Protocol J2A-MC-GZGH(b)

A Phase 1 Multiple-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of 2 Different Formulations of LY3502970 in Healthy Participants

NCT05341089

Approval Date: 14-Mar-2022

Title Page

Protocol Title: A Phase 1 Multiple-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of 2 Different Formulations of LY3502970 in Healthy Participants

Protocol Number: J2A-MC-GZGH

Amendment Number: b

Compound: LY3502970

Brief Title: A Multiple-Dose Study of 2 Different Formulations of LY3502970 in Healthy Participants

Study Phase: 1

Acronym: GZGH

Sponsor Name: Eli Lilly and Company

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

Regulatory Agency Identifier Number

IND: 142842

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

Approval Date: 14-Mar-2022 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	*04 February 2022*
Original Protocol	*17 November 2021*

Amendment b

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment

The protocol is amended to address comments from the Singapore DSRB.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Assessment	Addition of calcitonin test in early termination and follow-up visit	To address feedback received from the Singapore DSRB.
Section 1.1 Synopsis and Section 2.1 Study Rationale	Re-worded rationale as "The study is conducted to determine pharmacokinetics (PK) of LY3502970 upon administration of 2 different formulations in healthy participants. CCI [redacted]	Added additional text to further clarify the rationale of the study per Singapore DSRB feedback.
Section 2.3 Benefit/Risk Assessment	Added additional information on 2-year nonclinical studies on rats and mice.	Added to address the comments from the Singapore DSRB regarding pre-clinical findings from some other GLP-1 receptor agonists.
Section 2.3 Benefit/Risk Assessment	Added additional details on other LY3502970 clinical trial results.	Added to pre-emptively address some potential concerns regarding a participant who experienced ataxia in Study J2A-MC-GZGJ.
Section 5.2 Exclusion Criteria	Under medical conditions, added "have a personal or family history of medullary thyroid carcinoma or have Multiple Endocrine Neoplasia Syndrome Type 2"	Added to address the comments from the Singapore DSRB regarding pre-clinical findings from some other GLP-1 receptor agonists.

Section # and Name	Description of Change	Brief Rationale
Section 10.2.1 Blood Sampling Summary	• Addition of blood volume for calcitonin test in early termination/follow-up visit • Serology test "Hepatitis B Core Antibody" updated as "Hepatitis B Core Antibody, Total" • Footnote for calcitonin test updated	• Added per changes made in Section 1.3 Schedule of Assessment. • Updated for clarity • Updated as calcitonin test will be done in screening and early termination/follow-up visit
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore, not described.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title

A Phase 1 Multiple-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of 2 different formulations of LY3502970 in Healthy Participants

Brief Title

A Multiple-Dose Study of 2 Different Formulations of LY3502970 in Healthy Participants

Rationale

The study is conducted to determine pharmacokinetics (PK) of LY3502970 upon administration of 2 different formulations in healthy participants. CCI [redacted]

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the PK of 2 different formulations of LY3502970 after multiple oral doses in healthy participants	• C_{max}, AUC_{0-24}, and t_{max}
Secondary	
• To assess the safety and tolerability of 2 different formulations of LY3502970 in healthy participants	• Incidence of TEAEs and SAEs

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24 hours; 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 GZGH is a Phase 1, single-site, randomized, open-label, crossover study to assess PK, safety, and tolerability of 2 different formulations of LY3502970 in healthy participants. The study consists of a screening period, a dose titration period, 2 test periods, a terminal PK period and a safety follow-up visit.

Brief Summary

The purpose of this study is to assess PK, safety, and tolerability of 2 different formulations of LY3502970 in healthy participants.

