Protocol J2A-MC-GZGO(a)

A Single-Group, Open-Label, Single-Period, Phase 1 Study to Determine the Absolute Bioavailability of LY3502970 in Healthy Participants

NCT06085482

Approval Date: 05-Sep-2023

Title Page

Protocol Title: A Single-Group, Open-Label, Single-Period, Phase 1 Study to Determine the Absolute Bioavailability of LY3502970 in Healthy Participants.

Protocol Number: J2A-MC-GZGO

Amendment Number: [a]

Compound: LY3502970

Brief Title: A Phase 1 study to determine the absolute bioavailability of LY3502970 in healthy participants.

Study Phase: 1

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 Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-094513

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*28-Jun-2023*

Amendment [a]

Overall Rationale for the Amendment:

The overall rationale for the protocol amendment is to address site feedback.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion criterion 19 was clarified to state that any vaccinations were permitted with the exception of live vaccines as stated in exclusion criterion 26.	To provide further clarification to the site regarding exclusionary medications.
10.2.1 Blood Sampling Summary	The blood volume for the screening AMS sample was increased from 1 mL to 4 mL; this increased the total volume of blood taken during the study.	The site was unable to source a 1-mL tube; therefore, a 4-mL tube was required to be used.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Single-Group, Open-Label, Single-Period, Phase 1 Study to Determine the Absolute Bioavailability of LY3502970 in Healthy Participants.

Brief Title: A Phase 1 study to determine the absolute bioavailability of LY3502970 in healthy participants.

Regulatory Agency Identifier Number: IND 142842

Rationale: The purpose of this study is to determine the absolute bioavailability of LY3502970 in humans. Absolute bioavailability information will aid in the planning and design of future studies and may be used to interpret pharmacokinetic data from these studies.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To determine the absolute bioavailability of LY3502970 following a single oral dose of CCI mg LY3502970 and an IV dose of less than CCI-µg [^{14}C]-LY3502970 (hemicalcium salt) in healthy participants.	Absolute bioavailability of LY3502970.
Secondary	
To evaluate the PK of LY3502970, [^{14}C]-LY3502970, and total radioactivity following a single oral dose of CCI mg LY3502970 and an IV dose of [^{14}C]-LY3502970 (hemicalcium salt) in healthy participants.	AUC(0-∞) and C_{max} for plasma total radioactivity, [^{14}C]-LY3502970, and LY3502970.
To describe the safety of LY3502970 following a single oral dose of CCI mg LY3502970 along and an IV dose of [^{14}C]-LY3502970 (hemicalcium salt) in healthy participants.	Number and incidence of TEAEs and SAEs.

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; IV = intravenous; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design:

This study is an open-label, single-center study to determine the absolute bioavailability of LY3502970 in healthy participants following a single oral dose of [redacted] mg LY3502970 and an intravenous (IV) dose of less than [redacted]-µg [^{14}C]-LY3502970 (hemicalcium salt) containing approximately [redacted] nCi.

Brief Summary:

Study details include:

- The study duration will be approximately 9 weeks including:
  - Screening: Days -42 to -1
  - Clinical research unit confinement: Day -1 until Day 9
  - Follow-up visit: Day 16 ±3 days
- The treatment duration will be 1 day.

Study Population:

Overtly healthy men and women not of childbearing potential aged 21 to 70 years, inclusive, with a body weight of 45 kg or more and body mass index within the range 18.5 to 35.0 kg/m^2, inclusive.

Number of Participants:

Approximately 10 participants will be enrolled to target at least 6 participants complete the study.

Intervention Groups and Duration:

All participants will receive a single oral dose of [redacted] mg LY3502970 and an IV dose of less than [redacted]-µg [^{14}C]-LY3502970 (hemicalcium salt) containing approximately [redacted] nCi.

Ethical Considerations of Benefit/Risk:

In participants administered LY3502970 up to the highest single dose of [redacted] mg and multiple doses of [redacted] mg for a maximum of 36 weeks to date, the only safety or tolerability concerns have been

- Gastrointestinal (GI)-related effects that are consistent with GLP-1 pharmacology, and
- changes in vital signs that have resolved spontaneously over time.

Elevations in serum bilirubin, transaminase, alkaline phosphatase, and gamma-glutamyl transferase levels have been reported in patients receiving LY3502970. No participants fulfilled Hy's law laboratory criteria for increased risk of drug-induced liver injury.

GI AEs have been the most frequently reported events across all completed and ongoing studies including

- nausea
- constipation
- diarrhea
- vomiting
- abdominal distension
- eructation

- dyspepsia
- abdominal pain.

These AEs have been mostly mild in severity and the majority resolved without treatment. Three serious AEs (SAEs) were reported in study GZGC, none of which were deemed related to study treatment by the investigator. No other SAEs were reported in Phase 1 studies.

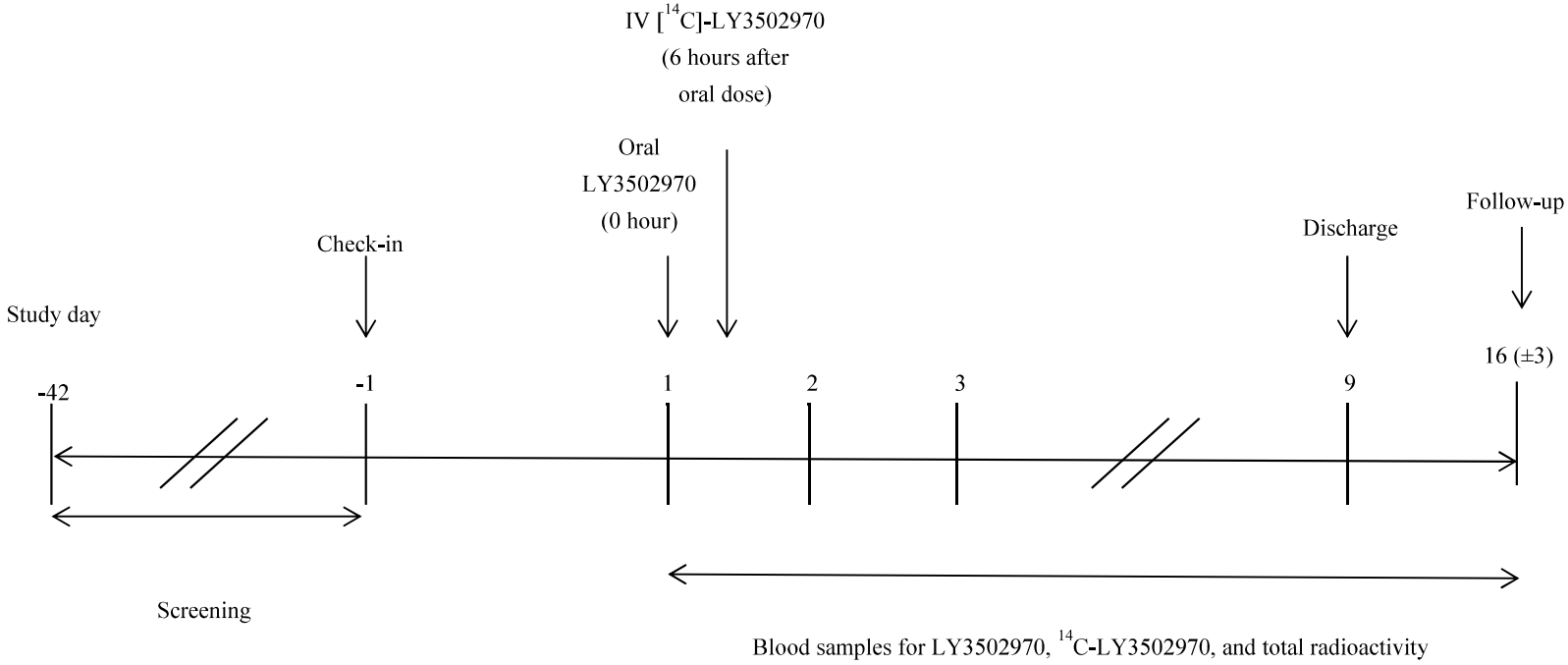
All completed and ongoing multiple-dose studies used starting doses of [redacted] and [redacted] mg, with an acceptable safety and tolerability profile, but with several participants experiencing nausea and vomiting in each study. The planned single dose of [redacted] mg for the present study is expected to be well tolerated.

