Protocol J2A-MC-GZGK (c)

A Multiple Dose Study in Healthy Overweight and Obese Participants to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3502970

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Title Page

Protocol Title: A Multiple Dose Study in Healthy Overweight and Obese Participants to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3502970.

Protocol Number: J2A-MC-GZGK

Amendment Number: GZGK (c)

Compound: LY3502970

Brief Title: A Multiple Dose Study of LY3502970 in Healthy Overweight and Obese Participants.

Study Phase: Phase 1

Sponsor Name: Eli Lilly and Company

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

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment (b)	14-Apr-2022
Protocol amendment (a)	21-Feb-2022
Original Protocol	25-Jan-2022

Amendment (c)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

This amendment was to clarify

- assessment timing
- assessment data entry
- exclusion criteria
- physical examinations
- vital signs, and
- clinical laboratory tests

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	• Single lead ECG changed to Single 12-lead ECG in the Procedure column.	To eliminate the discrepancy between the Schedule of Activities and Section 8.2.3.
Section 1.3. Schedule of Activities	• Additional information added to the comments section of the row for “VAS for appetite”.	To clarify the assessment timing.
Section 5.2. Exclusion Criteria	• Reframed exclusion criterion 5	The exclusion criterion was reframed for better clarity.
Section 5.2. Exclusion Criteria	• Abnormal thyroid stimulating hormone removed from exclusion criterion 11 and minor modification of the sentence was done.	Thyroid stimulating hormone is not deemed a necessary part of the screen and is therefore not listed as a test in Section 10.2 Appendix 2.
Section 5.2. Exclusion Criteria	• Central laboratory changed to “local laboratory” in exclusion criterion 14.	Typographical error
Section 5.2. Exclusion Criteria	• Reframed exclusion criterion 25	The exclusion criterion was reframed for better clarity.
Section 5.2. Exclusion Criteria	• Added “study” to the end of exclusion criterion 37	Typographical error

Section # and Name	Description of Change	Brief Rationale
Section 8.2.1. Physical Examinations	• Brief physical examination changed to "targeted physical examination".	To clarify the nature of the exam as targeted, to the liver, lungs, cardiovascular system and the abdomen, at a minimum, and any other organs as pertinent based on any prevailing symptoms.
Section 8.2.2. Vital Signs	• Blood pressure and pulse rate assessment position changed from supine to seated position.	To be consistent with description in exclusion criterion 9.
Section 8.5. Pharmacodynamics	• Instructions added for the recording of VAS data	To clarify how the VAS data will be recorded.
10.2. Appendix 2: Clinical Laboratory Tests	• Hemoglobin A1c[a] added to the list of clinical laboratory tests	Hemoglobin A1c is mentioned in Section 1.3. Schedule of Activities, but it was missed from this table.
Section 10.2.1. Blood Sampling Summary	• Corrected study number	Typographical error
Section 11. References	• Added two references	References contained in the text clarifying how the VAS data will be recorded.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multiple Dose Study in Healthy Overweight and Obese Participants to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3502970.

Brief Title: A Multiple Dose Study of LY3502970 in Healthy Overweight and Obese Participants.

Rationale:

LY3502970 is an oral non-peptide glucagon-like peptide-1 receptor agonist (GLP-1RA) that is being developed as a daily oral adjunct therapy to diet and physical activity for weight management in adults who have obesity or are overweight with weight-related comorbidities and to improve glycemic control in patients with Type 2 diabetes (T2D).

Unlike the peptide GLP-1RA approved by regulators to date, LY3502970 is a small molecule being developed for daily oral administration.

The primary and secondary objectives of the Study J2A-MC-GZGK (GZGK) will be to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple oral doses of LY3502970 1 mg vs. 2 mg as a starting dose with different titration schemes in 3 cohorts (2 cohorts will start on the 1 mg dose and 1 cohort will start on the 2 mg dose) over a 4-week time period in healthy participants who are overweight or have obesity.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of different dosing regimens	• Incidence of TEAEs and SAEs
Secondary	
• To characterize the PK of multiple doses of LY3502970	• AUC, C_{max}, t_{max}
• To evaluate the PD of different dosing regimens of LY3502970	• Weight change from baseline to 4 weeks and change in appetite (VAS scores)

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

Overall Design

Study GZGK is a Phase 1, multi-center, randomized, investigator and participant-blind, multiple dose study that will be conducted to assess safety, tolerability, PK, and PD of LY3502970 in healthy obese and overweight participants. The study consists of a screening period, a treatment period (randomization to three treatment arms with a randomization ratio of 1:1:1), and a safety follow-up visit.

Brief Summary:

The purpose of this study is to:

- determine the optimal initial starting dose titration scheme to improve tolerability,
- characterize the PK of multiple doses of LY3502970, and
- demonstrate overall safety as well as compare the incidence rates of gastrointestinal (GI) adverse events (AEs) (e.g., nausea and vomiting) over the 4-week study period in healthy participants who are overweight or have obesity and receiving LY3502970 1 mg starting dose vs. 2 mg starting dose with different titration schemes in the three study arms.

The study details include:

- *Screening Period*: Screening may occur within 28 days of the first dose of LY3502970. Participants who are not enrolled within 28 days of screening may be subjected to an additional medical assessment with or without clinical measurements to confirm their eligibility:.
- *Randomization:* A maximum of 72 participants will be randomly assigned to three treatment arms with a randomization ratio of 1:1:1 such that approximately 60 evaluable participants complete the study.
- *Treatment Schedule*: The study duration will be of 4-weeks (28 days). Three cohorts, of which two cohorts (Cohort 2 and 3) will start with the LY3502970 1 mg starting dose, and remaining cohort (Cohort 1) will start with the LY3502970 2 mg starting dose. Each of these 3 study cohorts will have a different titration scheme (Section 1.2).
- *Study visits:*
    - Treatment period: Participants will be admitted to the clinical research unit (CRU) on Day -1 and will undergo assessments as mentioned in Section 1.3.
    - Participants are planned to be discharged on Day 29. However, the duration of stay in the CRU may be extended at the discretion of the investigator for safety or operational reasons.
    - Participants will receive single oral doses of LY3502970 from Day 1 until Day 28.
    - Follow-up: 7 to 14 days post last dose of LY3502970.

Number of Participants:

It is planned that approximately 72 participants will be enrolled, such that 60 participants complete the study (24 participants enrolled per arm for 20 completers participants per arm).

Intervention Groups and Duration:

Participants will be randomized in a 1:1:1 ratio to each of the three study cohorts to receive daily doses of LY3502970 with two cohorts receiving the starting dose of 1 mg and the third cohort receiving the starting dose of 2 mg. Doses of LY3502970 will be titrated up within each of the three cohorts over a time period of 28 days with an end dose of 3 mg in each of the arms.