Study details are,

- The study duration is up to approximately 13 weeks.
- The treatment duration is up to 5 weeks.
  - Inpatient visits: 2 inpatient visits
  - Outpatient visits: 5 outpatient visits

Number of Participants

Approximately 38 healthy 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 prior to Day 1

Dose titration period: CCI days; Day CCI ; oral administration of CCI mg LY3502970 capsules once daily (QD)

Test Period 1: CCI days; CCI ; oral administration of CCI mg LY3502970 Formulation 1 or Formulation 2 capsules administered QD

Test Period 2: CCI days; Day CCI ; oral administration of CCI mg LY3502970 Formulation 2 or Formulation 1 capsules administered QD (crossover from Test Period 1)

Terminal PK period: CCI days; Day CCI

Follow-up period: between Day 41 and 49

Data Monitoring Committee: No


CCI

1.3. Schedule of Activities (SoA)

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

Procedure	Screening	Baseline	Early termination/Follow-up Visit	Comments
Day	**-42 to -2 days**	**-1**	**41 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 assessment	X		X	Full physical examination at screening. Symptom-directed examinations at all other time points.
Height/weight	X		X	Height at screening only. See Section 8.2.3
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	Serum pregnancy test at screening. Urine pregnancy test at all other times. Refer to Section 10.2
Follicle-stimulating hormone	X			For females with spontaneous amenorrhea for 6 to 12 months. Refer to Section 10.2
Serum calcitonin	X		X	Refer to Section 10.2
Serology tests	X			Appendix 2 (Section 10.2) for details.
Single 12-lead ECG	X		X	Refer to Section 8.2.4.

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.

Study Schedule for Treatment Period Procedures

Procedure	Titration Period	Test Period 1	Test Period 2	Terminal PK Period	Comments
Day	CCI				
Admission to CRU					
Discharge from CRU					
Outpatient visit					
Weight					See Section 8.2.3; Predose on Days 1 to 29
Vital signs					Predose; after at least 5 minutes supine
Safety laboratory tests[b]					Predose
Point-of-care safety glucose samples					Predose, fasting. Section 8.2.7.3
Pharmacogenetic sample					
Medical assessment					Symptom-directed examination
Single 12-lead ECG					≤2 hours predose; supine
Drug dispensing					
Study intervention (QD)	→	→	→		
Randomization					Predose
LY3502970 PK samples (hour)[b]	CCI				

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; 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] Day 39 procedures begin approximately 96 hours after the final dose.

[b] 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.

2. Introduction

LY3502970 is a chemically synthesized, oral 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 T2DM.

2.1. Study Rationale

The study is conducted to determine PK of LY3502970 upon administration of 2 different formulations in healthy participants. While both formulations will have LY3502970 in the form of an SDD, they will differ in the bulk physical properties (particle characteristics) of the SDD. The results from this study will help establish the bulk physical properties (and thus manufacturing controls) for the commercial drug product manufacture.

2.2. Background

Multiple GLP-1RA therapies are approved. These are most commonly administered QD or once weekly through subcutaneous injection. Even with several different GLP-1Ras approved for use in T2DM, the injection remains a barrier for many patients to initiate and to adhere to long-term therapy. 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 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 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- and multiple-ascending dose Study (J2A-MC-GZGA [GZGA]) in healthy subjects
- multiple-dose study (J2A-MC-GZGC [GZGC]) in patients with T2DM
- open-label study (J2A-MC-GZGF) in healthy subjects, and

- open-label 2-part drug-drug interaction Study J2A-MC-GZGG (no dosing with LY3502970) in healthy subjects.

Most frequent adverse events for LY3502970

The most frequent AEs were 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.

Study discontinuations due to AEs related to study intervention

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

Mitigation of GI tolerability issues

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.

Benefits for the participants

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 study.

Additional information

In 2-year studies in rats and mice taking a drug that works like LY3502970, cancerous and noncancerous tumors of the thyroid gland were found. The cause of these thyroid tumors with this medication in animals is not known, and it is not known whether this is relevant for humans. There were no LY3502970-related effects on the thyroid in any animal study.

CCI [redacted]

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the PK of 2 different formulations of LY3502970 after multiple oral doses in healthy participants	• C_{max}, AUC_{0-24}, and t_{max}
Secondary	
• To assess the safety and tolerability of 2 different formulations of LY3502970 in healthy participants	• Incidence of TEAEs and SAEs

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24 hours; 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 GZGH is a Phase 1, single-site, randomized, open-label, crossover study conducted to assess PK, safety, and tolerability of 2 different formulations of LY3502970 in healthy participants.

