Protocol Amendment J2A-MC-GZGF (b)

Disposition of [^{14}C]-LY3502970 Following Oral Administration in Healthy Male Participants

NCT04680767

Approval Date: 18-May-2021

Title Page

Protocol Title: Disposition of [^{14}C]-LY3502970 Following Oral Administration in Healthy Male Participants

Protocol Number: J2A-MC-GZGF

Amendment Number: b

Compound: LY3502970

Study Phase: 1

Short Title: Disposition of [^{14}C]-LY3502970 Following Oral Administration in Healthy Male Participants

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number: EudraCT: 2020-003160-60

Approval Date:

Protocol Electronically Signed and Approved by Lilly on 31 July 2020

Protocol Amendment (a) Electronically Signed and Approved by Lilly on 08 December 2020

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

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment (a)	*08-December-2020*
Original Protocol	*31-July-2020*

Amendment (b)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Added 'clinically significant' to Exclusion Criterion 7.	Clarified that participants with a history of nonclinically significant atopy as determined by the investigator may be included in the study.
10.1.1 Regulatory and Ethical Considerations	Text updated from **'**Any amendments to the protocol will require IRB/IEC approval' to 'Any **substantial** amendments to the protocol will require IRB/IEC approval'.	To clarify that only substantial protocol amendments require IRB/IEC approval before implementation, in accordance with the IRB/IEC guidelines.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: Disposition of [^{14}C]-LY3502970 Following Oral Administration in Healthy Male Participants

Short Title: Disposition of [^{14}C]-LY3502970 Following Oral Administration in Healthy Male Participants

Rationale:

LY3502970 is a chemically synthesized, oral glucagon-like peptide-1 receptor agonist being developed as a daily oral therapy as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. This study is being conducted to determine the disposition of radioactivity and pharmacokinetics (PK) of LY3502970 and total radioactivity in healthy male participants following a single oral dose of LY3502970 labeled with ^{14}C. The administration of radiolabeled LY3502970 enables identification of circulatory and excretory metabolites and understanding of the clearance pathways.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the disposition of radioactivity in healthy male participants following administration of a single oral dose of CCI (approximately 200 µCi) [^{14}C]-LY3502970.	• Urinary and fecal excretion of total radioactivity over time expressed as a percentage of the total radioactive dose.
Secondary	
• To determine the PK of LY3502970 in plasma and total radioactivity in plasma and whole blood. • To assess the mass balance of LY3502970 by quantifying radioactivity recovered in urine, feces, and expired air (if applicable). • To assess the metabolism of LY3502970 in plasma, urine, and feces (if applicable). • To assess the safety and tolerability of a single dose of LY3502970 in healthy male participants.	• $AUC(0\text{-}t_{last})$, $AUC(0\text{-}\infty)$, and C_{max} for LY3502970 in plasma and radioactivity in plasma and whole blood. • Total radioactivity recovered in urine, feces, and expired air (if applicable). • Identity and the total number of metabolites of LY3502970. • Incidence of AEs.

Abbreviations: AE = adverse event; $AUC(0\text{-}t_{last})$ = area under the concentration-time curve from time 0 to time of the last measurable concentration; $AUC(0\text{-}\infty)$ = area under the concentration-time curve from time 0 extrapolated to infinity; C_{max} = maximum observed concentration; PK = pharmacokinetics.

Overall Design:

Study J2A-MC-GZGF is an open-label, single-center study to determine the disposition of radioactivity and PK of LY3502970 and total radioactivity in healthy male participants following a single dose oral dose of CCI LY3502970 containing approximately 200 µCi of [^{14}C]-LY3502970.

Disclosure Statement:

This is an open-label single-dose study consisting of a single treatment group.

Number of Participants:

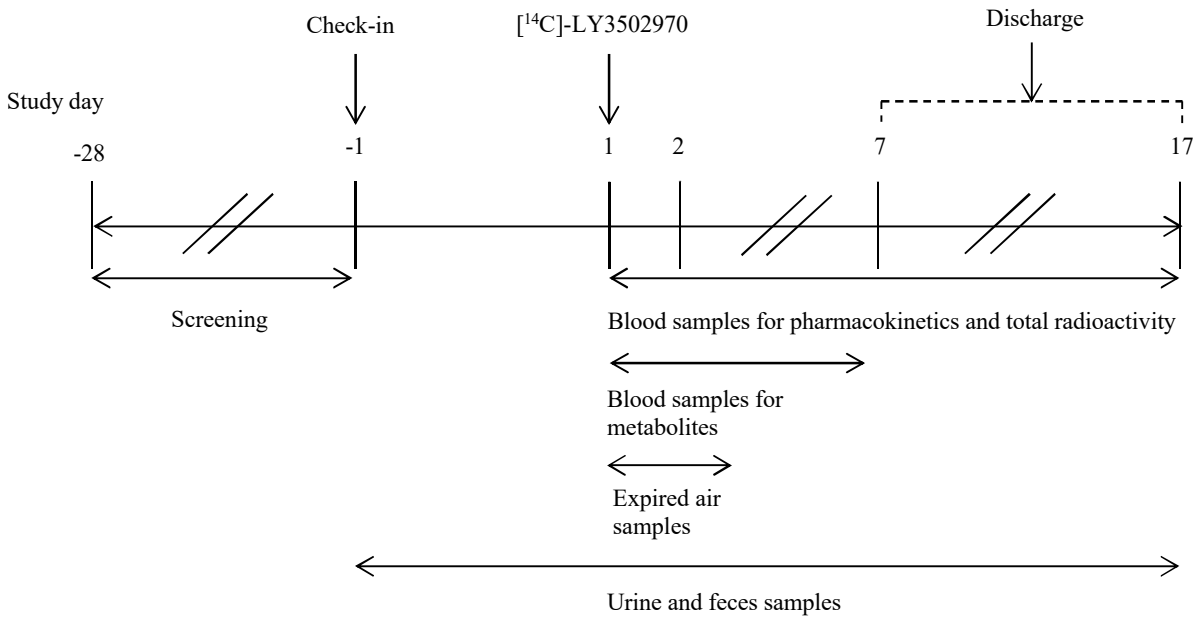
Up to 8 participants may be enrolled in the study. It is planned that up to 6 participants will be dosed initially and 2 additional participants may be dosed if needed, in order that a minimum of 4 participants complete the study.

Intervention Groups and Duration:

This study has a single treatment group with all participants receiving the same study intervention. The maximum study duration is 54 days.

Data Monitoring Committee: No

1.2. Schema


Check-in
[14C]-LY3502970
Discharge
Study day
-28
-1
1
2
7
17
Screening
Blood samples for pharmacokinetics and total radioactivity
Blood samples for metabolites
Expired air samples
Urine and feces samples

1.3. Schedule of Activities

Study Schedule Protocol J2A-MC-GZGF

Procedure	Screening	Check-in	Study Days			Discharge[a]	Follow-up[b]	Comments
	Days -28 to -2	Day -1	Day 1	Day 2	Days 3 to 6	Days 7 to 17	7±2 days after Discharge or ED	
Informed Consent	X							
Admission to CRU		X						
Discharge from CRU						X		
[^{14}C]-LY3502970 Administration			X (Time = 0)					
Medical History	X							
Height	X							
Weight	X	X				X[c]		
Vital Signs (supine)	X		X Predose, 1h, 2h & 4h	X 24h		X[c]		Supine blood pressure, supine pulse rate, and respiratory rate.
Clinical Lab Tests	X		X Predose	X 24h		X[c]		See Section 10.2, for details.
Glucose Monitoring			X Predose & 12h	X 24h & 36h	X 48h			Performed using a bedside glucose monitor.
Serology	X							
Urinary Drug Screen	X	X						See Section 10.2 for details of drug screen.