Data Monitoring Committee: No

1.2. Schema

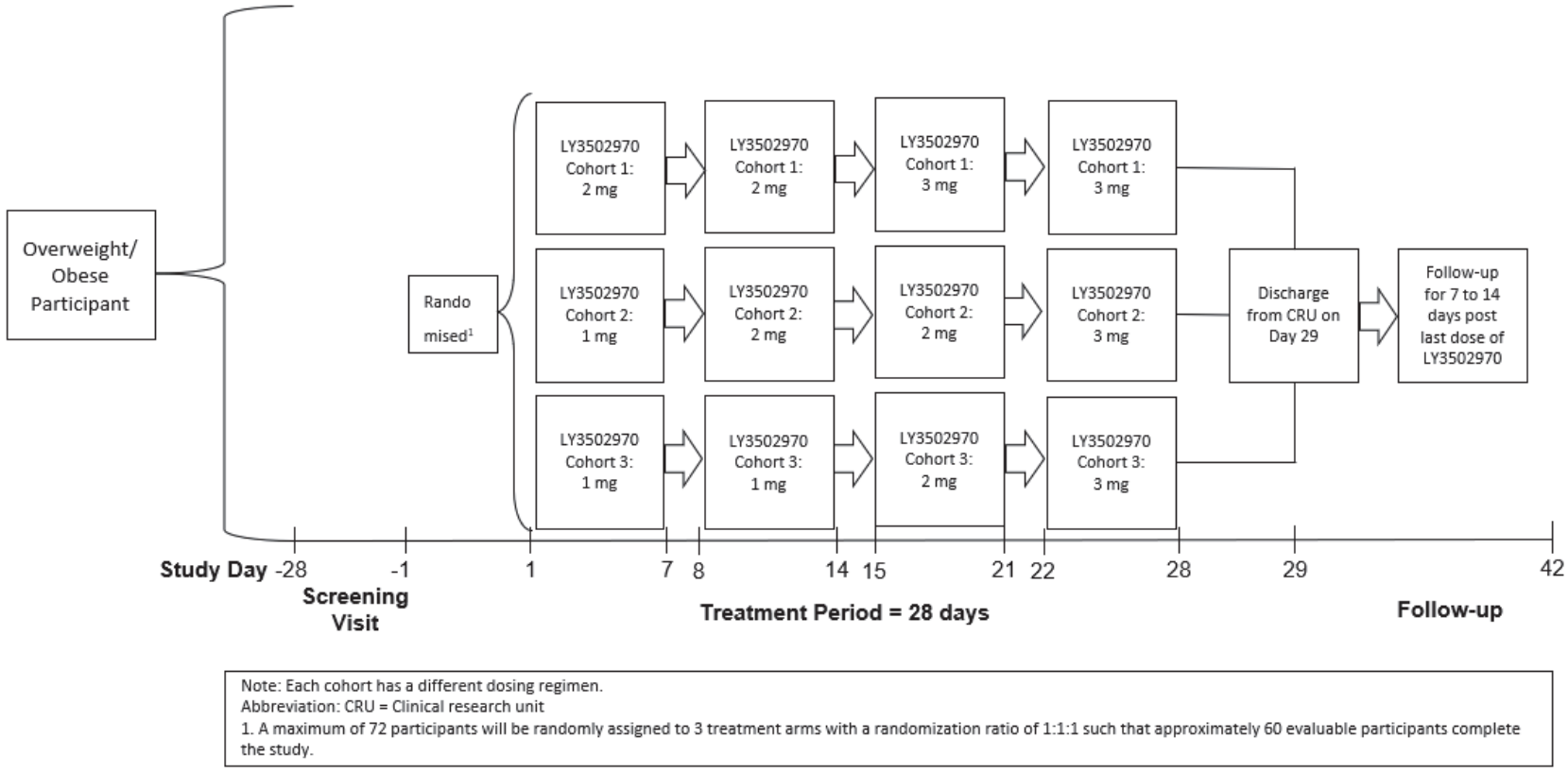

Figure GZGK.1.1. Study Schema.

1.3. Schedule of Activities

Procedure	Screening	Baseline	Treatment Period = 28 days										ED or Follow-up[a]	Comments
Days	**<28 days**	**-1**	**1**	**2-6**	**7**	**8-13**	**14**	**15-21**	**22**	**23-27**	**28**	**29**	**7-14 days**	
Informed Consent	X													
Admission to CRU		X												
Randomization			X											Predose
Weight	X		P			X		X	X			X	X	Weight measured predose on Days 1, 8,15, and 22
Height and body temperature	X													
Vital signs	X		P		X		X		X		X		X	
Clinical Lab Tests	X		P				X				X		X	
Pregnancy	X	X											X	Screening: Serum Other timepoints: Urine
Medical Assessment[b]	X	X	P				X				X		X	Screening: full physical examination Other timepoints: targeted physical examination
Urine drug/ethanol screen[c]	X	X												
Single 12-lead ECG	X		P										X	
VAS for appetite	X	X			X		X		X		X		X	To be collected postdose, prior to the breakfast meal. On Day -1, collected prior to the breakfast meal. At screening and ED/follow-up, collected any time that day.
C-SSRS	X													
Genetic sample		X												

Procedure	Screening	Baseline	Treatment Period = 28 days										ED or Follow-up[a]	Comments
Days	**<28 days**	**-1**	**1**	**2-6**	**7**	**8-13**	**14**	**15-21**	**22**	**23-27**	**28**	**29**	**7-14 days**	
LY3502970 PK			P, 0.5, 1, 2, 4, 6, 8, 12, 16h	24 h (D2)							P, 0.5, 1, 2, 4, 6, 8, 12, 16h	24 h		
HbA1c and fasting plasma glucose	X													
LY3502970 Dosing			X	X	X	X	X	X	X	X	X			
Discharge from CRU												X		

Abbreviations: CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; ED = early discontinuation; HbA1c = hemoglobin A1c; P = predose; PK = pharmacokinetic; VAS = Visual Analogue Scale

[a] Follow-up visit should occur 7 to 14 days after last dosing.

[b] Targeted physical examination for medical assessments at timepoints, other than screening, can be conducted at any time during the scheduled day.

[c] For ethanol screen, an alcohol breathalyzer test is acceptable.

2. Introduction

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

LY3502970 is being developed as a daily oral adjunct therapy to diet and exercise to improve weight loss and glycemic control in adults with type 2 diabetes mellitus (T2DM) and/or obesity or who are overweight.

2.1. Study Rationale

LY3502970 is an oral non-peptide GLP-1RA that is being developed as a daily oral adjunct therapy to diet and physical activity as a therapy for weight management in adults who have obesity or are overweight with weight-related comorbidities and to improve glycemic control in patients with type 2 diabetes (T2D).

Unlike the peptide GLP-1RA approved by regulators to date, LY3502970 is a small molecule being developed for once daily oral administration.

Study J2A-MC-GZGK (GZGK) will investigate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) of multiple oral doses of LY3502970 in healthy overweight and obese participants.