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 at the discretion of the investigator to confirm their eligibility.

Dose titration period (inpatient and outpatient visits)

There will be a dose titration period wherein participants will receive increasing doses of LY3502970 capsule for dose titration. Participants will be admitted in the CRU on Day -1 and will undergo assessments as mentioned in the SoA (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 [CCI] mg QD on Day 21. Participants will be provided take-home capsules for the remaining dose titration period. They will be required to visit the CRU on an outpatient basis during this period as mentioned in the SoA (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 randomly assigned to receive 2 different formulations of LY3502970. Serial blood samples for PK will be collected as mentioned in the SoA (Section 1.3). Refer to Section 6.1 for further details.

During Test Period 1 (Days 22 to 28), participants will receive 1 of the 2 different formulations of [CCI] mg LY3502970 capsules QD per randomization. They will crossover on Day 29 and will then receive the other formulation during Test Period 2 (Days 29 to 35).

Participants should follow local guidance and CRU precautions to minimize risk of coronavirus disease 2019 (COVID-19) infection. During this period, participants may be allowed to leave the CRU after completing the 2-hour fasting requirements postdose. However, they will 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 the last dose. Participants will undergo PK and safety assessments during this period as mentioned in the SoA (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 2 different formulations of LY3502970 at steady state in healthy participants. Within cohort escalation is required for this oral incretin to assess the PK profile 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 doses in healthy participants were escalated from 2 to 24 mg in Study GZGA. Therefore, performing the 2 formulation assessments after a similar period and similar dose escalation will limit the potential impact of a gastric emptying delay on the PK profile.

Repeat dosing over a period of 7 days with each formulation will allow the participants to reach steady-state PK, based on $t_{1/2}$ 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 a dose high enough for the study intervention. This crossover design also allows each participant to be used as her or his own control to limit the number of healthy participants needed for the assessment.

PK 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 2 different formulations of LY3502970. As the effect of food is unknown to date at a dose of 16 mg, all doses during both test periods will be administered in the fasted state to ensure that the baseline PK is representative of fasted status.

4.3. Justification for Dose

The planned LY3502970 doses, CCI mg, are 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 CCI were tolerated in the multiple-dose part of Study GZGA. The mean $t_{1/2}$ ranging from CCI supports a QD dosing regimen. Therefore, the proposed dosing regimen in this study, which is CCI dosing with within-treatment dose escalation every 7 days, is similar to the dosing regimens that have been previously administered and tolerated in the multiple-ascending dose study.
- In the first-in-human Study GZGA, Part A (single-ascending dose) investigated single doses of 0.3, 1, 3, and 6 mg of LY3502970 or placebo and Part B (multiple-ascending dose) 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 intervention.

- 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 intervention.

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 emerge, 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 is available 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 study.

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 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 aged 21 to 70 years, inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Participants whose health as determined through 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 a body weight of at least 45 kg and body mass index of 18.5 to 35.0 kg/m^2, inclusive.

Sex and contraceptive/barrier requirements

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

   Please refer to Section 10.4 for definitions and additional guidance related to contraception.

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.

   Please refer to Section 10.4 for definitions 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 ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical conditions

10. Participants who have significant previous or current history of comorbidities capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product (IP); or of interfering with the interpretation of data.
11. 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.
12. Participants who have an abnormal blood pressure, pulse rate, or both, which are deemed to be clinically significant by the investigator, at screening.
13. Participants who have a GI disorder, or disease, which impacts gastric emptying, for example gastric bypass surgery or pyloric stenosis.
14. Participants who have
    - a history or presence of chronic or acute pancreatitis
    - an elevation in serum amylase or lipase (>1.5-fold ULN)
15. Participants who currently have clinically significant atopy or have a history of clinically significant multiple or severe drug allergies or severe posttreatment hypersensitivity reactions, including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis.
16. Participants who have liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or have elevations in aminotransferase levels, ALT and AST greater than 2x ULN at screening.
17. 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.
18. Participants who have a history of or current psychiatric disorders that in the opinion of the investigator would adversely affect patient safety or compliance.
19. Participants who regularly use known drugs of abuse.
20. Participants who have a personal or family history of medullary thyroid carcinoma or have multiple endocrine neoplasia syndrome type 2.