The radioactive dose is an acceptable dose to give to healthy male participants and female participants of nonchildbearing potential.

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

Data Monitoring Committee: No

1.2. Schema



Abbreviations: IV = intravenous.

1.3. Schedule of Activities (SoA)

Procedure	Screening	Resident in CRU						Follow-up/ ED	Comments
Day	**-42 to -1**	**-1**	**1**	**2**	**3**	**4 to 8**	**9**	**16 (±3)**	
Informed Consent	X								
Admission to CRU		X							
Discharge from CRU							X		
Outpatient Visit	X							X*	* Outpatient visit for follow-up only.
Medical History	X								
Height	X								
Weight	X	X					X		
Plasma Sample for AMS Analysis	X								
BMI	X								
Urine Drug/Ethanol Screen	X	X							See Section 10.2.
Hematology, Chemistry, and Urinalysis	X	X						X	See Section 10.2.
HIV and Hepatitis	X								See Section 10.2.
Lipid Panel	X								See Section 10.2.
Serum Pregnancy Test	X								See Section 10.2.
Urine Pregnancy Test		X							See Section 10.2.
Follicle-Stimulating Hormone	X								See Section 10.2.
Calcitonin	X								See Section 10.2.
Complete Physical Examination		X							Targeted examinations conducted as needed.
Supine Vital Signs (Pulse Rate, Blood Pressure)	X		P	X	X	X	X	X	
Single 12-Lead ECG	X		P					X	
Blood Glucose Monitoring			P, 8, 12h	24, 36h	48h	72, 96h			Performed using bedside monitoring.
LY3502970 Sampling			P, 0.5, 1, 2, 4, 6, 6.5, 7, 8, 10, 12, 16h	24, 36h	48h	72, 96, 120, 144, 168h	192h	X	Sampling times are relative to the oral dose.

Procedure	Screening	Resident in CRU						Follow-up/ ED	Comments
Day	**-42 to -1**	**-1**	**1**	**2**	**3**	**4 to 8**	**9**	**16 (±3)**	
[^{14}C]-LY3502970 and Total Radioactivity Sampling			0 (immediately after IV dosing), 2, 5, 10, 15 min and 0.5, 1, 2, 4, 6, 10 h	18, 30 h	42 h	66, 90, 114, 138, 162 h	186 h	X	Sampling times are relative to the IV dose.
LY3502970 Oral Dose			X (0 h)						
[^{14}C]-LY3502970 (Hemicalcium Salt) IV Dose			X (6 h)						Administered 6 hours after the oral dose.
Genetic Sample			P						

Abbreviations: AMS = accelerated mass spectrometry; BMI = body mass index; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; HIV = human immunodeficiency virus; IV = intravenous; h = hour; min = minute; P = predose (oral).

Note: If multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture. Blood glucose samples should be taken after the PK sample, except in the event of a level 3 hypoglycemia, where the condition must be attended to promptly. Pharmacokinetic sampling times are given as targets to be achieved within reasonable limits.

Note: All times are given relative to the LY3502970 oral dose (time 0 hour; predose or postdose), with the exception of the [^{14}C]-LY3502970 and total radioactivity sampling, which is relative to the IV dose.

2. Introduction

LY3502970 is a chemically synthesized, oral GLP-1 RA that exhibits the antihyperglycemic actions of GLP-1.

LY3502970 is being developed as a daily oral adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes and as an adjunct therapy to healthy diet and physical activity for the treatment of overweight or obesity.

2.1. Study Rationale

The purpose of this study is to determine the absolute bioavailability of LY3502970 in humans. Absolute bioavailability information will aid in the planning and design of future studies and may be used to interpret PK data from these studies.

2.2. Background

Obesity is known to be the main risk factor for T2D, and data from clinical trials demonstrate the potential extent of overlap between people with T2D and overweight/obesity. The ongoing global obesity epidemic increases the incidence of T2D and other comorbidities, including hyperlipidemia and hypertension, resulting in an increased risk of micro- and macrovascular complications in individuals with these conditions. Glucose-lowering therapies that encompass weight loss may have a potential to improve treatment of T2D, slow its progression, and reduce the risk of chronic complications.

There is an unmet medical need for efficacious, safe, and well-tolerated oral formulations of GLP-1 RAs for the management of T2D and for the treatment of overweight or obesity. Oral formulations with fewer restrictions related to administration would allow for further tailoring of therapy to meet individual patient preferences and needs.

LY3502970 is a non-peptide chemically synthesized oral GLP-1RA that can be administered once daily without any food or water restrictions.

A detailed description of the chemistry, pharmacology, efficacy, and safety of LY3502970 is provided in the IB.

2.3. Benefit/Risk Assessment

In participants administered LY3502970 up to the highest single dose of [CCI] mg and multiple doses of [CCI] mg for a maximum of 36 weeks to date, the only safety or tolerability concerns have been

- GI-related effects that are consistent with GLP-1 pharmacology, and
- changes in vital signs that have resolved spontaneously over time.

Elevations in serum bilirubin, transaminase, ALP, and gamma-glutamyl transferase levels have been reported in patients receiving LY3502970. No participants fulfilled Hy's law laboratory criteria for increased risk of drug-induced liver injury.

