Protocol J2A-MC-GZPC(a)

A Phase 1, Parallel, Single-Dose, Open-Label, Single-Period Study of LY3502970 in Participants with Normal Renal Function and Participants with Renal Impairment.

NCT05936138

Approval Date: 10 May 2023

Title Page

Protocol Title: A Phase 1, Parallel, Single-Dose, Open-Label, Single-Period Study of LY3502970 in Participants with Normal Renal Function and Participants with Renal Impairment.

Protocol Number: J2A-MC-GZPC

Amendment Number: (a)

Compound: LY3502970

Brief Title: A single-dose pharmacokinetic study of LY3502970 in participants with normal renal function and participants with renal impairment.

Study Phase: Phase 1

Sponsor Name: Eli Lilly and Company

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

Regulatory Agency Identifier Number(s): IND 142842

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

Document ID: VV-CLIN-115660

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original	*12-April-2023*

Amendment (a)

Overall Rationale for the Amendment:

The protocol J2A-MC-GZPC has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to the protocol are described in the following table. Note that minor edits have been made throughout the protocol, which are not captured in the amendment summary table.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Wording updated to clarify screening period in Intervention Groups and Duration paragraph.	Previous wording regarding screening period unclear.
Section 10.6 Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments	Acetaminophen protein adducts now to be assayed by central laboratory instead of local laboratory.	None of the local laboratories for each site can perform the acetaminophen protein adducts.

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 1, Parallel, Single-Dose, Open-Label, Single-Period Study of LY3502970 in Participants with Normal Renal Function and Participants with Renal Impairment.

Brief Title:

A single-dose pharmacokinetic study of LY3502970 in participants with normal renal function and participants with renal impairment.

Regulatory Agency Identifier Number(s):

IND 142842

Rationale:

Study J2A-MC-GZPC is a Phase 1, parallel design, open-label study to assess pharmacokinetics (PK) and tolerability of a single oral dose of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease, compared to control participants with normal renal function.

LY3502970 is being developed as a therapy to improve glycemic control in adults with Type 2 diabetes mellitus. Renal impairment is common in diabetes, and it is therefore important to understand the influence of renal impairment on the PK of LY3502970. LY3502970 is eliminated predominantly via the fecal route (86.8%) with minimal excretion in urine (0.24%); therefore, this renal impairment study is being carried out using a reduced study design.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the PK of a single oral dose of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function	LY3502970 AUC(0-∞), AUC(0-t_{last}), and C_{max}
Secondary	
To evaluate the safety and tolerability of a single oral dose of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function	Number and incidence of SAEs and TEAEs

Abbreviations: AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; C_{max} = maximum observed drug concentration; PK = pharmacokinetic(s); SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design:

Study GZPC will be a multi-site, parallel, single-dose, open-label, single-period study of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function.

Brief Summary:

The purpose of this study is to measure the impact of severe renal impairment and end-stage renal disease on the PK of LY3502970.

Study details include:

- The study duration will be up to 42 days.
- Participants will be admitted to the clinical research unit (CRU) on Day -1 for an inpatient treatment period of up to 5 days.
- The follow-up visit will occur on Day 12 ± 2 days.

Study Population:

Males and female participants aged 18 to 85 years, inclusive, and body mass index within the range 18.5 to 42.0 kg/m^2 inclusive. Participants with normal renal function, severe renal impairment, or end stage renal disease, will be included in this study.

Number of Participants:

Approximately 26 participants may be enrolled with the aim of having at least 8 completers with normal renal function in Group 1, 6 completers with severe renal impairment in Group 2, and 6 completers with end-stage renal disease in Group 3.

Intervention Groups and Duration:

Eligible participants will be studied in 3 groups based on their renal function and receive a single oral dose of [redacted] mg LY3502970 on Day 1.

All participants will be screened for study inclusion within 28 days prior to dosing on Day 1. Participants will be admitted into the CRU on Day -1 and will remain resident in the CRU until discharge on Day 5. Participants will attend an outpatient visit on Day 12 ± 2 days.

Ethical Considerations of Benefit/Risk:

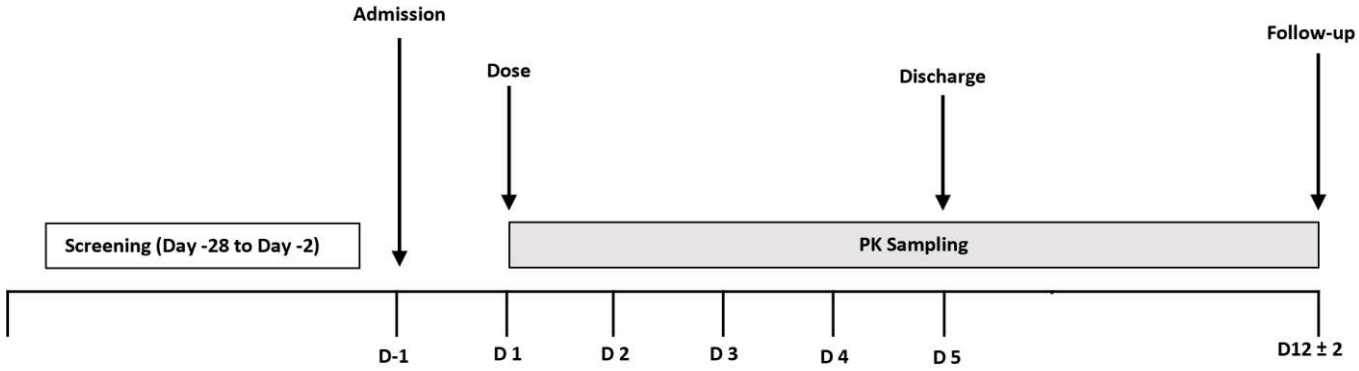
In participants administered with LY3502970 up to the highest single dose of [redacted] mg and multiple doses of [redacted] mg for a maximum of 12 weeks to date, the only safety or tolerability concerns have been gastrointestinal-related effects that are consistent with glucagon-like peptide-1 pharmacology, and changes in vital signs that have resolved spontaneously over time.

Gastrointestinal adverse events (AEs) including nausea, vomiting, constipation, abdominal distension, diarrhea, eructation, dyspepsia, and abdominal pain have been the most frequently reported events across all completed and ongoing studies. These AEs have been mostly mild in severity and the majority resolved without treatment.

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

Data Monitoring Committee: No.