Prior/concomitant therapy

21. Participants who have known allergies to LY3502970, related compounds, or any components of the formulation.
22. Participants who have used or intend to use over-the-counter or prescription medication including herbal medications or traditional medications within 14 days prior to dosing. Specific medications listed in Section 6.8, Concomitant Medications, may be allowed.
23. Participants who have used any drugs or substances that are known strong inducers or inhibitors of CYP3A within 14 days prior to the first administration of study drug and during the study or drugs that are P-gp/BCRP substrates with narrow therapeutic index. Please see Section 6.8 for details.

Prior/concurrent clinical study experience

24. Participants who are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.
25. Participants who have participated, within the past 3 months, in a clinical study involving an IP. If the previous IP has a long t½, 5 half-lives or 3 months (whichever is longer) should have passed since last dosing, prior to check-in.

Diagnostic assessments

26. Participants who show evidence of human immunodeficiency virus (HIV) infection, positive HIV antibodies, or both. A negative test within 6 months of screening would not need to be repeated.
27. Participants who show evidence of hepatitis C, positive hepatitis C antibody, or both. A negative test within 6 months of screening would not need to be repeated.
28. Participants who show evidence of hepatitis B, positive hepatitis B surface antigen, positive hepatitis B core antibody, or all. A negative test within 6 months of screening would not need to be repeated.
29. Participants who have a serum calcitonin level of
    a. ≥20 ng/L at screening, if estimated glomerular filtration rate ≥60 mL/min/1.73 m^2
    b. ≥35 ng/L at screening, if estimated glomerular filtration rate <60 mL/min/1.73 m^2

Other exclusions

30. Women of childbearing potential.
31. Women who are lactating.
32. Participants who are unwilling to comply with the dietary restrictions required for this study.
33. 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 discharge from the CRU
34. 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.

35. 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.
36. 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.
37. Participants who are employees of Eli Lilly and Company or the CRU.
38. 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 require to fast overnight for at least 10 hours.
- On Day 1 when prolonged PK profiles are collected, participants must also fast for 2 hours postdose.
- Meals will be provided at other times while resident at the CRU 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.

Test periods

- Participants will receive the dose after overnight fast for at least 10 hours and without breakfast.
- On Days 28 and 35 when prolonged PK profiles are collected, participants must also fast for 2 hours postdose.
- 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. Substance Use: 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 CRU, 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.

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 predose safety procedures, such as safety blood, ECGs, vital signs, and urinalysis, can be repeated as clinically indicated under the discretion of investigator or subinvestigator 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 or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Intervention Name	LY3502970
Type	Drug
Dose Formulation	Capsule, nominal particle size SDD capsule, large particle size SDD capsule
Unit Dose Strength(s)	CCI mg
Dosage Level(s)	CCI mg QD (as 1 capsule)
Route of Administration	Oral
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention containing dose strengths CCI mg of Formulation 1 will be provided in bottles. Each bottle will be labeled as required per country requirement. Formulation 2 will have to be prepared by the site using EP methods and instructions provided to them.

Abbreviations: IMP = investigational medicinal product; QD = once daily; SDD = spray-dried dispersion. EP = extemporaneous preparation

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.

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

6.1.2. Package and Labeling

The study intervention will be capsules for oral administration. Each dosage unit contains LY3502970 as an SDD equivalent to CCI mg of the LY3502970 drug substance. The CCI

CCI mg dose strengths, and the CCI mg dose strength of Formulation 1 will be provided to the site in bottles. Study intervention of Formulation 2 will have to be prepared by the site using extemporaneous preparation (EP) methods, following instructions and materials provided for the purpose. The study interventions should be stored according to instructions on the label, 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 CRU staff.

Instructions for EP of the study drug will be provided by the sponsor.

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 interventions 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 interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
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, CRU may destroy the clinical trial materials if, during the CRU selection, the evaluator has verified and documented that the CRU has appropriate facilities and written procedures to dispose of clinical trial materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization

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 1 of the 2 arms (Formulations 1 and 2) of the study, according to the randomization schedule generated prior to the study by the statistics department at sponsor.