The study rationale is:

- to determine the optimal initial starting dose titration scheme to improve tolerability,
- to investigate the safety, tolerability, and PK of multiple oral doses of 1 mg LY3502970 vs. 2 mg LY3502970 as a starting dose, with up titration to a dose of 3 mg over a 4-week time range in participants who are overweight or have obesity.

2.2. Background

Multiple GLP-1RA therapies are approved. These are most commonly administered subcutaneously either once daily (QD) or once weekly (QW). Even with several different GLP-1RAs approved for use in T2D, the injection remains a barrier for many patients to initiate and to adhere to therapy long-term. The recently approved oral semaglutide (Rybelsus®, Novo Nordisk) is expected to provide patients with a viable alternative to subcutaneous injection delivery. However, its administration requires the patient to adhere to a number of steps to improve bioavailability including: (Hedrington and Davis 2019; Rybelsus package insert, 2019)

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

Therefore, development of additional oral GLP-1RA therapies with improved ease of use remains an unmet need. LY3502970 is an oral GLP-1RA that exhibits:

- the antihyperglycemic and

- weight loss actions of GLP-1.

LY3502970 decreases appetite, delays gastric emptying, and is an insulin secretagogue and as such increases glucose-dependent insulin secretion after a glucose challenge.

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

2.3. Benefit/Risk Assessment

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

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

- first-in-human single-ascending dose (SAD) and multiple-ascending dose (MAD) study (J2A-MC-GZGA [GZGA])
- multiple-dose study (J2A-MC-GZGC [GZGC]) in participants with T2D
- open-label study (J2A-MC-GZGF) to determine the disposition of radioactivity in healthy male participants following administration of LY3502970
- open-label 2-part drug-drug interaction study J2A-MC-GZGG (no dosing with LY3502970), and
- multiple dose study (J2A-MC-GZGJ [GZGJ]) in fed and fasted healthy participants.

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

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

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

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

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of different dosing regimens	• Incidence of TEAEs and SAEs
Secondary	
• To characterize the PK of multiple doses of LY3502970	• AUC, C_{max}, t_{max}
• To evaluate the PD of different dosing regimens of LY3502970	• Weight change from baseline to 4 weeks and change in appetite (VAS scores)

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

4. Study Design

4.1. Overall Design

Study GZGK is a Phase 1, multi-center, randomized, investigator and participant-blind, multiple dose study in healthy obese and overweight participants as presented in the Schema (Section 1.2).

Screening Period

Screening may occur within 28 days of the first dose of LY3502970.

Participants who are not enrolled within 28 days of screening may be subjected to an additional medical assessment with or without clinical measurements to confirm their eligibility.

Randomization

A maximum of 72 participants will be randomly assigned to three treatment arms with a randomization ratio of 1:1:1 such that approximately 60 evaluable participants complete the study.

Treatment Schedule

The treatment arms include as shown in below table:

Days	LY3502970 Cohort 1 (dose = mg)	LY3502970 Cohort 2 (dose = mg)	LY3502970 Cohort 3 (dose = mg)
1-7	2	1	1
8-14	2	2	1
15-21	3	2	2
22-28	3	3	3
Note: Each cohort has a different dosing regimen.			

Study visits

Details of the study visits are presented in the schedule of activities (SOA) (Section 1.3).

The study will include the following visits:

- Treatment period: 28 days
  - Participants will be admitted to the CRU on Day -1 and will undergo assessments as mentioned in Section 1.3.
  - Participants are planned to be discharged on Day 29. However, the duration of stay in the CRU may be extended at the discretion of the investigator for safety or operational reasons.
  - Participants will receive single oral doses of LY3502970 from Day 1 until Day 28.
- Follow-up: 7 to 14 days post last dose of LY3502970
- Participants should follow local guidance and CRU precautions to minimize risk for coronavirus disease 2019 (COVID-19) infection.

Participant replacement

Replacement allowed if:

- Participant is randomized but not administered treatment. This is to ensure enough participants complete the study.
- Participant does not complete the entire treatment period of the study. This replacement is at the discretion of the sponsor.

Replacement not allowed if:

- Participant is withdrawn from the study due to safety reasons deemed related to LY3502970.

4.2. Scientific Rationale for Study Design

Gastrointestinal AEs are common with GLP-1 RA therapy, but there is a wide heterogeneity in incidence between individuals. A strategy of slow escalation of doses for an individual can improve the tolerability profile considerably, allowing patients to reach higher and therefore more effective doses. In this study, we aim to explore the optimal starting dose and dose escalation scheme in the first month of treatment with LY3502970.

This study will evaluate the incidence rate of GI AE (nausea, vomiting) of LY3502970 1 mg starting dose vs. the 2 mg starting dose with different titration scheme over 4 weeks' time range in three cohorts (two cohorts will start with 1 mg dose and one cohort will start with 2 mg dose) in participants who have obesity or are overweight.

Additional information on PK and PD data for the doses tested will be used for future study planning.

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable responses 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

In the Phase 1b studies, nausea was reported in up to 11 % with the 2 mg initial dose in the MAD part and <5% had vomiting in the first week.

In the T2D proof of concept study, at 3 mg starting dose, ~37% patients reported nausea or vomiting in the first week of dosing with reduced frequency in Weeks 2 to 4, and even fewer in the remaining 8 weeks.

Considering the incidence rate of nausea and vomiting for the 2 mg and 3 mg dose in above mentioned MAD trials we see the need to investigate the 1 mg starting dose and resulting titration scheme in the first 4 weeks to optimize tolerability of LY3502970 in the first 4 week of treatment start.

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

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study

A participant is considered to have completed the study if the participant has completed all periods of the study including the safety follow-up visit. A participant who has missing data for a small number of the study activities may still be considered to have completed the study after review by the sponsor team.

5. Study Population

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

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

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only unless otherwise specified, 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 18 years or the legal age of consent in the jurisdiction in which the study is taking place to 70 years of age inclusive, at the time of signing the informed consent

Weight

2) Have a stable body weight for one month prior to randomization (≤5 % body weight gain or loss)

3) Have a BMI of ≥27 kg/m^2

Sex and Contraceptive/Barrier Requirements

4) Male or female

- Women not of childbearing potential and men can participate in this study considering the following:
  - Male participants: Males who agree to use highly effective/effective methods of contraception may participate in this study.
  - Female participants: Women not of childbearing potential (WNOCBP) may participate in this study. Women of childbearing potential (WOCBP) are excluded from participation in this study.
- Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Appendix 10.4.

Note: Hormone replacement therapy in post-menopausal women is allowed, but women must be on stable therapy for three months prior to screening.

Informed Consent

5) Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Have any type of diabetes with a hemoglobin A1c (HbA1c) ≥6.5 %, fasting blood sugar level > 120 mg/dL or a history of random blood sugar level of 200 mg/dL.
2. Have a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder, for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder within the last two years of screening

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

3. Have a lifetime history of suicide attempt
4. On the Columbia-Suicide Severity Rating Scale (C-SSRS) prior to randomization:
   - a "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS

     or
   - a "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS

     or
   - a "yes" answer to any of the suicide related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS **and** the ideation or behavior occurred within the past month.
5. Have
   - a history or presence of acute or chronic pancreatitis
   - an elevation in serum lipase or amylase greater than 3 times the upper limit of normal (ULN).

