	pharmacokinetics
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

SoA	schedule of activities
t_{1/2}	half-life
T2D	type 2 diabetes
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.
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

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