Blinding

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 CRF.

Titration period

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be documented in the source documents and CRF and assessed by

- direct questioning
- counting returned capsules, and
- reviewing participant diaries.

A record of the number of LY3502970 capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, dose reductions, or both 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 at any time 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

Not applicable.

6.7. Treatment of Overdose

For this study, any dose of study intervention greater than the planned dose 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 or 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.

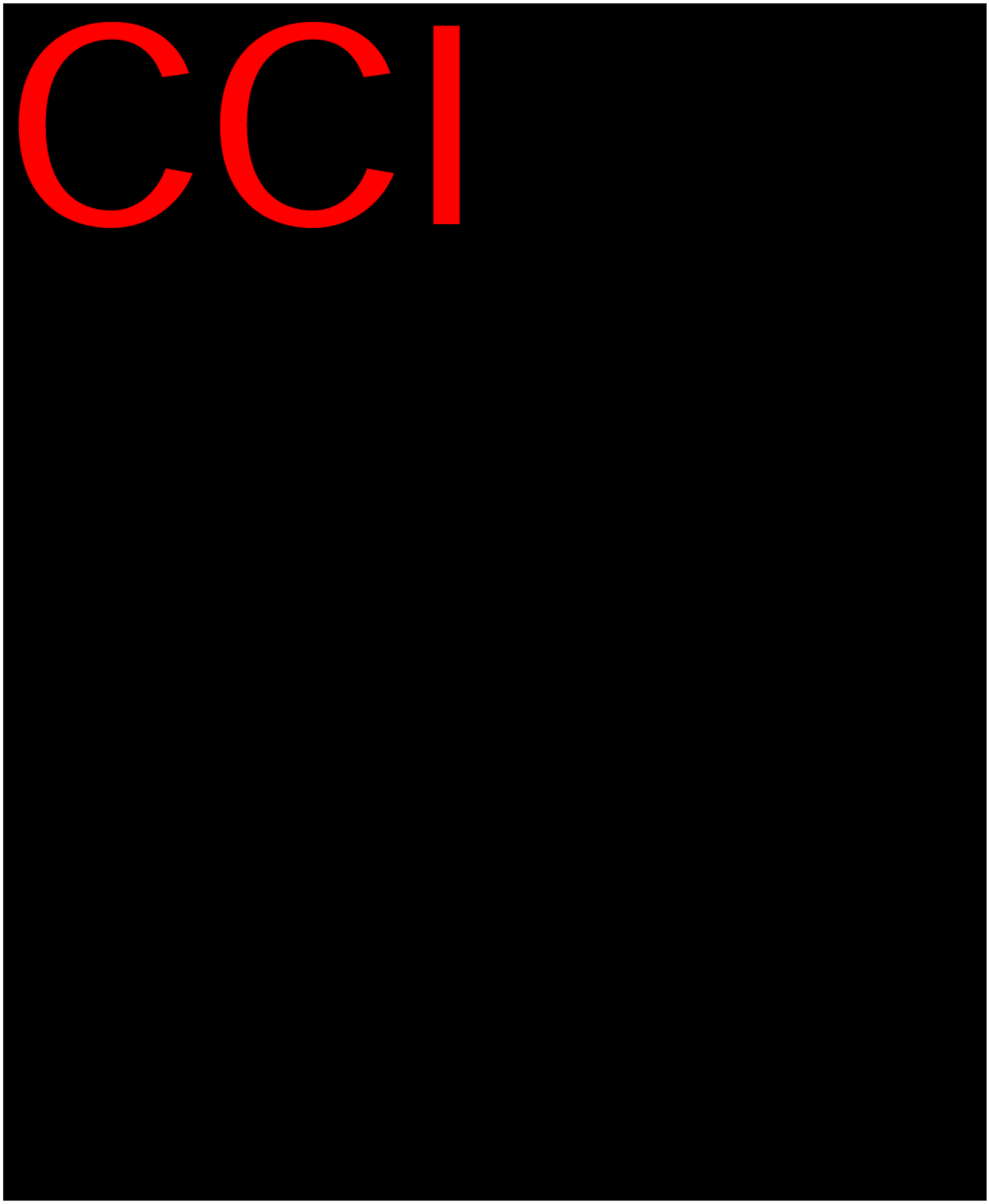
The Lilly CP or CRP or clinical research scientist should be contacted if there are any questions regarding concomitant or prior therapy.