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

6. Fasting serum triglyceride level of >500 mg/dL at screening
7. Have obesity induced by other endocrine disorders such as Cushing's syndrome or Prader-Willi syndrome
8. Have
   - known clinically significant gastric emptying abnormality, for example, severe gastroparesis or gastric outlet obstruction,
   - undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or
   - chronically take medications that directly affect GI motility

9. Have an abnormal blood pressure and/or pulse rate, including
    - seated systolic BP ≥160 mm Hg, or
    - seated diastolic BP ≥100 mm Hg,

   or otherwise deemed to be clinically significant by the investigator at screening.

10. Have a known self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma

11. Evidence of hypothyroidism or hyperthyroidism based on clinical evaluation that, in the opinion of the investigator, would pose a risk to participant safety. Participants who are on a stable dose of thyroid replacement therapy for at least the prior 3 months and who are anticipated to remain on this dose throughout the study period may be included in the study.

12. Have had any of the following within the last six months prior to screening:
    - myocardial infarction (MI),
    - unstable angina,
    - coronary artery bypass graft,
    - percutaneous coronary intervention (diagnostic angiograms are permitted),
    - transient ischemic attack
    - cerebrovascular accident (stroke) or decompensated congestive heart failure, or
    - currently have New York Health Association Class III or IV heart failure.

13. Have an ECG abnormality that may represent a safety risk at the discretion of the Investigator

14. Have signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the local laboratory during screening
    - alanine aminotransferase (ALT) level >3.0 X ULN for the reference range (as determined by the local laboratory at study entry)
    - alkaline phosphatase (ALP) level >1.5 X ULN for the reference range, or
    - total bilirubin level (TBL) >1.5 X ULN for the reference range (except for cases of known Gilbert's Syndrome)

15. Have a serum calcitonin level at screening of ≥ 20 ng/L

16. 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 five years prior to screening

17. Have evidence of human immunodeficiency virus (HIV), positive HIV antibodies or both historically or at screening

18. Evidence of hepatitis B and/or positive hepatitis B surface antigen.
19. Hepatitis C as defined by presence of hepatitis C virus (HCV) ribonucleic acid (RNA) or positive hepatitis C antibody (anti-HCV). Participants treated for hepatitis C (and diagnosed as cured) must have an RNA test at screening and also be RNA negative for at least three years prior to screening in order to be eligible for the study.
20. Have a history of a transplanted organ; corneal transplants (keratoplasty) are allowed.
21. Have donated blood of more than 500 mL within the previous 8 weeks of screening or a blood transfusion or severe blood loss within three months, or have known hemoglobinopathy, for example, hemolytic anemia or sickle cell anemia, or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with HbA1c measurements
22. Have evidence of a significant, active autoimmune abnormality, for example, lupus or rheumatoid arthritis, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next six months
23. Have evidence of significant active, uncontrolled medical condition or history of any medical problem capable of constituting a risk when taking the study medication or interfering with the interpretation of data, as judged by the investigator at screening
24. Have difficulty swallowing capsules

Prior/Concomitant Therapy

25. Unless otherwise specified, have had a dose change to concomitant medications within a period of 1 month prior to randomization
26. Have any exposure to dulaglutide, other GLP-1 analogs, or other related compounds within three months of screening or any prior history of hypersensitivity or allergies to these medications. Have known or suspected hypersensitivity to study medication, to selective GLP-1 RAs or GIP/GLP-1 or GLP-1/Gcg dual receptor agonists.
    - Participants who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability should not be randomized.
27. Have taken within one month prior to dosing of LY3502970 (prescribed or over the counter) or alternative remedies (including herbal/nutritional supplements) intended to promote weight loss

    Examples include, but are not limited to:

    - Saxenda® [liraglutide 3.0 mg] or other GLP-1RA
    - Xenical® [orlistat]
    - Meridia® [sibutramine]
    - Acutrim® [phenylpropanolamine]
    - Sanorex® [mazindol]
    - Adipex® [phentermine]
    - BELVIQ® [lorcaserin]

- Qsymia™ [phentermine/topiramate combination]
- Contrave® [naltrexone/bupropion]
- Wegovy™ (semaglutide 2.4 mg), and
- other similar body weight loss medication, including over-the-counter (OTC) medications, for example, allī®

28. Are receiving or have received within three months of screening chronic (>2 weeks) systemic glucocorticoid therapy, excluding topical, intraocular, intranasal, single intraarticular injection, or inhaled preparations, or have received such therapy within 4 weeks immediately prior to screening
29. CCI [redacted]
30. Have a history of use of marijuana or tetrahydrocannabinol (THC)-containing products within three months of enrollment or unwillingness to abstain from marijuana or THC-containing products use during the study

    Note: If a participant has used cannabidiol oil during the past three months but agrees to refrain from use for the duration of the study, the participant can be enrolled.
31. Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females).
32. Evidence of regular use of known drugs of abuse in the opinion of the investigator
33. Use of metformin, or any other glucose-lowering medication, whether prescribed for polycystic ovarian syndrome or diabetes prevention, is not permitted
34. Are currently taking a central nervous system stimulant, for example, Ritalin-SR with the exception of caffeinated beverages at screening

Prior/Concurrent Clinical Study Experience

35. Are currently enrolled in a clinical study involving an Investigational Product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study
36. Have participated, within the last 90 days, in a clinical study and received treatment, whether active or placebo. If the study involved an IP, at least five elimination half-lives or 90 days, whichever is longer, should have passed before dosing with LY3502970
37. Have previously completed or withdrawn from this study

Other Exclusions

38. Are women of child-bearing potential
39. Are women, acting as a surrogate, who are currently pregnant or breastfeeding, or who intend to become pregnant or to breastfeed at any time during the study or within 20 weeks after receiving the last dose of study drug

40. Are CRU/investigative site personnel directly affiliated with this study or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
41. Are employees of Eli Lilly and Company (Lilly) or are employees of a third-party organization involved in the study which requires exclusion of their employees
42. Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study

Other Medical Conditions

43. Have any other conditions (including known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol

5.3. Lifestyle Considerations

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

5.3.1. Meals and Dietary Restrictions

CCI [redacted]

On all dosing days (Days 1 to 28), participants need to be fasting for 8 hours prior to taking an oral dose of LY3502970.

On Days 1 and 28, no food will be allowed for at least 4 hours after LY3502970 dose. On other days (Days 2 to 27), participants may consume their meal 30 minutes after LY3502970 dose. On Days 1 and 28, fluids will be restricted from 1 hour prior to and until 1 hour after LY3502970 dosing, except for the water required for dose administration. Water may be consumed freely at all other times.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

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

No alcohol will be allowed at least 24 h before each CRU admission and outpatient visit and throughout the duration of each CRU visit. Between CRU visits, daily alcohol should not exceed three units for males and two units for females.