Procedure	Screening	Check-in	Study Days			Discharge[a]	Follow-up[b]	Comments
	Days -28 to -2	Day -1	Day 1	Day 2	Days 3 to 6	Days 7 to 17	7±2 days after Discharge or ED	
Alcohol Breath Test	X	X						
Physical Exam	X					X[c,d]		
Oral body temperature	X							
12-lead ECG	X		X Predose	X 24h		X[c]		
Genetic Sample			X Predose					
Urine Samples (^{14}C concentrations and Metabolite profiling and ID)		X -12-0h	X 0-6h, 6-12h, 12-24h	X	X	X		Samples collected for 24-hour intervals, except as specified predose on Day -1 and postdose on Day 1, until release criteria are met or up to the completion of the maximum CRU stay (Day 17).
Feces Samples (^{14}C concentrations and Metabolite profiling and ID)		X -12-0h	X	X	X	X		Samples collected for 24-hour intervals, except as specified predose on Day -1, until release criteria are met or up to the completion of the maximum CRU stay (Day 17).
Expired Air Samples (^{14}C concentrations)			X Predose, 2h, 4h, 8h, 12h	X 24h	X 48h			Additional expired air samples may be collected at some or all of the time points at which blood samples are drawn and only analyzed if needed

Procedure	Screening	Check-in	Study Days			Discharge[a]	Follow-up[b]	Comments
	Days -28 to -2	Day -1	Day 1	Day 2	Days 3 to 6	Days 7 to 17	7±2 days after Discharge or ED	
Blood and Plasma PK Samples (LY3502970 and ^{14}C concentrations)			X Predose, 0.5h, 1h, 2h, 4h, 8h, 12h, 16h	X 24h	X 48h, 72h, 96h, 120h	X 144h, 168h, 192h, 216h, 240h, 264h, 288h, 312h, 336h, 360h, 384h		PK samples will be collected until the study release criteria have been met (minimum stay of 6 days postdose [Day 7]) or until the maximum stay of 16 days postdose (Day 17). PK sampling times are given as targets to be achieved within reasonable limits (±10 minutes for time points earlier than or at 24 hours; ±1 hour for time points later than 24 hours)
Plasma Samples for Metabolite Profiling and ID			X 0.5h, 1h, 2h, 4h, 8h, 12h	X 24h	X 48h, 72h, 96h, 120h			Metabolite profiling samples will be collected separately from PK samples.
AEs/Concomitant Medications	X	X	X	X	X	X	X	Ongoing Assessment

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; ID = identification; min = minutes; PK = pharmacokinetics.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: venipuncture, ECG, then vital signs. Pharmacokinetic sampling times are given as targets to be achieved within reasonable limits. The allowable time deviations for each sample collection time point is provided in a separate study-specific Manual of Operations.

[a] Participants will be resident in the CRU for a minimum of 6 days postdose (Day 7) and may be discharged from the CRU at any time after Day 7 once the study release criteria have been met, up to a maximum stay of 16 days postdose (Day 17).

[b] Follow-up assessment will be conducted by telephone.

[c] Procedure will be conducted at discharge only.

[d] A Symptom-directed physical examination will be conducted at discharge.

2. Introduction

LY3502970 is a chemically synthesized, oral glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) being developed as a daily oral therapy as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

2.1. Study Rationale

Study J2A-MC-GZGF (GZGF) is being conducted to determine the disposition of radioactivity and pharmacokinetics (PK) of LY3502970 and total radioactivity in healthy male participants following a single oral dose of CCI LY3502970 containing approximately 200 µCi [^{14}C]-LY3502970. The total administered dose will be CCI, which is supported by the available safety data from the ongoing first-in-human (FIH) study. The 200-µCi dose of the radiotracer will be administered to each participant to facilitate characterization of physiological disposition and metabolism of LY3502970.

2.2. Background

With the prevalence of T2DM increasing world-wide, new antihyperglycemic agents offering significant improvements in glycemic control and secondary benefits, which would result in improved health outcomes, are highly desired.

Multiple GLP-1RA therapies have been approved, the most commonly prescribed being administered once daily or once weekly by subcutaneous injection. Even with several different GLP-1RAs approved for use in T2DM, the injection remains a barrier for many patients to initiate and to adhere to the therapy long-term. Oral semaglutide (Novo Nordisk) is expected to provide patients with a viable alternative to subcutaneous injection delivery. However, its administration requires the patient to adhere to multiple steps to ensure proper delivery of the medication through the gastric lining including: 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 (reviewed in Hedrington and Davis 2019). Therefore, providing additional oral GLP-1RA therapies remains an unmet need.

Nonclinical single-dose PK studies of LY3502970 in rats and monkeys showed that following oral administration, the rate of absorption is similar in both species with time of maximum observed concentration (t_{max}) ranging from 2.25 to 3.50 hours. The terminal elimination half-life ranged from 10.4 to 12.4 hours in rats and from 3.4 to 4.6 hours in monkeys following oral administration. LY3502970 had low to moderate oral bioavailability, ranging from CCI .

The excretion profile of LY3502970 was determined following a single oral dose of [^{14}C]-LY3502970 to rats and monkeys. In both species the majority of the administered dose was excreted in feces with a minor amount detected in urine.

An in vitro study of LY3502970 in liver microsomes and cryopreserved hepatocytes from mouse, rat, dog, monkey, and human showed that the compound is metabolized by hydroxylation and N-demethylation. No direct Phase 2 conjugative metabolites were detected.

To date, LY3502970 has been administered orally to 100 healthy participants in an ongoing Phase 1 FIH study which consists of 4 parts; single-ascending dose (SAD; Part A), multiple-ascending dose (MAD; Part B), single-dose food effects (Part C), and prototype-release (Part D).. No serious adverse events (SAEs) have been noted, and only 1 participant has discontinued due to an adverse event (AE) of "arthralgia," which was not considered related to the study drug by the investigator.

Part A of the study investigated escalating single doses of CCI of LY3502970. Single doses of CCI LY3502970 were also administered in Parts C and D of the study. The most frequent AEs occurring in 2 or more participants, following a single dose of LY3502970 (i.e., Parts A, C, and D) were nausea (28 events in 26 participants), headache (24 events in 20 participants), and vomiting (20 events in 13 participants). All AEs were mild in severity and were dose related with all nausea and vomiting events occurring at the highest doses of CCI LY3502970. At the CCI dose level 4 of the 24 participants (17%) reported 8 vomiting events and 6 participants (25%) reported 7 events of nausea. At the highest CCI dose level 4 of the 6 participants dosed (67%) reported 6 vomiting events and 3 participants (50%) reported 3 events of nausea. In the MAD portion of the study (Part B), with weekly dose escalations, once daily doses of CCI up to CCI were achieved, through titration, and tolerated in the majority of participants. Mild hypoglycemia was observed at all dose levels including placebo, with most events being asymptomatic. Overall, all doses were tolerated with AEs typical of GLP-1RAs.