1.2. Schema



Abbreviations: D = day; PK = pharmacokinetic

Note: For participants in Group 3 that require hemodialysis, administration of LY3502970 should occur 24 ± 2 hours after a hemodialysis session and should occur during the longest window between two hemodialysis sessions. Subsequent hemodialysis sessions should be scheduled as clinically appropriate.

1.3. Schedule of Activities (SoA)

Procedure	Screening	Baseline	Treatment Period					Follow -up/ED	Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**12(± 2)**	
Informed consent	X								
Admission to CRU		X							
Discharge from CRU							X		Stay may be extended at investigator discretion.
Non-residential Visit	X							X	
Medical Assessment	X								Includes medical history and complete physical examination at screening, and symptom-directed examination at other times.
HbA1c	X								
FSH	X								If needed to confirm postmenopausal status. See Appendix 2 in Section 10.2 for details.
Serum Pregnancy	X								Female participants only. See Appendix 2 in Section 10.2 for details.
Urine Pregnancy		X							Female participants only. See Appendix 2 in Section 10.2 for details. A serum pregnancy test may be used, if urine testing is not possible.
Urine drug screen	X	X							Salivary drug screen may be performed if a urine sample can't be obtained. See Appendix 2 in Section 10.2 for details.
Ethanol testing	X	X							See Appendix 2 in Section 10.2 for details.
Serology	X								See Appendix 2 in Section 10.2 for details.
Genetics sample		X							

Procedure	Screening	Baseline	Treatment Period					Follow -up/ED	Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**12(± 2)**	
Height	X								
eGFR	X	X							Local and central laboratory used for each testing occasion. See Section 9.2.2.
Cystatin C		P							
LY3502970 Administration			X						See footnote for schema in Section 1.2
Weight	X	X	P					X	
Vital signs	X	X	P	X	X	X	X	X	
Hematology, Clinical Chemistry, Urinalysis	X		P, 8*			X		X	Local Laboratory. See Appendix 2 in Section 10.2 for details. *Clinical chemistry only at 8 hours postdose.
Single 12-lead ECG	X		P					X	ECGs must be recorded before blood collection.
Plasma LY3502970 PK samples			0.5, 1, 2, 4, 6, 8, 12, 16	24, 36	48	72	96	X	Times are relative to dosing time. The exact date and time of sample collection must be recorded.
Plasma coproporphyrin 1			P, 4, 12	24					
LY3502970 protein binding			4, 8, 12						
Coproporphyrin 1 protein binding			P, 4, 12	24					
AEs/Concomitant Medications	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; BSA = body surface area; CKD = chronic kidney disease; CKD-EPI = chronic kidney disease epidemiology collaboration; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; P = predose; PK = pharmacokinetics.

Note: If multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture. PK sampling times are given as targets to be achieved within reasonable limits.

2. Introduction

2.1. Study Rationale

Study J2A-MC-GZPC is a Phase 1, parallel-design, open-label study to assess PK and tolerability of a single oral dose of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease, compared to control participants with normal renal function.

LY3502970 is being developed as a therapy to improve glycemic control in adults with T2DM. Renal impairment is common in diabetes, and it is therefore important to understand the influence of renal impairment on the PK of LY3502970. LY3502970 is eliminated predominantly via the fecal route (86.8%) with minimal excretion in urine (0.24%). Accordingly, this renal impairment study is being carried out using a reduced study design.

2.2. Background

Multiple GLP-1RA therapies are approved. These are most commonly administered either once daily or once weekly through subcutaneous injection. Even with several different GLP-1RAs approved for use in T2DM, the injection remains a barrier for many patients to initiate and to adhere to long-term therapy.

Therefore, oral GLP-1RA therapies with improved ease of use remain an unmet need.

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

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

2.3. Benefit/Risk Assessment

In participants administered with LY3502970 up to the highest single dose of [redacted] mg and multiple doses of [redacted] mg for a maximum of 12 weeks to date, the key safety or tolerability concerns have been GI-related effects that are consistent with GLP-1 pharmacology, and changes in vital signs that have resolved spontaneously over time.

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

- doses up to [redacted] mg in the first-in-human single-ascending dose and up to [redacted] mg in the multiple-ascending dose in study J2A-MC-GZGA
- doses up to [redacted] mg in participants with T2DM in the multiple-dose study J2A-MC-GZGC
- doses up to [redacted] mg in healthy participants in the multiple dose study J2A-MC-GZGD
- [redacted] mg doses in healthy participants in the open-label study J2A-MC-GZGF, and
- doses up to [redacted] mg in healthy participants in the open-label study J2A-MC-GZGJ.

Safety and tolerability assessments of LY3502970 are also based on 7 ongoing studies, GZGB, GZGE, GZGH, GZGI, GZGK, GZGL, and GZGM.

Gastrointestinal AEs including nausea, vomiting, constipation, abdominal distension, diarrhea, eructation, dyspepsia, and abdominal pain have been the most frequently reported events across all completed and ongoing studies. These AEs have been mostly mild in severity and the majority resolved without treatment. Three SAEs were reported in one Phase 1 study, GZGC, none of which were deemed related to study treatment by the investigator. No other SAEs were reported in Phase 1 Studies.

Based on data from completed and ongoing multiple-dose studies, the planned single dose of [redacted] mg is expected to be well generally well tolerated in this study.

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

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY3502970 are described in the IB.

3. Objectives and Endpoints

Objective	Endpoints
Primary	
To evaluate the PK of a single oral dose of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function	LY3502970 AUC(0-∞), AUC(0-t_{last}), and C_{max}
Secondary	
To evaluate the safety and tolerability of a single oral dose of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function	Number and incidence of SAEs and TEAEs
Exploratory	
To evaluate plasma concentrations of endogenous OATP1B biomarker coproporphyrin 1 in participants with severe renal impairment and participants with end-stage renal disease	Plasma concentrations of coproporphyrin 1
To evaluate the effect of renal impairment on plasma protein binding of LY3502970 and coproporphyrin 1	• Unbound LY3502970 PK including F_u, unbound AUC, and unbound C_{max} • Unbound coproporphyrin 1 including F_u, unbound AUC and C_{max}

Abbreviations: AUC = area under the concentration time curve, AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; C_{max} = maximum observed drug concentration; F_u = fraction unbound; PK = pharmacokinetic(s); OATP1B = organic anion–transporting polypeptide 1B; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study GZPC will be a multi-site, parallel, single-dose, open-label, single-period study of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function.