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

5.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity/exercise during the study; strenuous exercise within 24 hours prior to all visits should be avoided if possible.

When certain study procedures are in progress at the site, participants may be required to remain recumbent or seated.

5.4. Screen Failures

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

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

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

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

Not applicable.

6. Study Intervention and Concomitant Therapy

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

6.1. Study Intervention Administered

Intervention Name	**LY3502970**
Type	Drug
Dose Formulation	Capsule
Unit Dose Strength(s)	1, 2, 3 mg
Dosage Level(s)	1, 2, 3 mg QD (as 1 capsule)
Route of Administration	Oral
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Study intervention will be provided in bottles of capsules of different strength. Each bottle will be labeled as required per country requirement.
Abbreviations: IMP = Investigational Medicinal Product; NIMP = Non-Investigational Medicinal Products; QD = once daily	

Participants will be administered study drug orally with approximately 240 mL of room temperature water. See Section 5.3.1 for details on fasting requirements prior to taking an oral dose of LY3502970.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an Interactive Web Response Systems (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits summarized in SoA.

Participants will be randomly assigned to study intervention in a randomization ratio of 1:1:1 to the study treatment groups, including 24 participants per arm to target 20 completers participants per arm.

All doses of study drug capsules appear the same.

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

If a participant's study treatment assignment is unblinded, the participant must be discontinued from the study, unless the Investigator obtains specific approval from a Lilly clinical research physician/clinical research scientist (CRP/CRS) for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

In case of an emergency, the Investigator has the sole responsibility of determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. Where feasible and when the timing of the emergent situation permits, the Investigator should attempt to contact the Lilly medical monitor before unblinding a participant's treatment assignment. If the Investigator decides that unblinding is warranted, it is the responsibility of the Investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

If an investigator, CRU personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor CRP for the participant to continue in the study.

6.4. Study Intervention Compliance

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

6.5. Dose Modification

Dose modification will not be permitted in this study.

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

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

6.7. Treatment of Overdose

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

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until LY3502970 can no longer be detected systemically (at least 7 days). Refer to Section 8.3 for reporting details.
3. Obtain a plasma sample for PK analysis as soon as possible after the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the electronic case report form (eCRF).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Allowed concomitant medications should be taken according to label directions.

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

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

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


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

6.8.1. Management of Participants with Gastrointestinal Symptoms

In the Phase 1 programs, the most commonly reported TEAEs for participants receiving LY3502970 were nausea, vomiting, and diarrhea. To mitigate GI symptoms and manage participants with intolerable GI AEs, the Investigator should:

- Provide alternative meals to participant(s) if they cannot tolerate the standard meal provided. Proper documentation of meal adjustment will be provided in the meal log and communication will be provided to sponsor if related to AE.
- Prescribe symptomatic medication (for example, antiemetic or antidiarrheal medication) per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the eCRF.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

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

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will be discontinued from the study (Section 7.2). See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Possible reasons leading to permanent discontinuation of investigational product include:

- Participant decision
  - the participant or the participant's designee (for example, parents or legal guardian) requests to discontinue investigational product
- Investigator decision
  - the Investigator decides that the participant should be discontinued from the study medication
- Participants will be discontinued from the investigational product in the following circumstances:
  - Diagnosis of cirrhosis after randomization.
  - Pancreatitis or pancreatic cancer.
  - Diagnosis of medullary thyroid cancer (MTC) after randomization,
  - Diagnosis of an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization.
  - Any TEAE, SAE, or clinically significant laboratory value for which the Investigator believes that permanent study drug discontinuation is the appropriate measure to be taken.
  - A female participant becomes pregnant, and
- Significant noncompliance with the protocol.

If study drug is permanently discontinued, the participant should follow early termination procedures as per Section 1.3 (Schedule of Activities).

7.1.1. Liver Chemistry Stopping Criteria

The study drug should be interrupted or discontinued if one or more of these conditions occur:

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

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

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

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

7.1.2. Temporary Discontinuation

No dose modification including temporary discontinuation is allowed, unless directed by protocol language (Section 6.5, Section 7.1.1, and Section 8.3.3.2).

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,
- at the request of the participant's designee (for example, parents or legal guardian),
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons,
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, and

- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

Participants will be discontinued under the following circumstances:

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

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA (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 the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented, and the

participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Section 1.3 lists the SOA, detailing the study procedures and their timing (including tolerance limits for timing). The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.
- Appendix 2 (Section 10.2) lists the laboratory tests that will be performed for this study.
- Appendix 2 (Section 10.2.1) provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.
- Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

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

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded.
- A targeted physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

Medical assessments will be conducted according to the SoA (Section 1.3) and as clinically indicated.

8.2.2. Vital Signs

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

8.2.3. Electrocardiograms

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

Single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

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

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

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

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the participant for symptoms (e.g., palpitations, near syncope, and syncope) to determine whether the participant can continue in the study. The investigator or qualified designee is responsible for determining if any change in participant management is needed and must document the 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

Clinical laboratory tests include hematology, clinical chemistry, and urinalysis.

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within seven days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.5. Pregnancy Testing

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

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Participants who have obesity or are overweight are at increased risk for depression (Luppino et al. 2010). Depression can increase the risk for suicidal ideation and behavior. Therefore, study participants will be screened at trial entry and observed during the study for depression, suicidal ideation, and behavior.

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

Baseline assessment of suicidal ideation and behavior will be monitored during the study GZGK using C-SSRS.

8.2.7. Safety Monitoring

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

- trends in safety data,
- laboratory analytes, and
- adverse events.

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

Safety monitoring may include review of hepatic, pancreatic, cardiovascular, thyroid C-cell function, and renal safety data.

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

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

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

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and adverse events of special interests (AESIs) (as defined in Section 8.3.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	signing of the informed consent form (ICF)	participation in study has ended	As soon as possible upon site awareness	AE eCRF	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 informed consent form (ICF)	start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE# and SAE updates – after start of study intervention	start of intervention	participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	90 days or 3 months after last participant visit	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; eCRF = electronic case report form; NA = Not Applicable; PC = product complaint; SAE = serious adverse event.

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After learning of a pregnancy in the female partner of a study participant, the investigator will:
  - obtain a consent to release information from the pregnant female partner directly, and
  - within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

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

Female participants who become pregnant

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

8.3.3. Adverse Events of Special Interest

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

Other AESIs (Section 8.2) for this program include:

- cardiovascular events,
- hypoglycemia,
- hepatic events, and

- pancreatic events.

The following are additional AESI:

- hypoglycemia (Level 2 and 3),
- severe persistent hyperglycemia,
- thyroid malignancies and C-cell hyperplasia,
- hepatobiliary disorders,
- severe GI AEs, and
- acute renal events.