CCI

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

There is no anticipated therapeutic benefit for the participants.

Risks of LY3502970 have been consistent with risks associated with other GLP-1RAs currently marketed. Potential risks include, but are not limited to, gastrointestinal (GI) effects, acute pancreatitis, increases in heart rate, and hypoglycemic events (GLP-1RA class effect).

CCI

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 determine the disposition of radioactivity in healthy male participants following administration of a single oral dose of CCI (approximately 200 µCi) [^{14}C]-LY3502970.	• Urinary and fecal excretion of total radioactivity over time expressed as a percentage of the total radioactive dose.
Secondary	
• To determine the PK of LY3502970 in plasma and total radioactivity in plasma and whole blood. • To assess the mass balance of LY3502970 by quantifying radioactivity recovered in urine, feces, and expired air (if applicable). • To assess the metabolism of LY3502970 in plasma, urine, and feces (if applicable). • To assess the safety and tolerability of a single dose of LY3502970 in healthy male participants.	• AUC(0-t_{last}), AUC(0-∞), and C_{max} for LY3502970 in plasma and radioactivity in plasma and whole blood. • Total radioactivity recovered in urine, feces, and expired air (if applicable). • Identity and the total number of metabolites of LY3502970. • Incidence of AEs.

Abbreviations: AE = adverse event; AUC(0-t_{last}) = area under the concentration-time curve from time 0 to time of the last measurable concentration; AUC(0-∞) = area under the concentration-time curve from time 0 extrapolated to infinity; C_{max} = maximum observed concentration; PK = pharmacokinetics.

4. Study Design

4.1. Overall Design

This is a Phase 1, open-label, single-center study in healthy male participants following a single oral dose of CCI LY3502970 containing approximately 200 µCi of [^{14}C]-LY3502970.

Up to 8 participants may be enrolled in the study. It is planned that up to 6 participants will be dosed initially and 2 additional participants may be dosed if needed, in order that a minimum of 4 participants complete the study.

Participants will participate in a screening visit, a single study period, and a follow-up telephone assessment. Participants will be screened for SARS-CoV-2 (the virus that causes Coronavirus Disease 2019 [COVID-19]) in accordance with the clinical research unit (CRU) COVID-19 generic screening protocol and provided with a COVID-19 specific informed consent form (ICF).

Participants will be admitted to the CRU prior to dosing on Day -1 and will receive a single oral dose of [^{14}C]-LY3502970 on Day 1.

Participants will remain resident in the CRU for a minimum of 6 days postdose (Day 7), after which time each participant may be discharged if both the following release criteria have been met:

- ≥90% of the administered radioactivity (based on the actual dose) has been recovered, AND
- 24-hour urine and fecal samples from 3 consecutive collections (where both collections have occurred) where each combined urine and feces collection has a radioactivity level <1.0% of the total administered radioactivity.

Participants may remain in the CRU up to a maximum of 16 days postdose (Day 17), at which time they will be discharged.

A follow-up assessment will be conducted by telephone and will include recording of AEs and concomitant medication. The follow-up assessment will be performed 7 ± 2 days after each participant has been discharged from the study or following early discontinuation from the study.

Sequential blood samples will be obtained predose and after dose administration to quantify the PK of the total radioactivity in whole blood and plasma, and LY3502970 in plasma. Separate blood samples will also be taken at selected time points for metabolite profiling.

Sequential urine and fecal samples will be obtained to determine the mass balance of LY3502970 by quantification of radioactivity and to identify metabolites. Samples of expired air will also be collected for the analysis of $^{14}CO_2$ at selected time points. If a significant amount of administered radioactivity is present in expired air samples, these data will be extrapolated to estimate the radioactive dose recovery. The percent of the dose eliminated in excreta will be estimated by measuring the amount of radioactivity in the urine and/or feces for each collection period.

Safety evaluations will include recording of AEs, clinical laboratory tests, glucose monitoring, vital sign measurements, 12-lead electrocardiograms (ECGs), and physical examinations.

Study governance considerations are described in detail in Section 10.1.

The study design is illustrated in Schema in Section 1.2.

4.2. Scientific Rationale for Study Design

This clinical study will be conducted to determine the disposition of radioactivity and PK of LY3502970 in healthy male participants following a single oral dose of LY3502970 labeled with ^{14}C. The radiolabeled LY3502970 enables identification of circulatory and excretory metabolites and understanding of the clearance pathways.

Conducting the study in healthy participants mitigates the potential confounding effects of disease state and any concomitant medications. This study has an open-label design with no control treatment. This type of design is standard and widely used in radiolabeled studies.

Participants over 35 years of age will be used to minimize the risk to fertility in healthy participants.

Female participants will be excluded to align with regulatory guidance. The "as low as (is) reasonably achievable" (ALARA) principle prescribed by the International Commission in Radiological Protection (ICRP) which recommends that radiation exposure to participants should be kept ALARA; therefore, as no specific reason exists to include females (i.e., no available data suggests metabolism of LY3502970 is different in females versus males), then the radiation exposure to female participants should ideally be kept at zero by not including females in this radioactivity study and only enrolling and dosing male participants.

4.3. Justification for Dose

The quantitative whole-body autoradiography disposition study for LY3502970 in male pigmented rats was conducted by Covance Laboratories Inc. in Madison, Wisconsin (Study Number 8413179). The whole-body radiation dose (based on the effective dose) in a 70-kg man following administration of a single 100-µCi (3.7-MBq) dose of [^{14}C]-LY3502970 was calculated to be the equivalent of 119 mrem (1.19 mSv, allometrically scaled to 1.30 mSv). Therefore, a 200-µCi (7.4-MBq) dose of [^{14}C]-LY3502970 can be expected to result in a whole-body radiation dose, for a 70-kg man, equivalent to 238 mrem (2.38 mSv/2.6 mSv [allometrically scaled]).

This effective radiation dose is defined as being within dose limits for members of the public (Category II study; World Health Organization, 1977) with a minor to intermediate associated risk (risk Category IIb [1 to 10 mSv]; ICRP, 1992).

Based on the PK and dosimetry data, administration of a single oral 200-µCi (7.4-MBq) dose of [^{14}C]-LY3502970 is not expected to represent a significant radiation exposure risk to human males and is considered adequate to define the disposition of [^{14}C]-LY3502970.

CCI [redacted]

The study will be submitted for approval by the Administration of Radioactive Substances Advisory Committee.

4.4. End of Study Definition

A participant is considered to have completed the study if he has completed all required phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA). In the case that any assessments in the SoA are missed the designation a participant as a completer can be determined by the sponsor.

5. Study Population

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply at screening unless otherwise stated:

Informed Consent

1. Are capable of giving signed informed consent as described in Section 10.1.2, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

Participant Characteristics

3. Are male from 35 to 55 years of age, inclusive, at the time of signing the informed consent.

   Note: Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For contraception requirements of this protocol, see Section 10.4.