The schema in Section 1.2 illustrates the study design. PK blood sampling and safety assessments, including vital sign measurement, physical examination, clinical laboratory tests, safety ECGs, and AE recording, will be performed according to the SoA in Section 1.3.

Assignment to Treatment Groups

Participants will be enrolled within the groups shown:

Group	Classification	Specifications	Approximate Number of Participants to be Enrolled	Number of Participants to Complete
1	Normal renal function	eGFR: greater than or equal to 90 mL/min and without T2DM	26	8
2	Severe renal impairment	eGFR: 15-29 mL/min and not requiring hemodialysis		6
3	End-stage renal disease	eGFR: less than 15 mL/min or requiring hemodialysis		6

Abbreviations: eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.

Participants with T2DM will be permitted to enroll in Groups 2 and 3 only.

Participants will be assigned to Groups 1, 2 and 3 based on screening and baseline eGFR values determined by the CKD-EPI equation using serum creatinine and converted to absolute eGFR values by factoring in individual BSA, see Appendix 7 in Section 10.7. If the eGFR value differs for a participant between screening and baseline such that the participant would be classified into different treatment groups, then the value produced from the central laboratory baseline sample will be the definitive value used to assign that participant to a treatment group.

Participant Matching

Participants with normal renal function enrolled in Group 1 will be matched by age ±15 years, sex, and body weight ±10 kg, as far as is practically possible, to participants in Group 2 and 3.

Matching participants with normal renal function will be enrolled on up to a 1-to-1 basis; however, they may be matched to 2 participants with renal impairment, as long as the 2 are in different renal impairment groups. Participants who do not complete all the study procedures may be replaced in order to target the planned number of completers listed.

Study Visits

Screening

Participants will undergo screening procedures up to 28 days prior to enrollment.

Treatment and Assessment Period

Participants will be admitted to the CRU on Day -1.

Participants will be administered a single dose of LY3502970 on Day 1 and will remain in the CRU until after assessments are completed on Day 5. Participants may stay longer in the CRU at the investigator's discretion. For participants in Group 3 that require hemodialysis, administration of LY3502970 should occur 24 ± 2 hours after the end of a hemodialysis session and should occur during the longest window between 2 hemodialysis sessions.

Clinical laboratory tests, physical examination, vital signs, 12-lead ECGs, and AEs will be monitored to assess safety and tolerability.

Blood samples for PK analysis will be collected postdose through the final follow-up visit.

Follow-up

Participants will return for a follow-up on Day 12 ± 2 days.

4.2. Scientific Rationale for Study Design

In study J2A-MC-GZGF the total recovery of administered radioactivity was 88.3%. In this study 86.8% of administered [^{14}C]LY3502970-related radioactivity was eliminated via the fecal route, with minimal excretion in urine (0.24%). Thus, the renal route is believed to be a minor route of elimination of LY3502970. In addition, as LY3502970 is highly protein bound, hemodialysis is not expected to affect PK. Therefore, the effect of hemodialysis on PK of LY3502970 will not be evaluated. Accordingly, this study uses a reduced study design to support dosing recommendations for patients with impaired renal function.

Study GZPC is designed as a single-dose, parallel design study to investigate the PK of LY3502970 in participants with renal impairment.

Control participants with normal renal function will be enrolled in this study to serve as a reference group for interpretation of the results from participants in Groups 2 and 3.

The proposed PK sampling schedule and the duration of the treatment period is considered adequate to achieve the study objectives of enabling a thorough assessment of PK and impact of renal impairment, if any, on LY3502970 PK.

In vitro results indicate that CYP2J2 and CYP3A4 are responsible for CCI and CCI of the hepatic CYP mediated clearance of LY3502970, respectively, in human liver microsomes and that LY3502970 is a substrate of P-glycoprotein, OATP1B1, and OATP1B3 (hepatic) transporters. Measurement of the exploratory biomarker for OATP1B activity, coproporphyrin 1, is included to aid in mechanistic interpretation of change in LY3502970 exposure.

This study will be open label. As the primary endpoints are objective rather than subjective, investigators and participants do not need to be blinded.

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

4.3. Justification for Dose

The study will evaluate a single [redacted]-mg dose of LY3502970. The dose of [redacted] mg has been selected as this can be given as a single dose without significant risk of GI AEs. Higher doses carry the risk of increased incidence of GI AEs, including vomiting. This can lead to loss of administered drug, impacting the PK associated with the dose. Further, as the PK of LY3502970 is approximately linear across the clinical dose range and there is no evidence of time-dependent PK, the results from this study can be used to adequately estimate the effect of renal impairment on PK at other doses.

4.4. End of Study Definition

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

A participant is considered to have completed the study if the participant has completed the last scheduled procedure shown in the SoA in Section 1.3. A participant who has missing data for a small number of study activities or visits may still be considered to have completed the study after review by the sponsor team.

5. Study Population

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

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

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only unless otherwise specified, and not continuously throughout the trial.

Screening may occur up to 28 days prior to enrollment. Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. In such instances, repeat the following screening tests and procedures: medical assessment, vital signs, clinical laboratory tests, and ECG.

5.1. Inclusion Criteria

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

All Participants

Age

1. Participants must be 18 to 85 years of age inclusive, at the time of signing the informed consent.

Weight

2. BMI within the range 18.5 to 42.0 kg/m^2 inclusive.

Sex and Contraceptive/Barrier Requirements

3. Males and females may participate in this study.

   Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the definition of WOCBP, WNOCBP, postmenopausal state and contraception requirements of this protocol, see Appendix 4 in Section 10.4.

Informed Consent

4. Capable of giving signed informed consent as described in Appendix 1 in Section 10.1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusion criteria

5. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.
6. Have venous access sufficient to allow for blood sampling as per the protocol.

Additional Inclusion Criteria for Participants with Normal Renal Function in Group 1

7. Healthy males or females as determined by medical history, physical examination, and other screening procedures, with normal renal function, assessed by eGFR of greater than or equal to 90 mL/min at screening.
8. Have clinical laboratory test results within normal reference range for the population or investigator site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
9. Have normal BP and pulse rate, as determined by the investigator.