Sites should collect additional details and data regarding these AEs, as instructed on the applicable eCRFs, and detailed below.

8.3.3.1. Hypoglycemia

Upon ICF signing, all participants will be educated about the signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia.

Study drug discontinuation should be considered for recurrent hypoglycemia.

All hypoglycemic episodes will be recorded on a specific eCRF and should not be recorded as AEs unless the event meets serious criteria. If a hypoglycemic event meets severe criteria (see definition below), it should be recorded as serious on the AE and SAE eCRFs, and reported to Lilly as an SAE.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the blood glucose [BG] values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips) in accordance with the 2020 American Diabetes Association position statement on glycemic targets (ADA 2020) as below. Level 2 and Level 3 hypoglycemia events are considered as safety topics of special interest:

Level 1 hypoglycemia:

Glucose <70 mg/dL (3.9 mmol/L) and ≥ 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 <54 mg/dL (3.0 mmol/L): This is also referred to as documented or BG confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence of absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or

unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

Nocturnal hypoglycemia:

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

8.3.3.2. Pancreatitis

Diagnosis of acute pancreatitis

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

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

If acute pancreatitis is suspected, the investigator should:

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

Discontinuation for acute pancreatitis

If acute pancreatitis is suspected by the investigator, the participant must temporarily discontinue use of the IP. Afterwards, if pancreatitis is confirmed, the IP must be permanently discontinued, and the participant needs to be followed throughout the duration of the study. If the case is not confirmed, then the participant can restart the IP if the investigator deems as clinically appropriate as described in Section 6.5 (Dose Modification).

Asymptomatic elevation of pancreatic amylase and/or lipase

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

8.3.3.3. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or MEN2 will be excluded from the study. Participants who are diagnosed with MTC and/or MEN2 during the study will have study drug stopped and should continue follow-up with an endocrinologist

The assessment of thyroid safety during the trial will include reporting of any case of thyroid neoplasms (including MTC, papillary carcinoma, and others) and measurements of calcitonin. These data will be captured in specific eCRFs.

8.3.3.4. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG, which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 10.3.2 must be reported as SAEs.

8.3.3.5. Hepatobiliary Disorders

All events of TE biliary colic, cholecystitis, cholelithiasis, or other suspected events related to acute gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 10.6 (Appendix 6).

8.3.3.6. Severe Gastrointestinal Adverse Events

LY3502970 may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic or antidiarrheal use will be collected in the AE and concomitant medications eCRFs, respectively. For detailed information concerning the management of GI AEs, please refer to Section 6.8.1.

8.3.3.7. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute renal failure or worsening of preexisting chronic renal failure. Gastrointestinal AEs have been reported with LY3502970 including nausea, diarrhea, and vomiting. This is consistent with other GLP-1R agonists (Aroda and Ratner 2011). The events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Participants should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

8.4. Pharmacokinetics

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

8.4.1. Bioanalysis

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

Concentrations of LY3502970 will be assayed using a validated liquid chromatography tandem mass spectrometry method. Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism and/or protein-binding work.

8.5. Pharmacodynamics

Effect of LY3502970 on body weight will be evaluated each week during the titration (see Sections 8.2.1 and 9.3.3).

At the times specified in the SoA (Section 1.3), the participative rating of appetite sensations will be measured using a 100-mm Appetite Assessment VAS for parameters of hunger, fullness, satiety, and prospective food consumption.

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

“How hungry do you feel right now?”

“How satisfied do you feel right now?”

“How full do you feel right now?”

“How much food do you think you could eat right now?”

A staff member will use a caliper or ruler to measure the distance in millimeters from 0 to the mark that the participant placed on the Appetite Assessment VAS and record the measurement in the eCRF. Overall appetite score is calculated as the average of the 4 individual scores (van Can et al. 2014):

(satiety + fullness + [100 − prospective food consumption] + [100 − hunger]) / 4.

A higher overall appetite score indicates less appetite, and a lower score indicates more appetite.

8.6. Genetics

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

See Section 10.5 (Appendix 5) for information regarding genetic research and Section 10.1.12 (Appendix 1) for details about sample retention and custody.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

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

The study results may be pooled with the results of other studies for safety, tolerability, PK, and PD analysis purposes to better understand the ideal starting dose as well as titration scheme for future trials. Analyses will be fully detailed in the SAP.

9.1. Statistical Hypotheses

The primary study objective is to evaluate the safety and tolerability of different dosing regimens of LY3502970 in the healthy overweight and obese participants.

The secondary study objective is to:

- characterize the PK of multiple doses of LY3502970
- evaluate the PD of different dosing regimens of LY3502970.

No formal statistical hypothesis testing will be conducted in this study.

9.1.1. Multiplicity Adjustment

No multiplicity adjustments will be made due to the nature of the 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 assigned to treatment.
Safety Analysis set	All participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis Set	All enrolled participants who received LY3502970 and have evaluable PK samples.

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

9.3. Statistical Analyses

9.3.1. General Considerations

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.1, unless otherwise stated, and all CIs will be given at a 2-sided 90% level. Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data may be conducted as deemed appropriate.

Safety analyses will be conducted on the Safety Analysis Set. Additional pharmacokinetic analyses will be conducted on the PK Analysis Set. Exploratory analyses of the data may be conducted as deemed appropriate.

9.3.2. Primary Endpoint Analysis - Safety Analyses

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

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

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

All IP and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of AEs for each treatment will be presented by severity and by association with IP as perceived by the Investigator. Adverse events reported to occur prior to the first study dose will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities. The number of SAEs will be reported.

Summaries and analyses for incidence and severity of GI TEAEs (e.g. nausea, vomiting, diarrhea, nausea and vomiting combined, and 3 events combined), will be provided by each treatment.

9.3.3. Secondary Endpoint Analysis

Pharmacokinetic parameter estimates for LY3502970 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis of LY3502970 will be area under the plasma concentration-time curve from 0 to 24 hour (AUC_{0-24}), maximum observed concentration (C_{max}), and time to maximum observed concentration (t_{max}). Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported. If deemed necessary, additional model-based analysis may be performed. All PK parameters will be listed and summarized using descriptive statistics on the pharmacokinetic analysis set.

Body weight scores will be summarized with respect to observed values and change from baseline values to 4 Weeks by treatment using descriptive statistics.

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

9.3.4. Other Analyses

Details for other analyses may be documented in the SAP.

9.4. Interim Analysis

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

9.5. Sample Size Determination

Approximately 72 participants will be randomized such that 60 participants will complete the study (24 participants enrolled per arm for 20 completers subjects per arm).

The sample size is customary for Phase 1 studies evaluating safety and tolerability parameters and is considered sufficient to evaluate the primary objective of this 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 following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, 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 the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
  - 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. Financial Disclosure

Not applicable

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or the participant's legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Committees Structure

Not applicable

10.1.6. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

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

Reports

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

Data

The Sponsor does not proactively share data from Phase 1 clinical studies. Requests for access to Phase 1 clinical study 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.