4. Are overtly healthy as determined by medical evaluation including medical history, physical examination, clinical laboratory tests, vital signs, and ECGs.
5. Body weight within 50 and 100 kg, inclusive, and body mass index within the range 18.0 and 32.0 kg/m^2 (inclusive).

5.2. Exclusion Criteria

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

Medical Conditions

1. Have significant history of or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product (IP); or of interfering with the interpretation of data.
2. Have any abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study.
3. Have an abnormal blood pressure and/or pulse rate as determined by the investigator at screening.
4. Have evidence of active renal disease (e.g., diabetic renal disease, polycystic kidney disease) or an estimated creatinine clearance of <80 mL/minute, calculated using the

Chronic Kidney Disease-Epidemiology equation (Chronic Kidney Disease Epidemiology Collaboration, 2009).

5. Have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis), elevation in serum amylase or lipase (>upper limit of normal [ULN]).
6. Have a GI disorder (e.g., relevant esophageal reflux or gall bladder disease), or any GI disease which impacts gastric emptying (e.g., gastric bypass surgery, pyloric stenosis [with the exception of appendectomy]) or could be aggravated by GLP-analogs. Participants with dyslipidemia and participants who had cholecystolithiasis (with removal of gallstones) and/or cholecystectomy (removal of the gall bladder) in the past, with no further sequelae, may be included in the study, at the discretion of the investigator.
7. Have a history of clinically significant atopy or clinically significant multiple or severe drug allergies, or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).
8. Have a personal or family history of medullary thyroid carcinoma or have multiple endocrine neoplasia syndrome type 2, or a screening calcitonin ≥20 pg/mL.
9. Have a history of Gilbert's syndrome or have total bilirubin level (TBL) above ULN at screening.
10. Have liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or have elevations in aminotransferase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) greater than ULN at screening.
11. Have a history of malignancy within 5 years prior to screening.
12. Have a fasting serum triglyceride level greater than 5.65 mmol/L at screening.
13. Have evidence of significant active neuropsychiatric disease, as determined by the investigator.
14. Have a history of hypoglycemic events or have a blood glucose level below the lower limit of normal at screening.

Prior/Concomitant Therapy

15. Have had any exposure to LY3502970 or any other GLP-1 analogs, or other related compounds within the prior 3 months, or any history of allergies to these medications.
16. Have used or plan to use over-the-counter (OTC) or prescription medication, and/or herbal/vitamin/mineral supplements within 14 days (or 5 half-lives, whichever is longest) prior to dosing and for the duration of the study, including any medications that reduce GI motility, including, but not limited to, anticholinergics, antispasmodics, 5-hydroxytryptamine-3 receptor antagonists, dopamine antagonists, and opiates.
17. Have used or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days (or 5 half-lives, whichever is longest) prior to check-in, unless deemed acceptable by the investigator.

Prior/Concurrent Clinical Study Experience

18. Are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.
19. Have previously completed or withdrawn from this study or any other study investigating LY3502970, and have previously received the IP.
20. Have participated, within the last 3 months, in a clinical study involving an IP. If the previous IP has a long half-life, 5 half-lives or 3 months (whichever is longer) should have passed, prior to check-in.
21. Have participated in any clinical trial involving a radiolabeled IP within 12 months prior to check-in.

Diagnostic Assessments

22. Have a positive alcohol breath test result or positive urine drug screen at screening or check-in.
23. Show evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies.
24. Show evidence of hepatitis C and/or positive hepatitis C antibody.
25. Show evidence of hepatitis B and/or positive hepatitis B surface antigen.

Other Exclusions

26. Have an average weekly alcohol intake that exceeds 21 units per week, or are unwilling to stop alcohol consumption from 36 hours prior to check-in and while resident in the CRU (1 unit = 1/2 pint or 284 mL of beer; 25 mL of distilled spirits; 3 units = 250 mL of wine).
27. Are unwilling to refrain from consuming caffeine- or xanthine-containing food and drink from 36 hours prior to check-in and while resident in the CRU.
28. Are currently or have been smokers, users of tobacco, users of nicotine replacement products, or users of any vaping/e-cigarette devices within the 3 months prior to check-in and/or have positive cotinine test at screening or check-in.
29. Have had exposure to significant diagnostic, therapeutic, or employment-related radiation within 12 months prior to dosing (e.g., serial x-ray or computed tomography scans, barium meal, current employment in a job requiring radiation exposure monitoring).
30. Have a history of constipation or have had acute constipation within 3 weeks prior to check-in.
31. Have donated blood of more than 500 mL within 3 months prior to screening, donation of plasma from 2 weeks prior to screening, or platelets within 6 weeks prior to screening.
32. Are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
33. Are Lilly employees.
34. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

Throughout the study, participants may undergo medical assessments and review of compliance with requirements before continuing in the study.

5.3.1. Caffeine, Alcohol, and Tobacco

- Participants will refrain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 36 hours prior to check-in until discharge from the CRU.
- Participants will abstain from the consumption of alcohol for 36 hours prior to check-in until discharge from the CRU and will abide by study restrictions (i.e., no more than 3 units of alcohol per day - see Exclusion Criteria [25] for unit definition) at other times throughout the study.
- Participants will not be permitted to smoke, use tobacco, or use products containing nicotine within 3 months prior to check-in until discharge from the CRU.

5.3.2. Activity

Participants will abstain from strenuous exercise for 48 hours prior to check-in until discharge from the CRU.

5.3.3. Meals and Dietary Restrictions

Refrain from consumption of foods or beverages containing Seville orangesor grapefruit from 7 days prior to check-in until discharge from the CRU.

Participants will be required to fast overnight for at least 8 hours before being administered the [^{14}C]-LY3502970, and when clinical laboratory test samples are taken (SoA; Section 1.3). A meal will be offered to study participants at approximately 2 hours postdose. While resident in the CRU, participants will receive a standardized, high-fiber diet at scheduled times that do not conflict with other study-related activities. Prune juice may be administered on an as-needed basis to aid in normal bowel function and will not be considered a concomitant medication.

Water may be consumed freely during the study except during study drug administration; see Section 6.1.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are subsequently found not eligible to be enrolled in the study.

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

6. Study Intervention

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

6.1. Study Intervention Administered

Each dose of [^{14}C]-LY3502970 (approximately 50 mL) will be administered orally with 240 mL of room temperature water (this includes 100 mL of water that will be used for 2 x 50 mL dose container washes). All participants will fast overnight (at least 8 hours) and will refrain from consuming water for 1 hour prior to dosing. Participants will refrain from consuming water until 2 hours postdose, excluding the amount of water consumed at dosing, and will fast until 2 hours postdose.

Participants will be dosed in numerical order while seated and will not be permitted to lie supine for 2 hours after administration of [^{14}C]-LY3502970 except as necessitated by the occurrence of an AE and/or study procedures. The study regimen is indicated in Table 1.