Additional Inclusion Criteria for Participants with Severe Renal Impairment in Group 2

10. Have clinical laboratory test results with deviations that are judged by the investigator to be compatible with the renal condition of the participant and of no additional clinical significance for this study. Abnormalities of serum glucose, serum lipids, urinary glucose, and urinary protein consistent with T2DM are acceptable.
11. Have acceptable BP and pulse rate, as determined by the investigator at screening.
12. If participants have T2DM, they must have a HbA1c of less than or equal to 11.5% at the screening visit.
13. Are males or females with severe renal impairment as determined by a stable eGFR of 15-29 mL/min, not requiring hemodialysis.

Additional Inclusion Criteria for Participants with End-Stage Renal Disease in Group 3

14. Are males or females with end-stage renal disease
15. If participants require hemodialysis, they must have been on a stable hemodialysis schedule for at least 3 months prior to planned dosing.

5.2. Exclusion Criteria

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

All Participants

Medical Conditions

16. Have a current, functioning organ transplant. Non-functional renal allografts may be allowed.
17. Have a personal or family history of medullary thyroid carcinoma or have multiple endocrine neoplasia syndrome type 2.
18. Have AST or ALT greater than 2.5 × ULN or TBL greater than 1.5× ULN.
19. 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.
20. Have a history or presence of chronic or acute pancreatitis.
21. Have a history or presence of significant psychiatric disorders that may impair the participant's safety or their ability to provide an informed consent or to comply with study procedures, in the opinion of the investigator.

22. Regularly use known drugs of abuse or show positive findings on urinary drug screen that are not otherwise explained by permitted concomitant medications. A salivary drug screen may be performed on participants who are unable to produce a urine sample.
23. Have known QT prolongation or are receiving drugs known to prolong the QT interval, ventricular arrhythmia (torsades de pointes), hypokalemia, significant bradycardia, or taking Class IA or III antiarrhythmic.
24. Have evidence of acute or chronic liver disease of any etiology or have any clinical evidence of hepatic impairment.

Prior/Concomitant Therapy

25. Have known allergies to LY3502970, related compounds, or any components of the formulation, or history of severe atopy.
26. Intend to use over-the-counter medication within 7 days prior to dosing, or any prescription medication within 14 days or 5 half-lives (whichever is longer) prior to dosing, or any herbal preparations within the 14 days prior to screening, or plan to use any of these during the study, with the exception of the permitted medications detailed in Section 6.8 and Appendix 9 in Section 10.9.
27. Use any orally administered drugs or substances that are known strong and moderate inducers or inhibitors of CYP3A, strong OATP inhibitors, or use of select oral anti-fungal agents or select antibiotics specified in Appendix 9 in Section 10.9 are specifically excluded within 14 days or 5 half-lives (whichever is longer) prior to dosing. Further guidance regarding permitted prior and concomitant medication can be found in Section 6.8 and lists of strong and moderate CYP3A inhibitors and inducers, and strong OATP inhibitors are provided in Appendix 9 in Section 10.9.

Prior/Concurrent Clinical Study Experience

28. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
29. Have received any dose of an investigational drug within the last 30 days or 5 half-lives of this drug, whichever is longer, prior to dosing on Day 1.
30. Have previously withdrawn from this study.

Diagnostic Assessments

31. Show evidence of HIV or positive HIV antibodies.
32. Have evidence of, or test positive for, HCV. A positive test for HCV is defined as: positive for anti-HCV Ab and positive via a confirmatory test for HCV for example, HCV polymerase chain reaction. Participants with no history of HCV antiviral treatment may be eligible for inclusion in the study, provided they have no detectable HCV RNA at screening for this study.
33. Have evidence of, or test positive for, HBV by testing positive for: HbsAg; or HbcAb; in the case of HbcAb positive result, an HBV DNA positive test would need to be

performed to confirm exclusion. If the HbcAb is positive and the HBV DNA is negative, the participant is considered negative for HBV and is not excluded.

34. Have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin or in situ carcinomas of the uterine cervix that have been resected with no evidence of metastatic disease for 3 years.

Other Exclusion Criteria

35. Are lactating, pregnant, or intend to become pregnant, or to breastfeed during the study.
36. Are unable to abide by CRU restrictions.
37. Have an average weekly alcohol intake that exceeds 21 units per week (males up to age 85) and 14 units per week (females) or are unwilling to stop alcohol consumption 24 hours prior to dosing until discharged from the study or completion of all study procedures. 1 unit = 12 oz or 360 mL beer, 1½ oz or 45 mL liquor, or 5 oz or 150 mL wine. Note: Number of units = [total volume of drink (mL) x alcohol by volume (%)]/1000
38. Smoke more than 10 cigarettes or e-cigarettes, 3 cigars, or 3 pipes per day from 3 weeks prior to participant admission to CRU until study completion or are unable or unwilling to abide by investigative site smoking restrictions.
39. Have donated blood of 450 mL or more within the last 2 months.
40. Are investigator site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
41. Are Lilly employees.
42. Are determined to be unsuitable by the investigator for any reason.

<u>Additional Exclusion Criteria for Participants with Normal Renal Function in Group 1</u>

43. Have a significant history or presence of cardiovascular (for example, myocardial infarction, cerebrovascular accident), 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 study medication; or of interfering with the interpretation of data.

<u>Additional Exclusion Criteria for Participants with Severe Renal Impairment in Group 2 and Participants with End-Stage Renal Disease in Group 3</u>

44. If participants have T2DM, they should be excluded if they have taken any GLP1-RA (for example, dulaglutide) or a DPP4 inhibitor (e.g., sitagliptin) in the past 6 weeks or 5 half-lives (whichever is longer) prior to planned dosing. If they are on any other antidiabetic drugs, they must be at a stable dose for at least 8 weeks prior to planned dosing and be able to remain at that stable dose throughout the study.
45. Have hemoglobin <8.5 g/dL.
46. Have used any drug indicated for medical care of the participant's renal impairment, which is not established in dose and administered for at least 14 days before LY3502970 administration.

47. Have a significant and active cardiovascular (for example, myocardial infarction, or cerebrovascular accident within the past 3 months), respiratory, hepatic, GI, endocrine (except T2DM), hematological, or neurological disorders constituting a risk when taking the study medication or capable or of interfering with PK data interpretation.

5.3. Lifestyle Considerations

Throughout the study, participants must adhere to lifestyle restrictions as outlined below.