The safety, tolerability, PK, and PD of LY3502970 have been evaluated in 5 completed Phase 1 clinical pharmacology studies, which comprise

- doses up to [redacted] mg in in healthy participants in the first-in-human single-ascending dose and up to [redacted] mg in the multiple-ascending dose in study J2A-MC-GZGA
- doses up to [redacted] mg in participants with type 2 diabetes mellitus in the multiple-dose study J2A-MC-GZGC
- doses up to [redacted] mg in healthy participants in the multiple-dose study J2A-MC-GZGD
- [redacted]-mg dose in healthy participants in the open-label study J2A-MC-GZGF, and
- doses up to [redacted] mg in healthy participants in the open-label study J2A-MC-GZGJ.

Safety and tolerability assessments of LY3502970 include data from 7 ongoing studies, including GZGB, GZGE, GZGH, GZGI, GZGK, GZGL, and GZGM.

GI AEs have been the most frequently reported events across all completed and ongoing studies including

- nausea
- constipation
- diarrhea
- dyspepsia
- vomiting
- abdominal distension
- eructation
- abdominal pain.

These AEs have been mostly mild in severity and the majority resolved without treatment. Three SAEs were reported in study GZGC, none of which were deemed related to study treatment by the investigator. No other SAEs were reported in Phase 1 studies.

All completed and ongoing multiple-dose studies used starting doses of [redacted] and [redacted] mg, with an acceptable safety and tolerability profile, but with several participants experiencing nausea and vomiting in each study. The planned single dose of [redacted] mg for the present study is expected to be well tolerated.

The radioactive dose is an acceptable dose to give to healthy male participants and female participants of nonchildbearing potential. See Section 4.3 for further details.

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

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the absolute bioavailability of LY3502970 following a single oral dose of [redacted] mg LY3502970 and an IV dose of less than [redacted]-µg [^{14}C]-LY3502970 (hemicalcium salt) in healthy participants.	Absolute bioavailability of LY3502970.
Secondary	
To evaluate the PK of LY3502970, [^{14}C]-LY3502970, and total radioactivity following a single oral dose of [redacted] mg LY3502970 and an IV dose of [^{14}C]-LY3502970 (hemicalcium salt) in healthy participants.	AUC(0-∞) and C_{max} for plasma total radioactivity, [^{14}C]-LY3502970, and LY3502970.
To describe the safety of LY3502970 following a single oral dose of [redacted] mg LY3502970 and an IV dose of [^{14}C]-LY3502970 (hemicalcium salt) in healthy participants.	Number and incidence of TEAEs and SAEs.

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; IV = intravenous; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study GZGO is an open-label, single-center study to determine the absolute bioavailability of LY3502970 in healthy participants following a single oral dose of [redacted] mg LY3502970 and an IV dose of less than [redacted]-µg [^{14}C]-LY3502970 (hemicalcium salt) containing approximately [redacted] nCi.

Approximately 10 participants will be enrolled to target at least 6 participants complete the study. Participants will undergo screening procedures up to 42 days prior to enrollment and will be admitted to the CRU on Day -1. Participants will be administered a single dose of [redacted] mg LY3502970 and an IV dose of [^{14}C]-LY3502970 (hemicalcium salt) on Day 1 and will remain in the CRU until after completion of assessments on Day 9. Participants may stay longer in the CRU at the investigator's discretion. Participants will return a final follow-up visit or ED visit on Day 16, ±3 days.

Clinical laboratory tests, physical examination, vital signs, single 12-lead ECGs, and AEs will be monitored to assess safety and tolerability. Blood samples for PK analysis will be collected predose through the follow-up visit.

The schema in Section 1.2 illustrates the study design.

4.2. Scientific Rationale for Study Design

This study will be open-label because the primary endpoints of the study are considered objective. Conducting the study in healthy participants mitigates the potential confounding effects of the disease state and concomitant medications.

An IV microtracer method will be used to determine the absolute bioavailability of LY3502970 because this allows for simultaneous oral and IV dosing in the same participants. Simultaneous dosing is expected to result in less variability in the absolute bioavailability estimate, ensures the systemic clearance is consistent between the IV and oral doses, and involves administration of a minimal IV radiolabeled dose to minimize the risk from exposure to radiation. The IV dose of [^{14}C]-LY3502970 (hemicalcium salt) will be administered so that peak concentrations of the IV dose occur at approximately the t_{max} of the oral dose.

The inclusion of females in this study might elucidate any relevant differences in LY3502970 absorption, metabolism, and excretion between males and females. Females of childbearing potential will not be included to obviate any second-generation effects resulting from the exposure to radiation.

Based on the nonclinical data and the known PK of LY3502970, the sample collection timing and duration of this study are considered adequate to achieve the study objectives.

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

4.3. Justification for Dose

The study will evaluate a single [redacted]-mg oral dose of LY3502970. The oral dose of [redacted] mg has been selected as this can be given as a single dose without significant risk of GI AEs, as described in Section 2.3.

The radioactive dose of approximately [redacted] nCi of [^{14}C]-LY3502970 will present minimal radiation risk to healthy participants. The low levels of radioactivity planned will necessitate the use of AMS as a highly sensitive analytical technique for quantifying the radioactivity in plasma samples and [^{14}C]-LY3502970 plasma concentrations. The radioactive dose of approximately [redacted] nCi together with the use of AMS for analysis of radioactivity is expected to allow for completion of study objectives with minimal radiation exposure risk to healthy participants.

A dose of less than [redacted] µg has been selected for LY3502970 as a less than [redacted]-µg IV dose of LY3502970 is expected to pose no significant risk to study participants but is still sufficiently large enough to allow for the plasma exposure assessment of [^{14}C]-LY3502970 and total radioactivity following IV dosing. While the total IV dose will be less than [redacted] µg, the exact amount cannot be pre-specified as specific activity will vary during the manufacture of the drug substance but will be within the expected range.

4.4. End of Study Definition

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

If a participant has completed all the activities preceding the final safety follow-up visit, but does not complete the final safety follow-up, the PK data from such a participant may still be evaluable.

5. Study Population

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

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

5.1. Inclusion Criteria

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

Age

1. Participant must be 21 to 70 years of age, inclusive, at the time of signing the informed consent.

Type of participant

2. Are overtly healthy as determined by medical evaluation including medical history, physical examination, clinical laboratory tests, vital signs, and 12-lead ECGs that are within normal reference range for the population or investigator site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
3. Participants who are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures including dietary requirements.
4. Participants who have venous access sufficient to allow for blood sampling as per the protocol.

Weight

5. Body weight of 45 kg or more and body mass index within the range 18.5 to 35.0 kg/m^2, inclusive.

Sex and contraceptive/barrier requirements

6. Male or female
    a. Males who agree to use highly effective or effective methods of contraception may participate in this study.
    b. WNOCBP may participate in this study. WOCBP are excluded from the study.