Table 1. Study Intervention Details

Study Intervention Name	[^{14}C]-LY3502970
Dosage Formulation	Solution (50 mL of 2% Ethanol in 20% Captisol/Water)
Unit Dose Strength/Dosage Level	CCI LY3502970 (~200 µCi)/50 mL
Route of Administration	Oral
Delivery Method	By mouth

Except when they are using the toilet, study participants will be observed for approximately 4 hours postdose to ensure that they are not experiencing AEs, becoming nauseated, or experiencing emesis.

6.2. Preparation/Handling/Storage/Accountability

Preparation

Radiolabeled LY3502970 (powder) will be supplied by the sponsor (through Eurofins Biopharma Product Testing), along with the batch/lot numbers and Certificates of Analysis. Covance CRU will manufacture and label the IP from bulk supplies, such that each unit dose contains a total of CCI LY3502970 containing approximately 200 µCi (7.4 MBq) of [^{14}C]-LY3502970. A Certificate of Release authorized by a Qualified Person in the European Union will also be issued, by a Covance CRU Qualified Person, for the IP prior to administration to participants.

The sponsor will supply a sufficient quantity of the applicable study drug for the manufacture of the unit doses at Covance CRU. All excipients will be sourced by Covance. Specific instructions

regarding dose preparation will be mutually agreed upon between the sponsor and the appropriate clinical staff and will be presented in the Pharmacy Protocol.

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The study treatments will be transferred from bulk supplies into the participant's dose container by qualified clinical staff.

Handling and Storage

Only authorized site staff may supply or administer study intervention. Study interventions should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

Accountability

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

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials. Otherwise, the investigator or designee will return all unused study interventions to the sponsor or designee at the end of the study.

Further guidance and information for handling, storage, accountability, and final disposition of unused study interventions are provided in the Pharmacy Protocol.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization

This is a nonrandomized study. The study has a single group with all participants receiving the same study intervention.

Blinding

This study is open-label.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic Case Report

Form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's hands and mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 14 days before the study intervention (or 30 days before check-in if the drug is known to alter drug metabolism and/or elimination) or 5 half-lives (whichever is longer) until discharge from the study unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

A mild laxative (i.e., Milk of Magnesia®, Colace®) may be used to help with bowel movements if necessary.

Paracetamol, at doses of ≤ 3 grams/day, is permitted for use at the discretion of the investigator for treatment of headaches, etc. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

6.6. Dose Modification

Dose modification is not permitted in this study.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

This is a single-dose study.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his own request.
- at the request of his designee (for example, parents or legal guardian).
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- the study will be halted, and the risk to other potential participants evaluated, if any of the following criteria are met:
    - if serious adverse reaction (i.e., an SAE considered at least possibly related to [^{14}C]-LY3502970 administration) occurs in 1 (or more) participant(s);
    - severe non-serious adverse reactions (i.e., severe non-serious AE considered as at least possibly related to [^{14}C]-LY3502970 administration) in 2 participants, independent of within or not within the same system organ class.

  If, following an internal safety review, the sponsor deems it appropriate to restart the trial, this can be done following regulatory approval.
- if enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- if the participant, for any reason, requires treatment with 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.
- if the participant experiences emesis postdose they may be discontinued at the discretion of the investigator and the sponsor's clinical pharmacologist or clinical research physician (CRP); participants discontinued due to emesis may be replaced.

Discontinuation is expected to be uncommon.

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

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study and safety follow-up should be performed as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in Section 1.3 (SoA). Protocol waivers or exemptions related to eligibility criteria are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness.

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.

Assessment collection time

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 eCRF. Failure or being late (that is, outside stipulated time allowances) to perform procedures or obtain samples within the stipulated time allowances due to legitimate clinical issues (for example, equipment technical problems, venous access difficulty) will not be considered protocol deviations. However, the CRU is required to notify the sponsor in writing using a file note.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Complete physical examinations and symptom-directed physical examinations will be conducted at the time points specified in Section 1.3. Symptom-directed physical examinations may also be conducted, as determined by the investigator, if a participant presents with complaints. A complete physical examination will include, at a minimum, assessments of the:

- cardiovascular
- respiratory
- gastrointestinal, and
- neurological systems.

Height and weight will also be measured and recorded at the time points specified in Section 1.3.

8.2.2. Vital Signs

For each participant, vital signs measurements (supine blood pressure, supine pulse rate, respiration rate, and oral body temperature) should be conducted according to the SoA (Section 1.3).

Blood pressure and pulse rate should be measured after participants have been supine for at least 5 minutes.

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

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3).

Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high-quality records.

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. Ideally, the participant should be 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.

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

8.2.4. Clinical Safety Laboratory Assessments

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

Participants will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. 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 clinical laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5. Safety Monitoring

The sponsor clinical pharmacologist or CRP/scientist will monitor safety data throughout the course of the study.

The sponsor will review SAEs within time frames mandated by company procedures. The sponsor's clinical pharmacologist or CRP will periodically review:

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

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

8.2.5.1. Hepatic Safety

Close hepatic monitoring

Clinical laboratory tests (Section 10.6), including ALT, AST, alkaline phosphatase (ALP), TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine 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 ≥2x baseline (except for patients with Gilbert's syndrome)

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

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver test results should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should

include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including OTC), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

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

Comprehensive hepatic evaluation

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

If a participant with baseline results of...	develops the following elevation:
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 ≥1.5x baseline (except for patients with Gilbert's syndrome)

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

[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 earlier, as well as tests for prothrombin time-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography [CT] scan).

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

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and

- serum phosphatidylethanol.

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

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

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

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

- 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
- Elevation of 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
- 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
- Hepatic event considered to be an SAE

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

8.2.5.2. Nausea, Vomiting, and Diarrhea

Nausea, vomiting, and diarrhea events are considered AEs of interest; each occurrence will be recorded as a discrete AE in the eCRF. For each event assessment of severity, duration (actual date together with onset and end times) and the investigator's opinion of relatedness to IP and protocol procedure will be captured.

8.2.5.3. Pancreatic Safety

Further diagnostic assessments will be recommended whenever lipase and/or amylase are confirmed to be ≥3× ULN at any timepoint post treatment even if the participant is asymptomatic (as per the algorithm for the monitoring of pancreatic events in Section 10.7).

8.2.6. Glucose Monitoring

8.2.6.1. Hypoglycemia

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

The investigator should use the following classification of hypoglycemia:

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 particpants to treat hypoglycemia at this glucose alert value.

Level 2 hypoglycemia:

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

Level 3 hypoglycemia:

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

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

8.3. Adverse Events and Serious Adverse Events

Adverse 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 the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until participation in the study has ended.

All AEs will be collected from the signing of the ICF until completion of the follow-up assessment.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event eCRF.

Although all AEs after signing the ICF are recorded by the site in the eCRF/electronic data entry, SAE reporting to sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving LY3502970, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.6), 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). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., 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.

8.3.5. Pregnancy

Pregnancy (paternal exposure to study intervention) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Section 10.3 to collect data on the outcome for both mother and fetus.

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until the end of the study (i.e, completion of the follow-up visit).
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest for this program include:

- GI events (nausea, vomiting, and diarrhea)
- Acute pancreatitis
- Hypoglycemic events.

Each occurrence will be recorded as a separate AE in the eCRF. For each event assessment of severity, duration (actual date, time of onset, and end times), and investigator's opinion of relatedness to study intervention and protocol procedure will be captured.