10.1.7. 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 may include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (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).

- Study monitors will perform ongoing source data verification 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 (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

An electronic data capture system (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.

This study uses a web-based data collection system for CRF data collection. The investigator will have continuous access to the EDC system during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data collected via the sponsor-provided data capture systems will be stored at third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. 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/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.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. 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.

The first act of recruitment is the first participant to enter screening.

Study or Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.10. 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.

10.1.11. Investigator Information

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

10.1.12. Long-Term Sample Retention

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

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

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

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

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

Sample Retention Period

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

Abbreviation: PK = pharmacokinetics.

[a] Retention periods may differ locally

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the local laboratory, unless specified.
- In circumstances where the Sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

Hematology	**Clinical Chemistry**
Hematocrit	Sodium
Hemoglobin	Potassium
Hemoglobin A1c[a]	Bicarbonate
Erythrocyte count (RBC)	Chloride
Mean cell volume	Calcium
Mean cell hemoglobin	Phosphate
Mean cell hemoglobin concentration	Glucose, fasting
Leukocytes (WBC)	Urea
Differential WBC absolute counts of:	Total protein
Neutrophils	Albumin
Lymphocytes	Amylase
Monocytes	Lipase
Eosinophils	Creatinine
Basophils	Lipid panel[a]
Platelets	Total cholesterol
Urinalysis	Triglycerides
Specific gravity	Low-density lipoprotein cholesterol
pH	High-density lipoprotein cholesterol
Protein	Liver panel
Glucose	Total bilirubin
Ketones	Direct bilirubin
Bilirubin	Indirect bilirubin
Urobilinogen	Alkaline phosphatase
Blood	Aspartate aminotransferase
Nitrite	Alanine aminotransferase
Microscopic examination of sediment[b]	
Leukocytes	
Serology[a]	Calcitonin[a]
Hepatitis B surface antigen	Pregnancy test[c]
Hepatitis B core antibody	Follicle-stimulating hormone[a, d]
Hepatitis C antibody	
HIV	

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

Note: Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Inclusion or omission of calculated values will not be considered as a protocol deviation.

[a] Performed at screening only.

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

[c] For females only: Serum pregnancy tests will be performed at screening and follow-up with urine pregnancy testing at all other times indicated in the Schedule of Activities (Section 1.3).

[d] For females with spontaneous amenorrhea for 6 to 12 months, if needed, to confirm postmenopausal status.

10.2.1. Blood Sampling Summary

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

Protocol J2A-MC-GZGK Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	26	1	26
Safety laboratory tests[a]	17	5	85
Pharmacokinetics	2	20	40
Blood discard for cannula patency	0.3	18	5.5
Pharmacogenetics	10	1	10
Total			166.5
Total for clinical purposes (rounded up to nearest 10 mL)			170

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

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. • An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

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

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

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect • Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
f. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 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 PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints: o Deficiencies in labeling information, and o 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 studies are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements. • Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed. • An event may meet the definition of both a product complaint and an AE/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 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 Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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 adverse event 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 adverse event 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 adverse event 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 a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 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(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of 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 Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor or designee with a copy of any post-mortem 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 comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a 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	Females are considered a woman of childbearing potential if they have • had at least 1 cycle of menses, or • Tanner 4 breast development. Any amount of spotting should be considered menarche. If Tanner staging of breasts is performed as part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical study regarding Tanner staging.
Women not of childbearing potential	Females are considered women not of childbearing potential if they • have a congenital anomaly, such as Mullerian agenesis • are infertile due to surgical sterilization, or • are post-menopausal. Examples of surgical sterilization, include hysterectomy, bilateral oophorectomy, and tubal ligation.
Postmenopausal state	The postmenopausal state should be defined as: • a woman at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note, or • a woman at least 40 years old and up to 55 years old with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL, or • A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy. *Women should not be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.
Reproductive toxicology studies	Embryo-fetal studies are toxicity studies in pregnant animals designed to identify abnormalities in the development of fetuses, which could indicate potential for teratogenicity in humans. The relevant dosing period is during organogenesis.

10.4.2. Contraception Guidance

Topic	Guidance
For all men	Should refrain from sperm donation for the duration of the study and for 90 days or 3 months following last participant visit.
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study and for 90 days or 3 months following last participant visit.
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception.

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

Methods	**Examples**
Highly effective contraception	• Combination oral contraceptive pill and minipill • Implanted contraceptives • Injectable contraceptives • Contraceptive patch (only women <198 lbs or 90 kg) • Total abstinence • Vasectomy (if only sexual partner) • Fallopian tube implants (if confirmed by hysterosalpingogram) • Combined contraceptive vaginal ring • Intrauterine devices
Effective contraception	• Male or female condoms with spermicide • Diaphragms with spermicide or cervical sponges • Barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: The barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.
Ineffective forms of contraception	• Spermicide alone • Immunocontraceptives • Periodic abstinence • Fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, and symptothermal) • withdrawal • Postcoital douche • Lactational amenorrhea

10.5. Appendix 5: Genetics

Use/Analysis of Deoxyribonucleic Acid

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- Deoxyribonucleic acid samples will be used for research related to LY3502970 or T2D and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3502970 and/or interventions of this drug class and T2D. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3502970 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on LY3502970 continues but no longer than 15 years or other period as per local requirements.

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

Close hepatic monitoring

Laboratory tests, including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

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

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

Comprehensive hepatic evaluation

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

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms[a], or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms[a], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

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

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

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

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

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

Article I. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
- In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests

Article II. Elevated TBL to ≥ 2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
- In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline

Article III. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
- In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests

Article IV. Hepatic event considered to be a serious adverse event (SAE)

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

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

Diagnosis of acute pancreatitis

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

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

If acute pancreatitis is suspected, the investigator should

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

Discontinuation for acute pancreatitis

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

Asymptomatic elevation of serum amylase and/or lipase

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

10.7. 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 the local regulations.

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

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

Considerations for Making a Change

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

Informed Consent

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

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

Changes in Study Conduct during Exceptional Circumstances

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

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

Remote Visits

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

> **Telemedicine**: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include but are not limited to those described in the safety follow-up only.
> **Mobile healthcare**: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include but are not limited to those described in the safety follow-up visit only.

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

Documentation

Changes to study conduct will be documented.

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

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

10.8. Appendix 8: Diet Suggestions for Sites without Programs

Diet recommendations are based on the World Health Organization (WHO 2020) for everyone which is based on a Mediterranean eating pattern.