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For definitions and additional requirements related to contraception requirements of this protocol, see Section 10.4.

Informed consent

7. Are capable of giving signed informed consent as described in Section 10.1, 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

8. Participants who have significant history of or current cardiovascular, respiratory, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting risk when taking LY3502970; or of interfering with the interpretation of data.
9. Have a 12-lead ECG abnormality at screening that, in the opinion of the investigator, increases the risks associated with participating in the study or may confound ECG data analysis.
10. Participants who have abnormal blood pressure or pulse rate deemed to be clinically significant by the investigator at screening.
11. Fasting serum triglyceride level of greater than 500 mg/dL or 5.7 mmol/L.
12. Participants who have a history or presence of
    a. pancreatitis, for example, history of chronic pancreatitis or idiopathic acute pancreatitis
    b. elevation in serum amylase or lipase greater than 1.5×ULN, or
    c. GI disorder, for example, relevant esophageal reflux or gall bladder disease, or any GI disease that impacts gastric emptying, for example gastric bypass surgery, pyloric stenosis, with the exception of appendectomy, or could be aggravated by GLP-1 analogs.
13. 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.
14. Participants who have liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or have elevations in aminotransferase levels including ALT and AST greater than 2×ULN and TBL greater than 1.2×ULN, except for cases of known Gilbert's syndrome, at screening.
15. Have an active or untreated malignancy or have been in remission from a clinically significant malignancy, other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer, for less than 5 years prior to screening.
16. Participants who have a history of or current psychiatric disorders that in the opinion of the investigator would adversely affect participant safety or compliance with protocol.
17. Participants who have a history of renal impairment with an estimated glomerular filtration rate less than 70 mL/min/1.73 m^2.

Prior or concomitant therapy

18. Participants who have known allergies to LY3502970, related compounds, or any components of the formulation.
19. Participants who have used or intend to use OTC or prescription medication, herbal, vitamin, traditional medicines, or mineral supplements that may affect the safety or

objectives of the study, as considered by the investigator after discussion with the sponsor if required, within 14 days or 5 half-lives, whichever is longer, prior to dosing and for the duration of the study. Acetaminophen or acetaminophen-containing products at doses less than or equal to 3 grams per 24 hours and any vaccinations are permitted, with the exception of live vaccines as stated in exclusion criterion 26.

Prior or concurrent clinical study experience

20. Participants who are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
21. Participants who have previously completed or withdrawn from this study or any other study investigating LY3502970.
22. If the participant has participated in a clinical study involving a study intervention, 5 half-lives or 3 months, whichever is longer, should have passed since last dosing, prior to check-in.

Diagnostic assessments

23. Participants who show evidence of HIV infection or positive HIV antibodies. A negative test within 6 months of screening would not need to be repeated.
24. Participants who have a positive HCV antibody test. Participants with a positive HCV antibody test at screening can be included only if a confirmatory HCV RNA test is negative.
25. Participants who have a current infection with hepatitis B virus, that is,
    a. positive for hepatitis B surface antigen and hepatitis B core antibody, or
    b. negative for hepatitis B surface antigen and positive for hepatitis B core antibody and HBV DNA.
26. Participants who have had a recent infection or been exposed to a live vaccine within 12 weeks prior to screening or expected to need or receive a live vaccine including herpes zoster vaccination during the course of the study.
27. Participants who have serum calcitonin levels greater than or equal to 20 ng/L at screening.

Other exclusion criteria

28. Women who are lactating.
29. Participants who are unwilling to comply with the dietary restrictions required for this study.
30. Participants who have an average weekly alcohol intake that exceeds 21 units per week for males of 65 years or less and 14 units per week for all females and males over 65 years or are unwilling to stop alcohol consumption 24 hours prior to dosing until after collection of the final PK sample (number of units = [total volume of drink (mL) × alcohol by volume (%)]/1000).

31. Participants who smoke more than 10 cigarettes or the equivalent in the form of e-cigarettes, 3 cigars, or 3 pipes per day and are unable or unwilling to refrain from smoking while resident at the CRU.
32. Participants who regularly use known drugs of abuse or show positive findings on drug screen.
33. Participants who have donated blood of more than 500 mL within 3 months prior to screening, donation of plasma from 2 weeks prior to screening, or platelets within 6 weeks prior to screening.
34. 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.
35. Participants who are employees of Eli Lilly and Company or the CRU.
36. Participants who, in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.
37. Total ^{14}C radioactivity measured in plasma should not exceed 2.5 × standard biological carbon ratio, 50 pMC when analyzed with carbon carrier radiodilution or 250 pMC when analyzed without carbon carrier dilution.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Meals and fasting

Participants will be provided with standard high-fiber meals while resident in the CRU.

Participants will be required to fast overnight for 8 hours before collection of safety laboratory samples.

LY3502970 Oral Dose

The oral dose of LY3502970 will be administered with approximately 240 mL of water after an overnight fast of at least 10 hours and participants will remain fasted for approximately 2 hours post-oral dose.

Participants will receive a meal from 2 hours post-oral dose.

Water is permitted ad libitum during the fasting period, except for 1 hour before and after LY3502970 oral dose administration, other than the water provided during oral dosing.

[^{14}C]-LY3502970 Intravenous Dose

The IV dose of [^{14}C]-LY3502970 will be administered 6 hours after the oral dose of LY3502970. There are no fasting requirements or water restrictions for the IV dose.

Dietary restrictions

From 7 days before the start of study intervention until after collection of the final PK sample, participants must refrain from the consumption of

- red wine

- Seville oranges
- grapefruit or grapefruit juice
- pomelos
- exotic citrus fruits
- grapefruit hybrids, or
- those fruits listed above as fruit juices.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

Caffeine

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

Tobacco

Participants who use tobacco products will be instructed that use of nicotine-containing products, including nicotine patches, will not be permitted while resident in the CRU.

Alcohol

Participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the study for example, watching television or reading.

5.3.4. Donation of Blood, Plasma, or Platelets

Participants should be instructed not to donate blood, plasma, or platelets during the study.

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.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

Not applicable.

6. Study Interventions and Concomitant Therapy

Study intervention is defined as any medicinal product or medical device intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Interventions Administered

This table lists the interventions used in this clinical study.