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 preferably with discussion with the sponsor, the medication will not interfere with the study. COVID-19 vaccination is permitted.

Any medications that transiently affect gastric pH (antacids, milk of magnesia, etc.) should not be used on the days of LY3502970 administration. Any medications that maintain elevated gastric pH, including but not limited to histamine (H2)-receptor blockers and proton pump inhibitors, are specifically excluded for 14 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit.

Nausea, vomiting, or both during this study may be treated with antiemetics but these medications should not be used prophylactically.

Nonsteroidal anti-inflammatory medications (including ibuprofen and aspirin), paracetamol ≤3g/day, vaccinations, cough suppressants, antihistamines, vitamin/mineral supplements, antibiotics, and topical ointments may be used on an as-needed basis, unless they are specifically excluded in the following lists.


CCI

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

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 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).

The investigator should consider discontinuation of the study intervention for a participant if any of the following occur:

- an AE that is considered to be intolerable
- an abnormal safety laboratory test result, determined to be clinically significant by the investigator, or
- QTcF >500 msec and an increase from baseline in QTcF >60 msec, from at least 2 consecutive readings.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

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 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 an 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 intervention 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 nondrug etiology is identified.

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

7.1.3. Discontinuation due to 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

A participant experiencing intolerable GI events may skip up to 2 doses in succession during Days 2-14. In the presence of persistent GI events during the titration phase, 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.

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 or 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 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 interventions 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, they may request destruction of any samples taken and not tested, and the investigator must document this in the CRU study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the CRU. CRU 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 CRU.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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 that include 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 following subsections, 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

- 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

Participants will be weighed in light clothing at approximately the same time in the morning before dosing and after an overnight fast and evacuation of bowel and the bladder, if possible.

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

8.2.4. Electrocardiograms

For each participant, 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 corrected QT interval stopping criteria.

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. ECGs may be obtained at additional times, when deemed clinically necessary. All single ECGs recorded should be stored at the CRU.

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 CRF.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the CRU 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.

1. See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
2. 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.
3. 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.
    3.1. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    3.2. All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA (Section 1.3), standard collection requirements, and laboratory manual.
4. If laboratory values from nonprotocol-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 or urine pregnancy test will be conducted at screening and safety follow-up as detailed in the SoA (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:

1) trends in safety data
2) laboratory analytes, including ALT, AST, TBL, amylase, and lipase
3) AEs, including AESI (nausea, vomiting, and diarrhea), and
4) reported pancreatitis.

When appropriate, the Lilly CP, CRP, or 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, 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 ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

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

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver test results 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 laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

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

If a Participant with Baseline Results of	Develops the Following Elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms* or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.
*Hepatic signs or 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 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:

Article I. Elevation of serum ALT level to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT level <1.5x ULN).

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

Article II. Elevated TBL level to ≥2x ULN (if baseline TBL level <1.5x ULN) (except for cases of known Gilbert's syndrome)

- In participants with baseline TBL level ≥1.5x ULN, the threshold should be TBL level ≥2x baseline.

Article III. Elevation of serum ALP level to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP level <1.5x ULN)

- In participants with baseline ALP level ≥1.5x ULN, the threshold is ALP level ≥2x baseline on 2 or more consecutive blood tests.

Article IV. Hepatic event considered to be an SAE.

Article V. Discontinuation of study intervention due to a hepatic event.

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

8.2.7.2. Pancreatic Monitoring

Please refer to Section 10.7.