The Mediterranean eating pattern for a healthy diet consists of:

- legumes (for example, lentils and beans)
- nuts
- whole grains (for example, unprocessed wheat, maize, millet, oats, and brown rice)
- at least 5 portions of fruit and vegetables per day (excluding potatoes, sweet potatoes, cassava, and other starchy roots)
- less than 10% of total energy intake from free sugars (equivalent to 50 g or 12 level teaspoons), but ideally less than 5% of total energy intake. Free sugars are sugars added to foods and drinks, as well as sugars present in honey, syrups, fruit juices, and fruit juice concentrates
- less than 30% of total energy intake from fats. Unsaturated fats are preferred over saturated fats. Unsaturated fats are found in fish, avocado, nuts, sunflower, canola, and olive oils. Consumption of saturated fats, which are fats in fatty meat, butter, palm and coconut oil, cream cheese, ghee, and lard, should be reduced to less than 10% of total energy intake. Trans fats, which are found in industrially produced foods, should be avoided, and
- salt intake should not be more than 5 g (about 1 teaspoon) per day and should be iodized.

10.9. Appendix 9: Protocol Amendment History

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

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment (b)	14-Apr-2022
Protocol amendment (a)	21-Feb-2022
Original Protocol	25-Jan-2022

Amendment (b)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

Protocol was amended to clarify:

- blood pressure and pulse rate cut-offs to better characterize the exclusion criterion for participants with poorly controlled hypertension
- specifications and adjustments related to screening tests, medical assessments, and other procedures, in the Schedule of Activities and eligibility criteria, and
- meal specifications and adjustments, if required, for participants to mitigate and manage gastrointestinal symptoms associated with LY3502970.

Additional minor editorial changes have been made to the protocol that are not reflected in the table below.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 Synopsis	• Corrected title to 'Objectives and Endpoints'.	The table for 'Objectives and Endpoints' mentions no estimands for the endpoints.
Section 1.3 Schedule of Activities	• Added a row to indicate randomization to be conducted on Day 1, after admission. • Added footnote to indicate that targeted physical examination can be conducted at any time during the scheduled day. • Added footnote to indicate that an alcohol breathalyzer test is acceptable for an ethanol screen. • Added comment that VAS assessments for appetite to be collected post-dose, prior to the breakfast meal. • Replaced 'pre-dose' with 'P', where applicable.	Added as per site's recommendations to improve clarity regarding screening tests, medical assessments, and other procedures.

Section # and Name	Description of Change	Brief Rationale
Section 3 Objectives and Endpoints	• Corrected section heading to 'Objectives and Endpoints'.	The table for 'Objectives and Endpoints' mentions no estimands for the endpoints.
Section 5.2 Exclusion Criteria	• Specified blood pressure and pulse rate cut-offs in exclusion criterion 9.	To better characterize the exclusion criterion for participants with poorly controlled hypertension.
	• Specified local laboratory in exclusion criterion 14.	To clarify that hepatic tests will be conducted by local laboratory at screening.
	• Added 'before dosing with LY3502970' in exclusion criterion 36.	To clarify the time gap between any previous study the participant was involved in and the current study.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	• Removed the statement: 'Blinding will be maintained throughout the conduct of the study as described in the separate blinding plan.'	A separate blinding or unblinding plan is out of scope for Lilly's phase I trials, and therefore, no separate blinding plan will be created.
Section 6.8.1 Management of Participants with Gastrointestinal Symptoms	• Updated language for meal specifications and adjustments, if required, for participants.	To mitigate GI symptoms and manage participants with intolerable GI AEs.
Section 10.1.1 Regulatory and Ethical Considerations	• Updated language on investigator's responsibilities.	Updated as per EMA's "Guidance for the notification of serious breaches of Regulation No 536/2014 or the clinical trial protocol.".
Section 10.3.1 Definition of AE – Events Meeting the AE Definition	• Updated language on which events can be considered as AEs.	To accommodate medication error, misuse, or abuse of IMP as an AE.
Section 10.10 – Appendix 10: Abbreviations and Definitions	• Included abbreviation and definition of IMP.	Updated as 'IMP' has been mentioned in the protocol.

Abbreviations: AE = adverse events; GI = gastrointestinal; IMP = investigational medicinal product; P = pre-dose; VAS = visual analog scale.

Amendment (a)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

Protocol was amended to clarify

- fasting requirements along with meals and dietary restrictions, and
- solvent details to be used for the study drug.

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Revised footnote from Early Discontinuation visit to Follow-up visit	Clarifies follow-up visit should occur 7 to 14 days after last dosing.
Section 5.2. Exclusion Criteria	Deleted wording "diabetic" from "known clinically significant gastric emptying abnormality, for example, severe diabetic gastroparesis or gastric outlet obstruction	The wording "diabetic" was inadvertently added to the previous version of the protocol.
Section 5.3.1. Meals and Dietary Restrictions	Added below information. • Participants would need to be fasting for 8 hours prior to taking an oral dose of LY3502970. • On Days 1 and 28, no food will be allowed for at least 4 hours after LY3502970 dose. On other days (Day 2 to 27), participants may consume their meal 30 minutes after LY3502970 dose. On Days 1 and 28, fluids will be restricted from 1 hour prior to and until 1 hour after LY3502970 dosing, except for the water required for dose administration. Water may be consumed freely at all other times. Added "days" to below statement. 	Clarifies fasting requirements along with a minor editorial correction to the sentence on meals and dietary restrictions.

Section # and Name	Description of Change	Brief Rationale
	CCI	
Section 6.1. Study Intervention Administered	Added below information. • Participants will be administered study drug orally with approximately 240 mL of room temperature water. See Section 5.3.1 for details on fasting requirements prior to taking an oral dose of LY3502970.	Clarifies dosing details to be used for the study drug.
Section 8.5. Pharmacodynamics	Added time points (each week during the titration) for Pharmacodynamics.	Clarification of the time points for pharmacodynamics.
Section 8.6. Genetics	Deleted "saliva sample" from the following statement. • A blood or saliva sample for DNA isolation will be collected from participants.	Clarification on blood sample for DNA isolation.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore, not described.

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
$AUC_{(0-24)}$	area under the plasma concentration-time curve from 0 to 24 hour
BCRP	breast cancer resistant protein
BG	blood glucose
CFR	Code of Federal Regulations
CI	confidence interval
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
COVID-19	coronavirus disease 2019
CRF	Case report form: A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each study 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
CRS	Clinical research scientist
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IP	Investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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.
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.
IRB	Institutional Review Board
IWRS	Interactive Web Response Systems
Lilly	Eli Lilly and Company
MAD	multiple-ascending dose

MDD	Major Depressive Disorder
MI	myocardial infarction
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
participant	Equivalent to CDISC term "subject": An individual who participates in a clinical study, either as recipient of an investigational medicinal product or as a control.
PC	product complaint
PD	pharmacodynamics
P-gp	P-glycoprotein
PK	pharmacokinetics
QD	once daily
QW	once weekly
QTcF	QT interval corrected using Fridericia's formula
RNA	ribonucleic acid
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SIB	suicidal ideation and behavior
SoA	schedule of activities
$t_{1/2}$	half-life
T2D	type 2 diabetes
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
THC	tetrahydrocannabinol

ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

11. References

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