Intervention Name	LY3502970	[^{14}C]-LY3502970 (hemicalcium salt)
Dosage Formulation and Level	[redacted] mg capsule	Less than [redacted] µg (in terms of hemicalcium salt), approximately [redacted] nCi IV as an approximately [redacted]-mL solution
Route of Administration	Oral	Intravenous
Packaging and Labeling	Study interventions will be supplied by the sponsor or its designee in accordance with current GMP. Study interventions will be labeled as appropriate for country requirements.	Radiolabeled API (powder, as hemicalcium salt) will be supplied by the sponsor or its designee, along with the batch/lot numbers and certificates of analysis. A study site licensed pharmacist will manufacture and label the study intervention from bulk supplies. The completed drug product will be released by a GMP quality auditor under GMP conditions or by a second licensed pharmacist if under non-GMP conditions prior to administration to participants. The sponsor will supply a sufficient quantity of the applicable API for the manufacture of the unit doses at the study site. All excipients will be sourced by the study site. Specific instructions regarding dose preparation will be mutually agreed upon between the sponsor and the appropriate clinical staff and will be presented in a separate document.

6.1.1. Administration Details

Participants will receive a single oral dose of LY3502970 with 240 mL of room temperature water followed 6 hours later by a single dose of [^{14}C]-LY3502970 (hemicalcium salt) as an IV bolus over 1 minute. Details regarding fasting and water restrictions for the oral and IV doses are specified in Section 5.3.1.

Participants will not be allowed to lie supine for 2 hours after oral dosing, unless clinically indicated or for study procedures. Resuscitation equipment, emergency drugs, and appropriately trained staff must be available during the injection and for at least 2 to 4 hours after participants have completed their injection.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

6.3. Assignment to Study Intervention

This is an open-label, nonrandomized study. Participants will receive the same study intervention.

6.4. Blinding or Masking

Not applicable.

6.5. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

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

6.6. Dose Modification

Dose modification is not applicable for this study.

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

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

6.8. Treatment of Overdose

For this study, any dose of oral LY3502970 greater than [redacted] mg and any dose of IV [^{14}C]-LY3502970 (hemicalcium salt) greater than CCI µg will be considered an overdose.

Lilly does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should

- contact the medical monitor immediately, and
- closely monitor the participant for any AE or SAE and laboratory abnormalities until LY3502970 can no longer be detected systemically, for at least 7 days.

6.9. Prior and Concomitant Therapy

Any OTC or prescription medication, herbal, vitamin, traditional medicines, or mineral supplements, that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the

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

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy. Allowed concomitant medications should be taken according to the label directions.

Unless, in the opinion of the investigator and sponsor the medication will not interfere with the study, participants must abstain for 14 days or 5 half-lives, whichever is longer, prior to dosing and for the duration of the study the following:

- OTC or prescription medication
- herbal, vitamin, or traditional medicines, or
- mineral supplements.

If acetaminophen treatment is needed for pain management, the maximal allowed dose will be 3 g per 24 hours, from all acetaminophen-containing medicinal products.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

Not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee, for example, parents or legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or
- if enrolled in any other clinical study involving an investigational product or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

At the time of discontinuing from the study, if possible, the participant will complete procedures for ED, if applicable, as shown in the SoA in Section 1.3. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

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

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

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

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

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based 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.

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

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

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

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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. A targeted physical examination will also be performed, where necessary.

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

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA in Section 1.3. If warranted, additional vital signs may be measured.

Pulse rate and blood pressure should be measured after at least 5 minutes supine. Three subsequent pulse rate and blood pressure measurements should be obtained with approximately 1

minute between the measurements. When possible, measurements of blood pressure and pulse rate should be performed at approximately the same time of day at each scheduled time point.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured throughout the study per investigator discretion.

If orthostatic measurements are required, participants should be supine for at least 5 minutes and measurement obtained between 2 to 3 minutes after standing.

If the participant feels unable to stand, supine vital signs only will be recorded.

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA in Section 1.3 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All single ECGs recorded should be stored at the investigational site.

Single ECGs may be obtained at additional times when deemed clinically necessary, for example, to assess participants' safety.

ECGs must be recorded before collecting any blood samples. Participants must be supine for at least 5 to 10 minutes before ECG collection, and remain supine and awake, during ECG collection.

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

ECGs will be interpreted by the investigator, a physician or qualified designee, at the site as soon after the time of ECG collection as practical, to determine whether the participant meets entry criteria.

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

8.2.4. Clinical Safety Laboratory Tests

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

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

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

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

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

8.2.5. Safety Monitoring

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

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

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

When appropriate, the Lilly CP or CRP will consult with the functionally independent global patient safety therapeutic area physician or clinical research scientist.

8.2.5.1. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Drug Interruption or Discontinuation

This table summarizes actions to take based on abnormal hepatic laboratory or clinical changes.

Participants with normal or near normal baseline (ALT, AST, or ALP less than 1.5×ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study drug
ALT or AST greater than or equal to 3×ULN	X		
ALP greater than or equal to 2×ULN	X		
TBL greater than or equal to 2×ULN[b]	X		
ALT or AST greater than or equal to 5×ULN	X	X	
ALP greater than or equal to 2.5×ULN	X	X	
ALT or AST greater than or equal to 3×ULN with hepatic signs or symptoms[a]	X	X	X
ALT or AST greater than or equal to 5×ULN for more than 2 weeks	X	X	X
ALT or AST greater than or equal to 8×ULN	X	X	X
ALT or AST greater than or equal to 3×ULN and TBL greater than or equal to 2×ULN[b] or INR greater than or equal to 1.5	X	X	X
ALP greater than or equal to 3×ULN	X	X	X
ALP greater than or equal to 2.5×ULN and TBL greater than or equal to 2×ULN[b]	X	X	X
ALP greater than or equal to 2.5×ULN with hepatic signs or symptoms[a]	X	X	X

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, or eosinophilia greater than 5%.

[b] In participants with Gilbert's syndrome the threshold for TBL may be higher.

Participants with elevated baseline (ALT, AST, or ALP greater than or equal to 1.5×ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study drug
ALT or AST greater than or equal to 2×baseline	X		
ALP greater than or equal to 2×baseline	X		
TBL greater than or equal to 2×ULN[b]	X		
ALT or AST greater than or equal to 3×baseline or greater than or equal to 250 U/L (whichever occurs first)	X	X	
ALP greater than or equal to 2.5×baseline	X	X	
ALT or AST greater than or equal to 2×baseline or greater than or equal to 250 U/L (whichever occurs first) with hepatic signs or symptoms[a]	X	X	X

ALT or AST greater than or equal to 3×baseline or greater than or equal to 250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST greater than or equal to 4×baseline or greater than or equal to 400 U/L (whichever occurs first)	X	X	X
ALT or AST greater than or equal to 2×baseline or greater than or equal to 250 U/L (whichever occurs first) and TBL greater than or equal to 2×ULN[b] or INR greater than or equal to 1.5	X	X	X
ALP greater than or equal to 3×baseline	X	X	X
ALP greater than or equal to 2.5×baseline and TBL greater than or equal to 2×ULN[b]	X	X	X
ALP greater than or equal to 2.5×baseline with hepatic signs or symptoms[a]	X	X	X

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, or eosinophilia greater than 5%.