8.2.7.3. Hypoglycemia

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

Hypoglycemia level	**Glucose level or severity level**	**Characteristics**
Level 1	<70 mg/dL (3.9 mmol/L) and ≥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	<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 or absence of symptoms of hypoglycemia.
Level 3	severe hypoglycemia (in adults)	A severe event characterized by altered mental, physical, or both status requiring assistance for the 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
- 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 nonleading 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 up each participant at subsequent visits or contacts. All SAEs and AESI (as defined in Section 8.3.3) will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). 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 ICF	Participation in study has ended	As soon as possible upon site awareness	AE eCRF	NA
Serious Adverse Event					

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* - after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	NA	Promptly	SAE paper form	NA
Pregnancy					
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)	SAE paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	NA
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	NA
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	NA
PC (if investigator becomes aware)	Participation in study has ended	NA	Promptly	PC form	

Abbreviations: AE = adverse event; eCRF = electronic case report form; ICF = informed consent form; NA = not applicable; PC = product complaint; SAE = serious adverse event.

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive 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 up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported, regardless of 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 up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of 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 poststudy 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 AESI (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 IP concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time,

samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism and/or protein-binding work.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A blood sample for 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 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 determine the PK of 2 different formulations of LY3502970 after multiple oral doses 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.

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.

PK 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. Analyses will be fully detailed in the SAP.

9.3.2. Primary Endpoint(s) Analysis

PK parameter estimates for LY3502970 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis of LY3502970 will be AUC_{0-24}, C_{max}, and t_{max} at steady state. Other parameters, such as $t_{1/2}$, apparent clearance (CL/F), and apparent volume of distribution (V/F) may be calculated as appropriate. All PK parameters will be listed and summarized using descriptive statistics.

The data for AUC and C_{max} from Test Periods 1 and 2 will be log transformed. The log-transformed data will be analyzed using a linear mixed-effects model with treatment ([CCI]-mg capsule LY3502970 Formulation 1, [CCI]-mg capsule LY3502970 Formulation 2), period 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. The t_{max} will be analyzed using the Wilcoxon signed-rank test. The median for each treatment, the median difference between the 2 treatments, and corresponding approximate 90% CIs will be calculated.

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 regard 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 regard 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. AEs 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 multiple-dose study to investigate the pharmacokinetics, safety, and tolerability of 2 different formulations of LY3502970 in healthy participants. The sample size is based on a calculation of precision of the estimated ratio of AUC_{0-24} between [redacted]-mg capsule LY3502970 Formulation 1 and [redacted] mg capsule LY3502970 Formulation 2. [redacted], a sample size of 24 completed subjects will provide approximately 90% coverage probability to get a 90% CI for the ratio R of geometric mean AUC_{0-24} between treatments which will be within [0.899*R, 1.112*R].

Approximately 38 participants will be randomly assigned to study intervention such that approximately 24 evaluable participants complete the study. If a subject does not complete all the treatment periods of the study, they may be replaced by another participant if decided by the sponsor. This replacement participant will go through the same treatment sequence as the discontinued participant.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - applicable ICH GCP guidelines, and
  - applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for 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, 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.

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 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

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

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information, which would make the participant identifiable will not be transferred.
- The participant must be informed that 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, through phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately and continually use all efforts to reach investigators until contact is made and instructions verified.

Reports

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

Data

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

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs 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 clinical trial agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

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

An 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.

SAEs 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 following table 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 following table), 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, total	
Hepatitis C antibody	
HIV	Pregnancy test[d]
	Follicle-stimulating hormone[a,e]
Calcitonin[f]	

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

[a] Performed at screening only.

[b] Test only if dipstick result is abnormal 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.

[f] Performed as indicated in Schedule of Activities (Section 1.3).

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.

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-GZGH 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]	10	5	50
Serum calcitonin	6	1	6
Pharmacokinetics	2	36[b]	72
Blood discard for cannula patency	0.3	29	8.7
Pharmacogenetics	10	1	10
Total			172.7
Total for clinical purposes (rounded up to the nearest 10 mL)			180

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

[b] Additional 3 samples as per Section 8.4 included.

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
• 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
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign 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 AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (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 The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital 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 • 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.
e. Is a congenital anomaly/birth defect • Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
f. Other situations • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as important medical events, that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint
• A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs: o deficiencies in labeling information and o use errors for device or drug-device combination products due to ergonomic design elements of the product. • PCs related to study interventions used in clinical trials are collected 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

- When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic 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. AE or SAE information is reported on the appropriate eCRF page and PC information is reported on the PC Form.