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention.

The sponsor collects product complaints on IPs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he has a complaint or problem with the IP so that the situation can be assessed.

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Section 10.3 of the protocol.

8.3.7.1. Time Period for Detecting Product Complaints

Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug/device is used.

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug/device provided for the study, the investigator will promptly notify the sponsor.

8.3.7.2. Prompt Reporting of Product Complaints to Sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.

The Product Complaint Form will be sent to the sponsor by the method provided in the form. If the primary method is unavailable, then an alternative method provided in the form should be utilized.

8.3.7.3. Follow-up of Product Complaints

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

For this study, any dose of LY3502970 greater than the specified CCI dose will be considered an overdose. Treatment for overdose is supportive care. For additional details, refer to the LY3502970 IB.

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.
3. Document the quantity of the excess dose in the 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.

8.5. Pharmacokinetics

8.5.1. Whole Blood and Plasma Samples

Venous blood samples of approximately 7 mL will be collected as specified in the SoA to determine the whole blood and plasma concentrations of total radioactivity, and the 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 both the investigator and sponsor; this excludes any additional samples required for safety monitoring.

Additional samples of 15 mL blood will be collected for metabolite profiling (total number and identity) of LY3502970 at the times indicated in the SoA.

Instructions for the collection and handling of blood samples will be provided by the sponsor in a laboratory manual. The actual date and time (24-hour clock time) of each sampling will be recorded.

Plasma samples for metabolite profiling will be stored frozen pending confirmation from the sponsor of which samples are to be analyzed.

8.5.2. Urine and Feces Sampling

Urine and feces samples will be collected for the determination of total radioactivity and metabolite profiling (total number and identity) only.

Urine and feces will be collected before IP administration (control samples); however, the inability to produce a fecal sample will not be considered a protocol deviation. After dosing with IP, cumulative feces and urine samples will be collected in specified containers according to the SoA until the specified release criteria have been met.

Urine will be collected at the specified intervals, into 1 or more containers (depending on volume excreted), according to the SoA until the specified release criteria have been met. Aliquots of each sample will be collected for analysis to yield the percentage radioactivity recovered within that interval and to determine its metabolic profile.

Feces from each bowel movement will be collected and the time of collection will be noted. Fecal samples will be pooled over each 24-hour collection period (if applicable), see the SoA, and analyzed to yield the percentage radioactivity recovered over that period as well as to determine its metabolic profile.

8.5.3. Expired Air Samples

A sample of expired breath will be collected for analysis of $^{14}CO_2$ at the times indicated in the SoA. If a significant amount of the radioactivity is present in breath samples, the raw data will be extrapolated to provide an estimate of the percentage dose eliminated via $^{14}CO_2$. Additional breath samples may be collected at some or all of the times that blood samples are drawn and only analyzed if needed.

8.5.4. Vomitus Collection

For participants experiencing emesis within 16 hours following oral dosing, vomitus will be collected. Attempts will be made to collect vomitus from participants experiencing emesis after 16 hours postdose. All vomitus collected will be stored for possible analysis as deemed appropriate.

8.5.5. Bioanalysis and Radioanalysis

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. Metabolite identification will be determined using appropriate techniques such as liquid chromatography (LC)/radiodetection and LC/mass spectroscopy.

Whole blood, plasma, expired air, urine, and fecal concentrations of radioactivity will be determined using liquid scintillation counting techniques. Whole blood and feces will be combusted prior to the liquid scintillation counting.

Bioanalytical and radioanalytical samples collected during radiolabeled studies will be retained for a maximum of 2 years following the discharge of the last participant from the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as additional metabolism and/or protein binding work.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

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

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity will not be evaluated in this study.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

No hypotheses are planned to be tested in this study.

9.2. Sample Size Determination

Up to 8 participants may be enrolled. It is planned that up to 6 participants will be dosed initially and 2 additional participants may be dosed if needed, in order that a minimum of 4 participants complete the study.

The sample size is customary for [^{14}C]-disposition studies (Penner et al. 2009) and is chosen to provide adequate PK data while limiting the number of participants exposed to radiopharmaceuticals in non-therapeutic research.

9.3. Populations for Analyses

The following populations are defined:

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

9.4. Statistical Analyses

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

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

The SAP will be finalized prior to first participant visit and it will include a more technical and detailed description of the statistical analyses described in this section.

9.4.1. General Considerations

Data listings will be provided for all data that are databased. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted.

Summary statistics and statistical analysis will only be presented for data where detailed in the SAP. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

9.4.2. Pharmacokinetics

The primary PK endpoints to determine the disposition of total radioactivity following administration of [^{14}C]-LY3502970 are as follows:

PK Parameter	Description
$F_{eu, ef, ea}$	Fraction/percentage of administered radioactive dose excreted in urine, feces, expired air
Cumulative $F_{eu, ef, ea}$	Cumulative $f_{eu, ef, ea}$ from 0 to t_{last} hours

Pharmacokinetic parameter estimates for LY3502970 will be calculated by standard noncompartmental methods of analysis. The primary PK outcome endpoints of LY3502970 and total radioactivity derived from the whole blood and plasma concentration-time profiles following oral administration of [^{14}C]-LY3502970 are as follows:

PK Parameter	Description
AUC(0-∞)	Area under the concentration-time curve (AUC) from time 0 extrapolated to infinity
AUC(0-t_{last})	AUC from time 0 to the time of the last measurable concentration
C_{max}	Maximum observed concentration
T_{max}	Time of C_{max}
AUC(0-∞) Plasma LY3502970/ Total Radioactivity Ratio	AUC(0-∞) of plasma LY3502970 relative to AUC(0-∞) of plasma total radioactivity
AUC(0-∞) Blood/ Plasma Ratio	AUC(0-∞) of whole blood total radioactivity to AUC(0-∞) of plasma total radioactivity

Other noncompartmental parameters, such as apparent $t_{1/2}$, apparent total clearance, and apparent volume of distribution may be reported, where applicable. The PK endpoints used to determine mass balance derived from total radioactivity in urine, feces, and expired air (if applicable) are as follows:

PK Parameter	Description
$A_{eu, ef, ea}$	Amount of administered radioactive dose excreted in urine, feces, expired air
Cumulative $A_{eu, ef, ea}$	Cumulative $A_{eu, ef, ea}$ from 0 to t_{last} hours

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

As a secondary outcome the identity and quantity of drug metabolites in plasma,blood, urine and feces may be determined.

9.4.3. Safety

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

In addition to AEs, safety parameters that will be assessed include clinical laboratory tests, vital signs, and hypoglycemic events. Electrocardiogram parameters will be recorded for monitoring purposes only and will not be presented in the clinical study report.

9.5. Interim Analyses

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.

9.6. Data Monitoring Committee

Not applicable.

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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., 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 substantial amendment to the protocol will require regulatory authority approval before implementation.

Any substantial 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.

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 the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

10.1.2. Informed Consent Process

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

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the

requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act 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 re-consented to the most current version of the ICF(s) during their participation in the study.