[b] In participants with Gilbert's syndrome the threshold for TBL may be higher.

8.2.5.1.1. Close Hepatic Monitoring

If a participant develops any one of these changes, initiate close hepatic monitoring:

Participants with normal or near normal baseline (ALT, AST, or ALP less than 1.5×ULN)	**Participants with elevated baseline (ALT, AST, or ALP greater than or equal to 1.5×ULN)**
ALT or AST greater than or equal to 3×ULN or	ALT or AST greater than or equal to 2×baseline or
ALP greater than or equal to 2×ULN or	ALP greater than or equal to 2×baseline or
TBL greater than or equal to 2×ULN[a]	TBL greater than or equal to 2×ULN[a]

[a] In participants with Gilbert's syndrome the threshold for TBL may be higher.

Close hepatic monitoring should include these actions:

- Laboratory tests detailed in Section 10.6, including ALT, AST, ALP, TBL, direct bilirubin, CBC with differential, and gamma-glutamyl transferase, with additional tests for creatine kinase should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values.
- In addition to laboratory tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include
    - physical examination and a thorough medical history, including current symptoms

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

8.2.5.1.2. Comprehensive Hepatic Evaluation

If a participant develops any one of the following laboratory or clinical changes, initiate a comprehensive hepatic evaluation:

Participants with normal or near normal baseline (ALT, AST, or ALP less than 1.5×ULN)	**Participants with elevated baseline (ALT, AST, or ALP greater than or equal to 1.5×ULN)**
ALT or AST greater than or equal to 5×ULN or	ALT or AST greater than or equal to 3×baseline or greater than or equal to 250 U/L (whichever occurs first) or
ALP greater than or equal to 2.5×ULN or	ALP greater than or equal to 2.5×baseline or
ALT or AST greater than or equal to 3×ULN with hepatic signs or symptoms[a] or	ALT or AST greater than or equal to 2×baseline or greater than or equal to 250 U/L (whichever occurs first) with hepatic signs or symptoms[a] or
ALT or AST greater than or equal to 5×ULN for more than 2 weeks or	ALT or AST greater than or equal to 3×baseline or greater than or equal to 250 U/L (whichever occurs first) for more than 2 weeks or
ALT or AST greater than or equal to 8×ULN or	ALT or AST greater than or equal to 4×baseline or greater than or equal to 400 U/L (whichever occurs first) or
ALT or AST greater than or equal to 3×ULN and TBL greater than or equal 2×ULN[b] or INR greater than or equal 1.5	ALT or AST greater than or equal to 2×baseline or greater than or equal to 250 U/L (whichever occurs first) and TBL greater than or equal to 2×ULN[b] or INR greater than or equal to 1.5

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, or eosinophilia greater than 5%.

[b] In participants with Gilbert's syndrome the threshold for TBL may be higher.

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for
  - PT-INR
  - viral hepatitis A, B, C, and E

  - autoimmune hepatitis, and
  - an abdominal imaging study, for example, ultrasound or CT scan.

- Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for
  - hepatitis D virus
  - cytomegalovirus
  - Epstein-Barr virus
  - acetaminophen levels
  - 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, and additional tests including
  - magnetic resonance cholangiopancreatography
  - endoscopic retrograde cholangiopancreatography
  - cardiac echocardiogram, or
  - a liver biopsy.
- Clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until levels normalize or return to approximate baseline values.

All the medical information and tests results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.5.1.3. Study Drug Interruption or Discontinuation

If a participant develops any one of the following laboratory or clinical changes, interrupt the study drug and continue close monitoring and comprehensive hepatic evaluation as described in Sections 8.2.5.1.1 and 8.2.5.1.2.

Participants with normal or near normal baseline (ALT, AST, or ALP less than 1.5×ULN)	**Participants with elevated baseline (ALT, AST, or ALP greater than or equal to 1.5×ULN)**
ALT or AST greater than or equal to 3×ULN with hepatic signs or symptoms[a] **or**	ALT or AST greater than or equal to 2×baseline or greater than or equal to 250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST greater than or equal to 5×ULN for more than 2 weeks **or**	ALT or AST greater than or equal to 3×baseline or greater than or equal to 250 U/L (whichever occurs first) for more than 2 weeks **or**
ALT or AST greater than or equal to 8×ULN **or**	ALT or AST greater than or equal to 4×baseline or greater than or equal to 400 U/L (whichever occurs first) **or**
ALT or AST greater than or equal to 3×ULN and TBL greater than or equal to 2×ULN[b] or INR greater than or equal 1.5 **or**	ALT or AST greater than or equal to 2×baseline or greater than or equal to 250 U/L (whichever occurs first) and TBL greater than or equal to 2×ULN[b] **or**
ALP greater than or equal to 3×ULN **or**	ALP greater than or equal to 3×baseline **or**
ALP greater than or equal to 2.5×ULN and TBL greater than or equal to 2×ULN[b] **or**	ALP greater than or equal to 2.5×baseline and TBL greater than or equal to 2×ULN[b] **or**
ALP greater than or equal to 2.5×ULN with hepatic signs or symptoms[a]	ALP greater than or equal to 2.5×baseline with hepatic signs or symptoms[a]

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] In participants with Gilbert's syndrome the threshold for TBL may be higher.

Interruption or discontinuation of study drug should include these actions:

- While the participant is not receiving the study drug, clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until liver tests normalize or return to approximate baseline values.
- If the hepatic event continues past the anticipated end of the study, that is, data lock, the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study, that is, data lock date.
- All the medical information and tests results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study drug after interruption for a hepatic reason can be considered only in consultation with the Lilly designated medical monitor and only if the liver test results returned to near baseline and if a self-limited non-study-drug etiology is identified. Otherwise, the study drug should be permanently discontinued.

8.2.5.2. Pancreatic Monitoring

Diagnosis of acute pancreatitis

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

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

If acute pancreatitis is suspected, the investigator should

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

Discontinuation for acute pancreatitis

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

Asymptomatic elevation of serum amylase or lipase

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

8.2.5.3. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2.2.

8.2.5.4. Glucose Monitoring

For safety monitoring, blood glucose measurements will be performed using a bedside glucose monitor as specified in the SoA in Section 1.3. Additional safety blood glucose measurements may also be taken during the study as deemed necessary by the investigator.

8.2.5.5. Hypoglycemia

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

Investigators should use the following classification of hypoglycemia:

Level 1 hypoglycemia:

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

Level 2 hypoglycemia:

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

Level 3 hypoglycemia:

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

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

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

Nocturnal hypoglycemia:

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

8.2.6. Pregnancy Testing

In females, a serum and urine pregnancy test will be conducted as indicated in the SoA in Section 1.3.