  Note: 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.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the 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 the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

  An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/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 the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
Follow-up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings, including histopathology.

10.3.5. Reporting of Serious Adverse Events

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

10.3.6. 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 an 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	Females are considered a woman of childbearing potential if • they have had at least 1 cycle of menses, or • they have Tanner 4 breast development. 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.
Women not of childbearing potential	Females are considered women not of childbearing potential if they • have a congenital anomaly such as Mullerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral oophorectomy, tubal ligation.
Postmenopausal state	The postmenopausal state should be defined as 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 aged at least 40 years and up to 55 years 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 aged 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or 4. A woman aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy * 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.
Reproductive Toxicology Studies	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.

10.4.2. Contraception Guidance

The following table describes contraception guidance for men.

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for 90 days or 3 months after last participant visit
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study, and for 90 days or 3 months after 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	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide 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.

Methods	**Examples**
Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • postcoital douche • lactational amenorrhea

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.
- DNA samples will be used for research related to LY3502970 or T2DM 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 T2DM. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to LY3502970 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on LY3502970 continues but no longer than 15 years or other period as per local requirements.

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

Hepatic evaluation testing

See Section 8.2.7.1 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)	Alkaline phosphatase (ALP)
Leukocytes (WBCs)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Alkaline phosphatase isoenzymes
Platelets	Copper
Cell morphology (RBC and WBC)	Ethanol screen
	Haptoglobin
Coagulation	Immunoglobulin IgA (quantitative)
Prothrombin time, international normalization ratio (PT-INR)	Immunoglobulin IgG (quantitative)
Serology	Immunoglobulin IgM (quantitative)
Hepatitis A virus (HAV) testing:	**Urine Chemistry**
HAV IgM antibody	Drug screen
Hepatis B virus (HBV) testing:	**Other Serology**
Hepatitis B surface antigen (HBsAg)	Anti-nuclear antibody (ANA)
Hepatitis B surface antibody (anti-HBs)	Anti-smooth muscle antibody (ASMA)[a]
Hepatitis B core total antibody (anti-HBc)	Epstein-Barr virus (EBV) testing:
Hepatitis B core IgM antibody	EBV antibody
Hepatitis B core IgG antibody	EBV DNA[b]
HBV DNA[b]	Cytomegalovirus (CMV) testing:
Hepatis C virus (HCV) testing:	CMV antibody
HCV antibody	CMV DNA[b]

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

Abbreviations: Ig = immunoglobulin; RBC = red blood cell; WBC = white blood cell.

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

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

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

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 ≥3x 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 IPs.

Asymptomatic elevation of serum amylase and/or lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck 2016; Steinberg et al. 2017a,b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes (lipase and/or p-amylase ≥3x 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 hours
BCRP	breast cancer resistance protein
CI	confidence interval
C_{max}	maximum observed concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CP	clinical pharmacologist
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
CT	computed tomography
CYP	cytochrome P450
DSRB	Domain Specific Review Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

Term	Definition
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.
EP	extemporaneous preparation
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
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
P-gp	P-glycoprotein
PK	pharmacokinetics

Term	Definition
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SDD	spray-dried dispersion
SoA	schedule of activities
$t_{1/2}$	half-life
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time to maximum observed concentration
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

10.10. Appendix 10: Protocol Amendment History

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

Amendment [a]: 04-February-2022

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The protocol was amended to increase the number of participants from 30 to 38 to increase the probability of at least 24 participants completing the study in the event of discontinuations.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 9.5. Sample Size Determination	Overall number of participants has been updated to 38.	The number of participants has been increased to increase the probability of at least 24 evaluable participants completing the study in the event of discontinuations.

11. References

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Leo Document ID = e4d9e055-24cc-4ba8-bfe3-99ffe88a82af

Approver: PPD

Approval Date & Time: 11-Mar-2022 21:10:42 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 14-Mar-2022 13:02:12 GMT

Signature meaning: Approved