5.3.1. Meals and Dietary Restrictions

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

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

Participants will refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, or grapefruit hybrids from 7 days before the start of study intervention until after the final PK sample collection.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

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

Participants should not consume alcohol for at least 24 hours prior to dosing until discharged from the study or completion of all study procedures.

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

5.3.3. Activity

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

5.4. Screen Failures

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

If participants have minor deviations in screening assessments, for example, laboratory safety tests or vital signs, that are likely due to a transient condition or technical or sample handling error, these may be repeated at the investigator’s discretion to confirm eligibility without this being considered a rescreening.

Individuals who do not meet the criteria for participation in this study may be rescreened once. The interval between screenings should be at least 2 weeks. Rescreened participants should be assigned a new participant number for every screening or rescreening event.

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

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

Table GZPC.1 details the intervention used in this clinical study.

Table GZPC.1. Study Intervention Administered

Intervention Name	LY3502970
Type	IMP
Dose Formulation	[redacted] mg capsule
Dosage Level	[redacted] mg on Day 1
Route of Administration	Oral
Packaging and labeling	Study intervention will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study intervention will be labeled as appropriate for country requirements.

6.1.1. Administration Details

Capsules of LY3502970 will be administered orally on Day 1 with approximately 100 mL of room temperature water in the morning in a sitting position. Participants will be fasted overnight for at least 10 hours before administration and will remain fasted for 2 hours following administration, at which time a meal will be served. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures, or under special circumstances for participants with renal impairment, as permitted by the principal investigator.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

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.

6.3. Assignment to Study Intervention

This is an open-label study. All participants will receive the same study intervention.

6.4. Study Intervention Compliance

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

6.5. Dose Modification

Not applicable.

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

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

6.7. Treatment of Overdose

For this study, any dose of LY3502970 greater than [redacted] mg will be considered an overdose.

Lilly does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should

- contact the medical monitor immediately,
- closely monitor the participant for any AE/SAE and laboratory abnormalities until LY3502970 can no longer be detected systemically (at least 7 days),
- obtain a plasma sample for PK analysis as soon as possible if requested by the medical monitor (determined on a case-by-case basis), and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.8. Prior and Concomitant Therapy

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

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

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

Allowed concomitant medications should be taken according to label instructions. Specifically, medications that may be affected by an increase in gastric pH, such as levothyroxine, bisphosphonates, and ferrous sulfate, should be separated from study intervention administration by at least 2 to 4 hours.

Participants must abstain from taking orally administered strong and moderate CYP3A inhibitors, strong and moderate CYP3A inducers, and strong OATP inhibitors. To be eligible for screening into this study, those drugs need to be washed out for at least 14 days or 5 half-lives (whichever is longer) and the participant should be on a stable dose of alternative medications for at least 14 days prior to dosing. These exclusions do not apply to topical administration.

Lists of strong and moderate CYP3A inhibitors, strong and moderate CYP3A inducers and strong OATP inhibitors are provided in Appendix 9 in Section 10.9. These lists are intended to be exhaustive, but with available information continually evolving, the status of every relevant drug cannot be guaranteed.

Other restricted medications and potential substitutions are indicated in Appendix 9 in Section 10.9.

Participants who chronically use these drugs should be excluded.

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

If acetaminophen/paracetamol treatment is needed for pain management, the maximum allowed dose cannot exceed 3 g per day for participants in all groups.

Thyroid hormone supplement, hormonal replacement therapy, and vitamin/mineral supplements are permitted.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the sponsor.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

Participants discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per the SoA in Section 1.3 of this protocol.

7.1. Discontinuation of Study Intervention

Not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an IP, or enrolled 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 a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, as shown in the SoA in Section 1.3.

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

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

Section 1.3 lists the SoA, detailing the study procedures and their timing, including tolerance limits for timing.

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.

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

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

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

Appendix 2 in Section 10.2 lists the laboratory tests that will be performed for this study.

Appendix 2 in Section 10.2 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination should be conducted according to the SoA in Section 1.3 and will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded.

Additional symptom-directed physical examinations may be performed according to the SoA in Section 1.3 or at the discretion of the investigator.

Any clinically significant findings in a physical examination should be reported as AEs.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA in Section 1.3 and as clinically indicated.

Blood pressure and pulse rate should be measured after at least 10 minutes in the supine position.

If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes.

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

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

8.2.3. Electrocardiograms

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

For each participant, a single 12-lead ECG will be collected according to the SoA in Section 1.3. ECGs must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

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

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

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2 in Section 10.2 for the list of clinical laboratory tests to be performed and the SoA in Section 1.3 for the timing and frequency.

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

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

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 in Section 10.2, must be conducted in accordance with the SoA in Section 1.3, standard collection requirements, and laboratory manual.

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

If a central vendor is used for the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

8.2.5. Safety Monitoring

The Lilly Clinical Pharmacologist or Clinical Research Physician or scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly Clinical Pharmacologist or Clinical Research Physician will periodically review

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

When appropriate, the Lilly Clinical Pharmacologist or Clinical Research Physician will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

8.2.6. Pancreatic Monitoring

Diagnosis of acute pancreatitis

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

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

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase

- perform imaging studies, such as abdominal computed tomography scan with or without contrast, or abdominal magnetic resonance imaging
- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone/gall bladder disease, hypertriglyceridemia, and concomitant medications.

Asymptomatic elevation of serum amylase and/or lipase

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

8.2.7. Hepatic Monitoring

Close Hepatic Monitoring

Laboratory tests detailed in Appendix 2 in Section 10.2 including ALT, AST, ALP, TBL, direct bilirubin, and gamma-glutamyl transferase should be repeated, with additional tests for creatine kinase within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

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

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the

participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive Hepatic Evaluation

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

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

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, or eosinophilia greater than 5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for

- prothrombin time
- international normalized ratio
- viral hepatitis A, B, C, or E
- autoimmune hepatitis, and
- an abdominal imaging study for example, ultrasound or computerized tomography scan.

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

- hepatitis D virus,
- cytomegalovirus,
- Epstein-Barr virus,

- acetaminophen levels,
- acetaminophen protein adducts,
- urine toxicology screen,
- Wilson's disease,
- blood alcohol levels,
- urinary ethyl glucuronide, and
- blood phosphatidylethanol.