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

The definitions of AEs, SAEs, and product complaints can be found in Section 10.3.

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.

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest as defined in Section 8.3.3 will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3. For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature or causality. Further information on follow-up procedures is provided in Section 10.3.

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

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

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	Until AE has resolved	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Until AE has resolved	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Until event has resolved	Within 24 hours of awareness	SAE paper form	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A; continues indefinitely	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	90 days after end of study	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
Product complaint associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product complaint form	N/A
Product complaint not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product complaint form	N/A
Updated product complaint information	—	—	As soon as possible upon site awareness	Originally completed Product complaint form with all changes signed and dated by the investigator	N/A
Product complaint (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product complaint form	

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

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

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

- obtain a consent to release information from the pregnant female partner directly, and

- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status, such as presence or absence of anomalies, or indication for the procedure.

Female participants who become pregnant

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

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status, including 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, defined as occurring at less than 20 weeks gestational age, or still birth, defined as occurring at greater than or equal to 20 weeks gestational age, is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study. If the participant is discontinued from the study, 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 and Other Safety Topics

AEs of special interest and other safety topics for this study comprise

- hepatic disorders
- severe GI AEs including nausea, vomiting, and diarrhea
- arrhythmias and cardiac conduction disorders
- major adverse cardiovascular events
- hypotension, orthostatic hypotension, and syncope

- hypoglycemia
- hypersensitivity reaction
- pancreatitis
- acute renal events, and
- gallbladder and biliary tract disorders.

If AEs of special interest and other safety topics are reported, site will be prompted to collect additional details/data.

8.4. Pharmacokinetics

At the visits and times specified in the SoA in Section 1.3, blood samples will be collected to determine the plasma concentrations of LY3502970, [^{14}C]-LY3502970, and total radioactivity.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded.

8.4.1. Bioanalysis

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

Plasma concentrations of LY3502970 will be measured by a validated liquid chromatography mass spectrometry method. Plasma concentrations of total radioactivity will be determined using AMS; plasma concentrations of [^{14}C]-LY3502970 will be determined using high performance liquid chromatography fractionation followed by AMS.

Bioanalytical samples collected during radiolabeled studies will be retained for a maximum of 2 years following last participant visit for the study.

During this time, sample remaining after the bioanalyses may be used for exploratory analyses including but not limited to bioanalytical assay validation, metabolism assessments, or protein binding determinations.

8.5. Pharmacodynamics

Not applicable.

8.6. Genetics

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

See Section 10.5 for information regarding genetic research and Section 10.1.10 for details about sample retention and custody.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

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

9.1. Statistical Hypothesis

There are no formal statistical hypotheses planned to be tested in this study.

9.1.1. Multiplicity Adjustment

No multiplicity adjustments will be made in this study.

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 who were assigned to study intervention, regardless of whether they take any doses.
Safety	All participants who receive at least 1 dose of study intervention whether or not they completed all protocol requirements.
Pharmacokinetic	All participants who receive at least 1 dose of study intervention and have evaluable PK data.

9.2.1. Study Participant Disposition

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

9.2.2. Study Participant Characteristics

The participant's age, sex, weight, height, race, ethnicity, and other demographic characteristics will be recorded.

9.2.3. Treatment Compliance

The date and time of study intervention administration will be recorded and listed.

9.3. Statistical Analyses

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

9.3.1. General Considerations

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

9.3.2. Pharmacokinetic Endpoint Analyses

9.3.2.1. Pharmacokinetic Parameter Estimation

PK analyses will be conducted on data from all participants who receive at least 1 dose of the study intervention and have evaluable PK data.

PK parameter estimates for total radioactivity, [^{14}C]-LY3502970, and LY3502970 will be calculated by standard noncompartmental methods of analysis.

The primary PK endpoint will be the absolute bioavailability of LY3502970.

The secondary PK endpoints will be plasma AUC(0-∞) and C_{max} for total radioactivity, [^{14}C]-LY3502970, and LY3502970. Other noncompartmental parameters, such as AUC(0-t_{last}), t_{max}, apparent $t_{1/2}$, apparent total clearance, and apparent volume of distribution may be reported, where applicable.

9.3.2.2. Pharmacokinetic Statistical Inference

PK parameters will be summarized using descriptive methodology. No formal statistical analysis will be performed.

9.3.3. Safety Endpoint Analyses

9.3.3.1. Clinical Evaluation of Safety

Safety analyses will be conducted for all enrolled participants who received study intervention, whether or not they completed all protocol requirements. The secondary safety endpoint will be the evaluation of TEAEs and SAEs. All study intervention and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

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

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

9.3.3.2. Statistical Evaluation of Safety

No formal statistical analysis will be performed.

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

Approximately 10 participants will be enrolled to target at least 6 participants complete the study. No formal statistical assessment of sample size has been conducted as this study does not have a hypothesis. The sample size chosen for this study is common in human radiolabeled studies and is considered sufficient to achieve the objectives of the study.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for

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

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

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

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

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

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and IRB/IEC consenting guidance.

A copy of the ICF must be provided to the participant and is kept on file.

10.1.3. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

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

The participant must be informed through the informed consent by site personnel that their medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the GDPR.

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, for example, by phone or email, as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly

personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

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

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

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

10.1.5. Data Quality Assurance

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

The investigator must maintain accurate documentation, source data, that supports the information entered in the CRF. Source data includes laboratory tests, medical records, and clinical notes.

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

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

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

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

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

The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in

accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, 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 will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

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

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports or 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.

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

10.1.6. Source Documents

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

Data reported on or entered in the CRF 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 the site confirmation of source data.

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

- for study termination due to discontinuation of further study intervention development
- for site termination due to
    - failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
    - inadequate recruitment, evaluated after a reasonable amount of time, of participants by the investigator, or
    - 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 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. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.1.10. 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.

Sample Type	Custodian	Retention Period
Pharmacokinetic	Sponsor or Designee	2 years
Genetics	Sponsor or Designee	15 years

10.2. Appendix 2: Clinical Laboratory Tests

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

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing, in the table below, the local laboratory must be qualified in accordance with applicable local regulations.

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[b]
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Platelets

Differential WBC absolute counts of:
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Urinalysis[b]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Leukocyte esterase
- Blood
- Nitrite
- Microscopic examination of sediment[c]

Serology[a]
- Hepatitis B surface antigen
- Hepatitis B core antibody
- Hepatitis C antibody
- HIV[d]

Clinical Chemistry[b]
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Phosphate
- Glucose (fasting)
- Urea
- Creatinine[f]
- Total protein
- Albumin
- Total bilirubin
- Direct bilirubin
- Indirect bilirubin
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Gamma-glutamyl transferase
- Amylase
- Lipase

Fasting Lipid Panel[a]
- Total cholesterol
- Triglycerides
- Low density lipoprotein cholesterol
- High density lipoprotein cholesterol

Ethanol testing[b]
Urine drug screen[b]
Pregnancy test (females only)[b,e]
FSH (post-menopausal females only)[a]
Calcitonin[a]

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

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

[a] Performed at screening only.