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

10.1.3. Data Protection

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

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

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

10.1.4. Dissemination of Clinical Study Data

Communication of suspended or terminated dosing

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

Reports

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

Data

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

10.1.5. Data Quality Assurance

Investigator responsibilities

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

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

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

Data monitoring and management

Monitoring details describing strategy (e.g., 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 (e.g., contract research organizations).

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

Records retention and audits

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

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by 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.

All individual, participant-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion. 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 eCRF.

All data generated from external sources (e.g., laboratory and bioanalytical data), and transmitted to the sponsor or designee electronically, will be integrated with the participant's eCRF data in accordance with the Data Management Plan.

10.1.6. Source Documents

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

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

Definition of what constitutes source data can be found in Section 10.1.5.

10.1.7. Study and Site Start and Closure

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

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

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

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

- 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 of participants by the investigator
- Discontinuation of further study intervention development.

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 assures appropriate participant therapy and/or follow-up.

10.1.8. Publication Policy

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

10.1.9. Investigator Information

Principal Investigator	Study Site
Firas Almazedi MBChB, MSc, CPI, DipPharmMed	Covance Clinical Research Unit Ltd. Springfield House Hyde Street Leeds, LS2 9LH United Kingdom

10.1.10. 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 is discharged from the study.

The maximum retention times may be shorter, if specified in local regulations and/or if IECs/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 Type	Custodian	Retention Period after Last Participant Discharge[a]
PK (Bioanalysis and Radioanalysis)	Sponsor or designee	2 years
Metabolite Profiling and Identification	Sponsor or designee	2 years
Genetics	Sponsor or designee	15 years

Abbreviations: PK = pharmacokinetics.

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

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

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

Investigators must document their review of each laboratory safety report.

Safety Laboratory Tests

Hematology	**Clinical Chemistry (fasting)**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Chloride
Mean cell volume	Calcitonin[a]
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Creatinine
Leukocytes (WBC)	Glucose
Absolute Counts of	Total protein
Neutrophils	Albumin
Lymphocytes	Direct bilirubin
Monocytes	Total bilirubin
Eosinophils	Alkaline phosphatase (ALP)
Basophils	Aspartate aminotransferase (AST)
Platelets	Alanine aminotransferase (ALT)
	Total CO_2
Urinalysis	Total cholesterol[a]
Specific gravity	Triglycerides[a]
pH	Inorganic phosphate
Protein	Amylase
Glucose	Lipase
Ketones	
Urobilinogen	**Drug Screen**
Blood	Amphetamines/methamphetamines
Microscopy	Barbiturates
	Benzodiazepines
Serology[a]	Cocaine (metabolite)
Hepatitis B surface antigen	Methadone
Hepatitis B core antibody, total	Phencyclidine
Hepatitis C virus serology (anti-HCV)	Opiates
Human immunodeficiency virus (HIV)	Tetrahydrocannabinol/ cannabinoids
	Tricyclic antidepressants
	Cotinine test

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

[a] Measured at screening only.

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.

Blood Sampling Summary Table

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Clinical laboratory tests[a] (central laboratory)	7.5	4	30
Serology	3.5	1	3.5
Pharmacokinetics (LY3502970 and total radioactivity)	7	24 (+3)	189
Metabolite profiling and identification	15	11	165
Pharmacogenetic sample (stored)	10	1	10
Total			397.5
Total for clinical purposes (rounded up to the nearest 10 mL)			400

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

10.3. Appendix 3: 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 patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., 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 conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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 (e.g., 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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

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 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 (e.g., 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

f. Other situations:

- Medical or scientific judgment should be exercised 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. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- 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 AE/SAE CRF page.
- 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 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. 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 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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 Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of 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.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via SAE Report
• Facsimile transmission of the SAE paper CRF 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 CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SAE Report.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Females of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Females NOT of Childbearing Potential

Women in the following categories are not considered of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., mullerian agenesis, androgen insensitivity).
- Postmenopausal female is defined as, women with:
  - 12 months of amenorrhea for women >55 years old, with no need for follicle-stimulationg hormone (FSH)
  - 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that induced amenorrhea)

Contraception Guidance:

10.4.1.1. Male Participants

Male participants, regardless of their fertility status, with partners who are nonpregnant females of childbearing potential, must agree to either

- remain abstinent (if this is their preferred and usual lifestyle), or
- use condoms plus 1 additional highly effective contraception method.

Male participants with pregnant or breastfeeding partners must agree to use condoms during intercourse.

Male participants must agree to continue abstinence or contraception methods for the duration of the study plus 90 days.

Male participants with female partners of nonchildbearing potential will be required to use condoms during intercourse for the duration of the study.

Male participants should refrain from sperm donation for the duration of the study plus 90 days, which corresponds to approximately 3 months

10.4.1.2. Contraception Methods

Abstinence

Participants who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) must agree to remain abstinent without sexual relationships

Same-sex relationships

Participants who are in a same-sex relationship will be required to use condoms during intercourse for the duration of the study.

Highly effective contraception methods

Highly effective methods of contraception (less than 1% failure rate)	
Combined oral contraceptive pill and mini-pill	Intrauterine device (such as Mirena® and ParaGard®)
NuvaRing®	Contraceptive patch – ONLY women less than 198 pounds (90 kg)
Implantable contraceptives	Vasectomy – for men in clinical trials
Injectable contraceptives (such as Depo-Provera®)	Fallopian tube implants (Essure®) if confirmed by hysterosalpingogram
Total abstinence	

Unacceptable contraception methods

Unacceptable methods of contraception include

- periodic abstinence, such as
  - calendar
  - ovulation
  - symptothermal, or
  - post-ovulation methods
- declaration of abstinence just for the duration of the trial, and
- withdrawal.

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 obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. 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 including fetal status (presence or absence of anomalies) and indication for the procedure.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

DNA samples will be used for research related to the drug target and mechanism of action of LY3502970 or diabetes, obesity, and diabetic complications including non-alcoholic steatohepatitis (NASH) and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3502970 and interventions of this drug class and diabetes, obesity, and diabetic complications including NASH. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

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

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

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

The samples will be retained while research on LY3502970, similar study interventions of this class, or diabetes, obesity, and diabetic complications including NASH continues but no longer than 15 years or other period as per local requirements.

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

See Section 8.2.5.1 for guidance on appropriate test selection.

The sponsor-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

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

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

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

Abbreviations: Ig = immunoglobulin; INR = international normalization ratio; PT = prothrombin time.

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

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

[c] Not required if anti-smooth muscle antibody is tested.

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

10.7. Appendix 7: Pancreatic Monitoring

Glucagon-like peptide 1 agonists have been associated with a possible risk of acute pancreatitis. In 2006, the US prescribing information for exenatide was revised to include the event of pancreatitis. In 2007, the US prescribing information for this medication was amended to include pancreatitis under "Precautions". Epidemiologic studies have indicated that there is an increased incidence and prevalence of pancreatitis in persons with T2DM.

To enhance understanding of the natural variability of pancreatic enzymes in the T2DM population and, to assess for any potential effects of LY3502970 on the exocrine pancreas, amylase, and lipase values will be monitored in all current and future clinical trials with LY3502970.