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

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

Additional Hepatic Data Collection (Hepatic Safety CRF) in Study Participants who have Abnormal Liver Tests During the Study

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

1. Elevation of serum ALT to greater than or equal to 5 × ULN on 2 or more consecutive blood tests (if baseline ALT is less than 1.5 × ULN)
   - In participants with baseline ALT greater than or equal to 1.5 × ULN, the threshold is ALT greater than or equal to 3 × baseline on 2 or more consecutive tests
2. Elevated TBL to greater than or equal to 2 × ULN (if baseline TBL is less than 1.5 × ULN; except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL greater than or equal to 1.5 × ULN, the threshold should be TBL greater than or equal to 2 × baseline
3. Elevation of serum ALP to greater than or equal to 2 × ULN on 2 or more consecutive blood tests (if baseline ALP less than 1.5 × ULN)
   - In participants with baseline ALP greater than or equal to 1.5 × ULN, the threshold is ALP greater than or equal to 2 × baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study intervention due to a hepatic event

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

8.2.8. Hyperglycemia

For participants with T2DM, episodes of hyperglycemia, that is fasting plasma/serum glucose greater than 270 mg/dL or 15 mmol/L will be reported by the investigator or designated physician who will be responsible for advising the participant on what further actions to take. Additional monitoring may be requested at the investigator's discretion.

If the fasting plasma/serum glucose during the dosing period exceeds the acceptable level defined as hyperglycemia on 3 or more separate days over any 2-week period between screening and the end of the dosing period, the participant will be evaluated further at the CRU. If fasting plasma or serum glucose continues to exceed the acceptable level, the study intervention will be discontinued, and treatment with an appropriate antidiabetic agent may be initiated by the investigator. If hyperglycemia occurs during the follow-up period, the participant will remain in the study until completion of the planned follow-up.

8.2.9. Hypoglycemia

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

Investigators should use the following classification of hypoglycemia:

Level 1 hypoglycemia:

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

Level 2 hypoglycemia:

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

Level 3 hypoglycemia:

Severe hypoglycemia: 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 report form and report it to Lilly as an SAE.

Nocturnal hypoglycemia:

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

8.2.10. Pregnancy Testing

Pregnancy testing will be performed at the time points detailed in the SoA in Section 1.3.

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

The definitions of AEs, SAEs, and PCs can be found in Appendix 3 in Section 10.3.

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

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

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

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

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

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

8.3.1. Timing and Mechanism for Collecting Events

Table GZPC.2 describes the timing, deadlines, and mechanism for collecting events.

Table GZPC.2. Timing and Mechanism for Collecting Events

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the ICF	Until AE has resolved.	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Until AE has resolved.	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Until event has resolved	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A; continues indefinitely	Within 24 hours of awareness	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	30 days following final dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

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

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

- obtain a consent to release information from the pregnant female partner directly, and
- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

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

Female participants who become pregnant

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

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

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

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Event of Special Interest and Other Safety Topics

AESIs and other safety topics for this study include

- hepatic disorders
- severe GI AEs including nausea, vomiting and diarrhea
- arrhythmias and cardiac conduction disorders
- major adverse cardiovascular events
- hypotension, orthostatic hypotension, and syncope
- hypoglycemia, see Section 8.2.9
- pancreatitis, see Section 8.2.6
- acute renal events, and
- gallbladder and biliary tract disorders.

8.4. Pharmacokinetics

At the visits and times specified in the SoA in Section 1.3, venous blood samples of approximately 2 mL each will be collected to determine 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. The timing of sampling may be altered during the course of the study based on newly available data (for example, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

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

8.4.1. Bioanalysis

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

Concentrations of LY3502970 will be assayed using a validated liquid chromatography tandem mass spectrometry method. Fraction unbound of LY3502970 will be determined using a qualified bioanalytical method.

Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 1 year following last participant visit for the study.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

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

See Appendix 5 in Section 10.5 for information regarding genetic research and Appendix 1 in Section 10.1 for details about sample retention and custody.

8.7. Biomarkers

8.7.1. Coproporphyrin 1

At the visits and times specified in the SoA in Section 1.3, venous blood samples of approximately 3 mL will be collected to determine the plasma concentrations of coproporphyrin 1. The actual date and 24-hour clock time of each sampling will be recorded.

Concentrations of coproporphyrin 1 will be assayed using a validated liquid chromatography tandem mass spectrometry method.

Fraction unbound of coproporphyrin 1 will be determined using a qualified bioanalytical method.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

9.1. Statistical Hypotheses

The primary objective of the Study GZPC is to estimate the PK parameters of LY3502970 after a single [redacted] mg dose in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function. There are no formal statistical hypotheses planned to be tested in this study.

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. Analyses Sets

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

Participant Analysis Set	Description
Entered	All participants who sign the ICF.
Enrolled	All participants who were assigned to LY3502970, regardless of whether they take any doses.
Safety	All participants who receive 1 dose of LY3502970, whether or not they completed all protocol requirements.
Pharmacokinetic	All participants who receive 1 dose of LY3502970 and have evaluable PK data.
Coproporphyrin 1 Biomarker	All participants who receive 1 dose of LY3502970 and have evaluable coproporphyrin 1 data.

9.2.1. Study Participant Disposition

All participants who discontinue from the study will be identified and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be documented.

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

9.2.2. Study Participant Demographics

The participant's age, sex, weight, height, smoking habits, and other demographic characteristics will be recorded and may be used in the PK and safety analyses as quantitative or classification variables. Study participants' renal status grouping will be determined using screening and

baseline eGFR estimate, determined by the CKD-EPI equation and based on measurements of serum creatinine levels obtained on Day -1 and converted to absolute eGFR by factoring in individual BSA values. Note: absolute eGFR (mL/min) = eGFR reading (mL/min/1.73m^2) * BSA/1.73; where BSA (m^2) = sqrt(height (cm)* body weight (kg)/3600).

9.3. Statistical Analyses

9.3.1. General Considerations

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

PK analyses will be conducted on data from all participants who received at least one dose of the IP and have evaluable PK.

Safety analyses will be conducted for all enrolled participants who received study intervention, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety, PD, and population PK analysis purposes to understand the totality of the evidence to avoid the limited number of participants from each study.

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

9.3.2. Pharmacokinetic Analyses

9.3.2.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3502970 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis of LY3502970 will be AUC(0-∞), AUC(0-t_{last}), and C_{max}. Other noncompartmental parameters, such as time of C_{max}, half-life, apparent clearance, and apparent volume of distribution, may be reported as appropriate. Unbound AUC(0-∞), AUC(0-t_{last}), and C_{max} may also be calculated.