[b] Performed at the times indicated in the SoA.

[c] Test only if urinalysis result is abnormal.

[d] These tests may be waived if performed within 6 months prior to screening, and if test results are available for "review".

[e] Serum pregnancy test at screening and urine pregnancy test at all other time points.

f Estimated glomerular filtration rate will be calculated from creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation at screening.

10.2.1. Blood Sampling Summary

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

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a,b]	28	1	28
Hematology and chemistry[a]	8	2	16
Plasma LY3502970[c]	2	22	44
Plasma total radioactivity and [^{14}C]-LY3502970[c]	10	21	210
Pharmacogenetics	10	1	10
Total			308
Total for clinical purposes			310

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

b Includes 4 mL required for plasma sample for AMS analysis.

c Three additional samples may be drawn if warranted and agreed upon by the investigator and sponsor.

10.2.2. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection, ideally prior to the next dose after the event, to assess post-event return-to-baseline values.

Timing	Laboratory Test[a]
Collect from 30 minutes to 4 hours after the start of the event. ● Note: The optimal collection time is from 1 to 2 hours after the start of event.	total tryptase

a All samples for hypersensitivity testing will be assayed by the local laboratory. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

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 AE

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, or investigational combination product, whether or not related to the medicinal investigational product or investigational combination product.

Events meeting the AE definition

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

Events <u>NOT</u> meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure, for example, endoscopy, appendectomy. The condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur, social or convenience admission to a hospital.
- Anticipated day-to-day fluctuations of pre-existing disease or condition present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

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

10.3.3. Definition of Product Complaints

Product complaint

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:

- Deficiencies in labeling information, and
- Use errors for device or drug-device combination products due to ergonomic design elements of the product.

Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.

An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

10.3.4. Recording and Follow-up of AE and/or SAE and Product Complaints

AE, SAE, and product complaint recording

When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation, for example, hospital progress notes, laboratory reports, and diagnostics reports, related to the event.

The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the product complaint form.

Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint 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 CRF page for AE/SAE and the product complaint form for product complaints.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis, not the individual signs or 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 one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/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, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB in their assessment.

The investigator **must** review and provide an assessment of causality for each AE/SAE and document this in medical notes.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements 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 SAEs

SAE reporting via SAE 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

SAE 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 evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information, for example, summary or listing of SAEs, from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

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

10.4.2. Contraception Guidance

10.4.2.1. Females

Female participants of childbearing potential are excluded from the trial.

10.4.2.2. Males

The table below 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
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • use highly effective/effective methods of contraception, and must use condoms (if not part of highly effective/effective method of contraception used) during intercourse for the duration of the study, and for 90 days
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 (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women less than 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
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide

Ineffective forms of contraception	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal, • post coital douche • lactational amenorrhea

10.5. Appendix 5: Genetics

Use or analysis of DNA

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

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

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3502970 or study interventions of this class to understand study disease or related conditions.

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

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

The samples will be retained while research on LY3502970 or study interventions of this class or T2DM 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 8.2.5.1 for guidance on appropriate test selection. Testing by an investigator-designated local laboratory should be performed for all testing defined by this guidance. The local laboratory must be qualified in accordance with applicable local regulations.

Hepatic Hematology Panel	**Hepatic Clinical Chemistry Panel**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Alkaline phosphatase isoenzymes
Platelets	Ceruloplasmin
Cell morphology (RBC and WBC)	Copper
Hepatic Coagulation Panel	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Hepatitis A virus (HAV) testing:	Immunoglobulin IgA (quantitative)
HAV total antibody	Immunoglobulin IgG (quantitative)
HAV IgM antibody	Immunoglobulin IgM (quantitative)
Hepatitis B virus (HBV) testing:	Phosphatidylethanol (PEth)
Hepatitis B surface antigen (HBsAg)	**Urine Chemistry**
Hepatitis B surface antibody (anti-HBs)	Drug screen
Hepatitis B core total antibody (anti-HBc)	Ethyl glucuronide (EtG)
Hepatitis B core IgM antibody	**Other Serology**
HBV DNA[b]	Anti-nuclear antibody (ANA)
Hepatitis C virus (HCV) testing:	Anti-smooth muscle antibody (ASMA)[a]
HCV antibody	Anti-actin antibody[c]
HCV RNA[b]	Epstein-Barr virus (EBV) testing:
Hepatitis D virus (HDV) testing:	EBV antibody
HDV antibody	EBV DNA[b]
HDV IgM antibody	Cytomegalovirus (CMV) testing:
Hepatitis E virus (HEV) testing:	CMV antibody
HEV IgG antibody	CMV DNA[b]
HEV IgM antibody	Herpes simplex virus (HSV) testing:
HEV RNA[b]	HSV (Type 1 and 2) antibody
Microbiology Culture:	HSV (Type 1 and 2) DNA[b]
Blood	Liver kidney microsomal type 1 (LKM-1) antibody
Urine	

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

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

[c] Not required if ASMA is tested.

10.7. Appendix 7: 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 ERBs, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required, for example, upon implementation and suspension of changes. All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with 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,"
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

- Telemedicine - Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments.

- Mobile 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.
- Other alternative locations.

Data capture

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

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence.
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMS	accelerated mass spectrometry
AST	aspartate aminotransferase
AUC(0-∞)	area under the concentration versus time curve from zero to infinity
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, GCP, and applicable regulatory requirements.
CRF	case report form: A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CT	computed tomography
ECG	electrocardiogram
ED	early discontinuation
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the ICF directly or through their legally acceptable representatives.
GCP	good clinical practice
GDPR	EU General Data Protection Regulation

GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated ICF.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IV	intravenous
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.

misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription.
OTC	over the counter
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
QTc	corrected QT interval
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.
SUSAR	suspected unexpected serious adverse reactions Refers to an AE occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
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 of maximum observed drug concentration
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

11. References

Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379-2400.

Koizumi M, Takada T, Kawarada Y, et al. JPN guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2006;13(1):25-32.

Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab*. 2016;18(3):203-216.

Steinberg WM, Buse JB, Ghorbani MLM, et al, LEADER Steering Committee; LEADER Trial Investigators. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: Results from the LEADER randomized trial. *Diabetes Care*. 2017a;40(7):966-972. [Erratum in: *Diabetes Care*. 2018 Jul;41(7):1538.]

Steinberg WM, Rosenstock J, Wadden TA, et al. Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: Secondary analyses of pooled data from the SCALE clinical development program. *Diabetes Care*. 2017b;40(7):830-848.

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