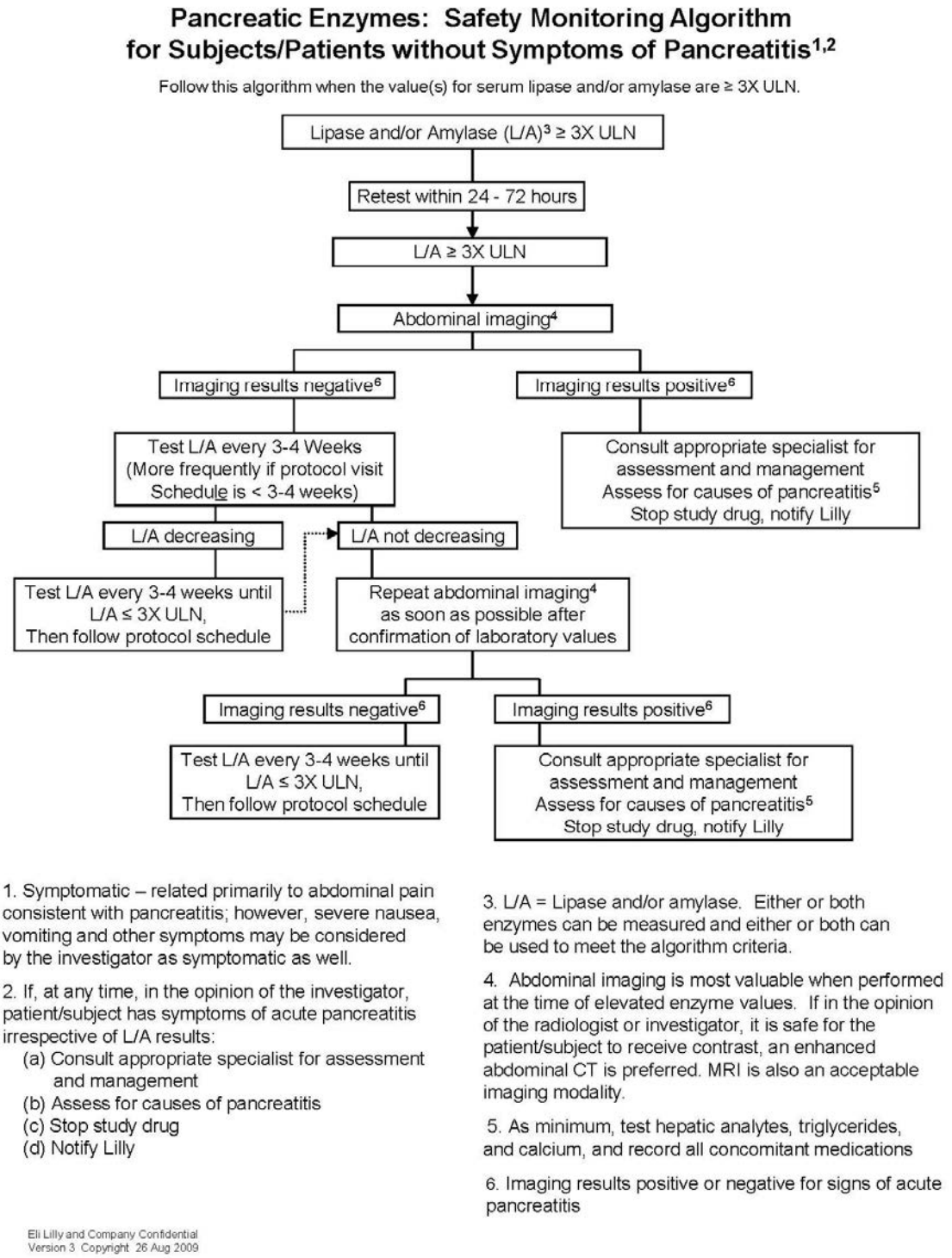
Additional monitoring will be requested for amylase or lipase values ≥3X the ULN at any visit after randomization, even in asymptomatic participants (see Figure 1). Lipase and amylase may also be obtained at any time during the clinical trials for any participant suspected of having symptoms suggestive of pancreatitis (such as severe GI signs and/or symptoms), at the investigator's discretion.

Acute pancreatitis is an AE defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase >3X ULN
- characteristic findings of acute pancreatitis on the computed tomography scan or magnetic resonance imaging

Most participants with acute pancreatitis experience abdominal pain that is located generally in the epigastrium and radiates to the back in approximately one-half of the cases. The pain is often associated with nausea and vomiting. However, experience with GLP-1RAs has demonstrated that some participants asymptomatic for classic pancreatitis may demonstrate significant elevations of lipase and/or amylase. For participants considered by the investigators to be asymptomatic for pancreatitis, but whose value(s) for lipase and/or amylase are ≥3X ULN, an algorithm is in place to follow these participants safely and to quickly reach (or not reach) a diagnosis of pancreatitis.

Participants diagnosed with pancreatitis will be discontinued from the study. Investigators will be responsible for following, through an appropriate health care option, these pancreatitis AEs until the events resolve or are explained. Adverse events that meet the diagnostic criteria of acute pancreatitis will be captured as SAEs. For all other pancreatic AEs (such as idiopathic or asymptomatic pancreatic enzyme abnormalities), the investigator will be responsible for determining the seriousness of the event (AE or SAE) and the relatedness of the event to IP.



Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; ULN = upper limit of normal.

Figure 1.

10.8. Appendix 8: Abbreviations

Term	Definition
AE	adverse event
ALARA	"as low as (is) reasonably achievable"
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC(0-∞)	area under the concentration-time curve from time 0 extrapolated to infinity
AUC(0-t_{last})	area under the concentration-time curve from time 0 to time of the last measurable concentration
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice, and applicable regulatory requirements.
COVID-19	Coronavirus Disease 2019
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic Case Report Form
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.
FIH	first-in-human

FSH	follicle-stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICRP	International Commission in Radiological Protection
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.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Boards
LC	liquid chromatography
MAD	multiple-ascending doses
NASH	non-alcoholic steatohepatitis
OTC	over-the-counter
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PK	pharmacokinetics
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
$t_{1/2}$	terminal half-life
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
t_{max}	time of C_{max}
ULN	upper limit of normal

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).

Amendment (a): 08 December 2020

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Text updated from ">1.5-fold the ULN" to ">ULN" in Exclusion Criterion 5.	To address feedback received from the regulatory authority
5.2. Exclusion Criteria	Text updated from "above 1.5X ULN" to "above ULN" in Exclusion Criterion 9.	To address feedback received from the regulatory authority
5.2. Exclusion Criteria	Text updated from "greater than 2X ULN" to "greater than ULN" in Exclusion Criterion 10.	To address feedback received from the regulatory authority
5.2. Exclusion Criteria	Added Exclusion Criterion 14 "Have a history of hypoglycemic events or have a blood glucose level below the lower limit of normal at screening."	To address feedback received from the regulatory authority
10.1.1 Regulatory and Ethical Considerations	Added "Any substantial amendment to the protocol will require regulatory authority approval before implementation."	To address feedback received from the regulatory authority
10.5. Appendix 5: Genetics	Removed the phrase "or analysis of the entire genome".	Removed the phrase to clarify that analysis of the entire genome will not be performed in the study. The previous language was included by mistake.

11. References

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