9.3.2.2. Pharmacokinetic Statistical Inference

The main analysis is the evaluation of log-transformed AUC(0-∞), AUC(0-t_{last}), and C_{max} using a linear regression model with baseline absolute eGFR as a continuous covariate. The PK parameters will be summarized for each renal function group. The differences between each impaired renal function group versus control group will be back-transformed to present the ratios of geometric means and the corresponding 90% CI. Other baseline covariates such as body weight may be included in the model. The details will be described in the SAP.

Table GZPC.3. Renal Function Classification for Primary Analyses

Group	Classification	eGFR (mL/min/)[a]
1	Control (normal renal function)	Greater than or equal to 90
2	Severe renal impairment	15-29 and not requiring hemodialysis
3	End-stage renal disease	Less than 15; or requiring hemodialysis

Abbreviations: BSA = body surface area; eGFR = estimated glomerular filtration rate.

[a] Per enrollment classification; eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation and converted to absolute eGFR by factoring in individual BSA values.

Scatter plots of log-transformed total and unbound AUC(0-∞), AUC(0-t_{last}), and C_{max} versus baseline absolute eGFR with a linear regression line and 90% CI may be produced.

The time to C_{max} will be analyzed using a Wilcoxon rank sum test.

9.3.3. Biomarker Analyses

Coproporphyrin 1 data will be listed and summarized. Parameter estimates AUC(0-t_{last}) and C_{max} for Coproporphyrin 1 will be calculated by standard noncompartmental methods of analysis. Unbound AUC(0-t_{last}) and C_{max} may also be calculated.

9.3.4. Safety Analyses

9.3.4.1. Clinical Evaluation of Safety

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

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

9.3.4.2. Statistical Evaluation of Safety

All safety analyses will be made on the Safety Analysis Set.

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

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

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

9.3.5. Other Analysis

Details for other analyses may be documented in the SAP.

9.4. Interim Analysis

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

9.5. Sample Size Determination

The primary objective of the study GZPC is to estimate the PK parameters of LY3502970 after a single [redacted] mg dose in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function. There are no formal statistical hypotheses planned to be tested in this study.

Approximately 26 participants will be enrolled so that at least 20 complete the study. At least 8 participants to complete for the control group. At least 6 participants to complete for each of the severe renal impairment and end-stage renal impairment groups.

The sample size is not selected to satisfy a prior statistical requirement to make PK comparison between each tested renal impairment group and the healthy control group. Rather, the sample size is chosen to fulfil the regulatory requirement to provide adequate precision of the PK parameters of interest (AUC and C_{max}) for each tested group using regression model with absolute eGFR as a regressor (Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing, FDA draft guidance 2020). The aforementioned sample size will provide at least 80% probability that the 90% CI of PK parameters AUC and C_{max} is within 60% and 140% of the geometric mean estimate of the PK parameters in each renal function group. The coefficient of variation used for sample size calculation are 36.5% and 39.5% for AUC and C_{max}, respectively.

Participants who do not complete all the study procedures may be replaced in order to target the planned number of completers listed.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH Good Clinical Practice Guidelines
- Applicable laws and regulations

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

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

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

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

10.1.2. Informed Consent Process

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

Potential participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that

meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

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

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

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

Participants who are rescreened are required to sign a new ICF.

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

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

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

10.1.4. Committees Structure

Not applicable.

10.1.5. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone 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.

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

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

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in Appendix 1 in Section 10.1.6.

10.1.8. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.9. 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.

10.1.10. Investigator Information

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

10.2. Appendix 2: Clinical Laboratory Tests

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

The local laboratory must be qualified in accordance with applicable local regulations.

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

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

Investigators must document their review of the laboratory safety results.

Safety Laboratory Tests

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

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

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

Serology[a, c]
- Hepatitis B surface antigen[a, e]
- Hepatitis B core antibody[a, e]
- Hepatitis C antibody[a, e]
- HIV[a,]

Clinical Chemistry
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Phosphate
- Glucose, fasting
- Amylase
- Lipase
- Creatinine[f]
- Total protein
- Albumin
- Urea

Lipid panel[a]
- Total cholesterol
- Triglycerides
- Low density lipoprotein (LDL) cholesterol
- High density lipoprotein (HDL) cholesterol

Liver panel
- Total bilirubin
- Direct bilirubin
- Indirect bilirubin
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase

Cystatin C[g]

- Pregnancy test[c]
- FSH[a, d]
- HbA1c[a]
- Ethanol testing
- Urine drug screen[h]

Abbreviations: FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HDL = high density lipoprotein; HIV = human immunodeficiency virus; LDL = low density lipoprotein; RBC = red blood cells; WBC = white blood cells.

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

[a] Performed at screening only

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

[c] For female participants only. Serum pregnancy test performed at screening. Urine pregnancy test at all other timepoints indicated in the Schedule of Activities. A serum pregnancy test may be used if urine testing is not possible.

[d] For female participants only. If needed to confirm postmenopausal status.

[e] A positive result will be confirmed by polymerase chain reaction test.

[f] eGFR will be calculated from creatinine. A separate sample at each timepoint will be collected and analyzed by a central laboratory for creatinine used for the calculation of eGFR.

[g] Analyzed by central laboratory.

[h] Salivary drug screen may be performed if a urine sample cannot be obtained.

10.2.1. Blood Sampling Summary

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

Protocol J2A-MC-GZPC Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Hematology, Clinical Chemistry[a]	12	5	60
Creatinine (central laboratory)	2.5	2	5
Cystatin C	2.5	1	2.5
LY3502970 pharmacokinetics	2	14	28
LY3502970 protein binding	20	3	60
Coproporphyrin 1 biomarker	3	4	12
Coproporphyrin 1 biomarker protein binding	20	4	80
Additional pharmacokinetics, if needed	2	3	6
Blood discard for cannula patency	1	1	1
Genetics	10	1	10
Total	120	39	309.5
Total for clinical purposes			310

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

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

10.3.1. Definition of Adverse Event

AE Definition

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition

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

Events <u>NOT</u> Meeting the AE Definition

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

10.3.2. Definition of Serious Adverse Event

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

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

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

10.3.3. Definition of Product Complaints

Product Complaint

- A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
    - Deficiencies in labeling information, and
    - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- PC related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

10.3.4. Recording and Follow-Up of Adverse Event, Serious Adverse Events, or both, and Product Complaints

AE, SAE, and Product Complaint Recording

- When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the PC Form.
- Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the PC Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of Serious Adverse Events

SAE Reporting via SAE report

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

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

Prompt notification by the investigator to the sponsor of a 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, IRB/IEC, and investigators.

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

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

10.4.2. Contraception Guidance

Female Participants

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle:

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to treatment exposure.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective. These forms of contraception must be used during the study and for at least 30 days after the last dose of the study intervention.

10.4.2.1. Male Participants

No male contraception is required except in compliance with specific local government study requirements.

Examples of highly effective, effective, and ineffective methods of contraception can be found below:

Methods	Examples
Highly effective contraception	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner)

Methods	Examples
	• fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices.

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide.

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

10.5. Appendix 5: Genetics

Use/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 bloodsample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to LY3502970 and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3502970. 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 continues but no longer than 7 years or other period as per local requirements.

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

Hepatic Evaluation Testing

See Section 8.2.7 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

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

The local laboratory must be qualified in accordance with applicable local regulations.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatitis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA[b]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA[b]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	**Hepatitis E virus (HEV) testing:**
Direct bilirubin	HEV IgG antibody
Alkaline phosphatase (ALP)	HEV IgM antibody
Alanine aminotransferase (ALT)	HEV RNA[b]
Aspartate aminotransferase (AST)	**Anti-nuclear antibody (ANA)**
Gamma-glutamyl transferase (GGT)	**Anti-smooth muscle antibody (ASMA)**[a]
Creatine kinase (CK)	**Anti-actin antibody**[c]
Hepatic Coagulation Panel	**Immunoglobulin IgA (quantitative)**
Prothrombin time, international normalized ratio (PT-INR)	**Immunoglobulin IgG (quantitative)**
Urine Chemistry	**Immunoglobulin IgM (quantitative)**
Drug screen	**Epstein-Barr virus (EBV) testing:**
Haptoglobin	EBV antibody
Acetaminophen protein adducts	

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Alkaline phosphatase isoenzymes	CMV antibody
Ceruloplasmin	CMV DNA[b]
Copper	**Herpes simplex virus (HSV) testing:**

Ethyl alcohol (EtOH)	HSV (Type 1 and 2) antibody
Phosphatidylethanol (PEth)	HSV (Type 1 and 2) DNA[b]
Urine Chemistry	Liver kidney microsomal type 1 (LKM-1) antibody
Ethyl glucuronide (EtG)	**Microbiology**
Epstein-Barr virus (EBV) testing:	Culture:
EBV DNA[b]	Blood
	Urine

a Not required if anti-actin antibody is tested.

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

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

10.7. Appendix 7: Calculation of Estimated Glomerular Filtration Rate

eGFR will be determined using the CKD-EPI (Delgado et al. 2021). The CKD-EPI equation is validated across a wide variety of populations and clinical conditions and has improved bias especially in population with higher levels of eGFR.

eGFR calculation (using creatinine and adjusting for body surface area; 2021 equation per Delgado et al. 2021) should be performed using the following:
https://www.kidney.org/professionals/kdoqi/gfr_calculator

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

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

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

Considerations for making a change

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

Informed consent

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

- participation in remote visits, as defined in Section Remote Visits, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

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

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

Other alternative locations

Data capture

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

Safety reporting

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

Return to on-site visits

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

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.9. Appendix 9: Prohibited Medications

Strong CYP3A inhibitors and inducers

Strong CYP3A inhibitors and inducers are not permitted in this study. The FDA has provided a list of strong CYP3A inhibitors and CYP3A inducers, comprising:

- boceprevir,
- cobicistat,
- danoprevir and ritonavir,
- elvitegravir and ritonavir,
- grapefruit juice,
- indinavir and ritonavir,
- itraconazole,
- phenytoin,
- enzalutamide,
- nelfinavir,
- ketoconazole,
- lopinavir and ritonavir,
- paritaprevir and ritonavir and ombitasvir and dasabuvir,
- posaconazole,
- ritonavir,
- saquinavir and ritonavir,
- telaprevir,
- apalutamide,
- mitotane,
- carbamazepine,
- tipranavir and ritonavir,
- telithromycin,
- troleandomycin,
- voriconazole,
- clarithromycin,
- nefazodone,
- rifampin, and
- St. John's wort.

Moderate CYP3A inhibitors and inducers

Moderate CYP3A inhibitors and inducers are not permitted in this study. Examples of moderate CYP3A inhibitors and inducers include, but are not limited to:

- aprepitant,
- atazanavir,
- atazanavir and ritonavir,
- berotralstat,
- cimetidine,
- ciprofloxacin,
- clotrimazole,
- crizotinib,
- diltiazem,
- dronedarone,
- duvelisib,
- erythromycin,
- fedratinib,
- fluconazole,
- fluvoxamine,
- fosnetupitant and palonosetron,
- isavuconazole,
- istradefylline,
- ledipasvir/sofosbuvir,
- lefamulin,
- letermovir,
- magnolia vine (Schisandra sphenanthera),
- netupitant,
- nilotinib,

- cyclosporine,
- darunavir,
- amprenavir,
- tofisopam,
- verapamil,
- voxelotor,
- lorlatinib,
- modafinil,
- nafcillin,
- imatinib,
- indinavir,
- bosentan,
- cenobamate,
- dabrafenib,
- danshen (Salvia miltiorrhiza),
- pentobarbital,
- primidone,
- thioridazine,
- efavirenz,
- elagolix,
- encorafenib,
- etravirine,
- genistein,
- lopinavir,
- tipranavir and ritonavir, and
- tocilizumab.

Strong OATP inhibitors

Strong OATP inhibitors are not permitted in this study. Examples of strong OATP inhibitors include, but are not limited to:

- rifampin,
- cyclosporine,
- faldaprevir,
- tipranavir/ritonavir,
- glecaprevir/pibrentasvir,
- telaprevir,
- sofobuvir/velpatsasvir/voxilaprevir,
- lopinavir/ritonavir,
- darunavir/ritonavir, and
- elvitegravir/cobicistat/emtricitabine /tenofovir disoproxil fumerate.

Anti-fungal agents

To be eligible for screening into this study the following conditions apply to anti-fungal agents:

If a participant is taking any of the following anti-fungal agents, they should discontinue taking these medications for at least 14 days or 5 half-lives (whichever is longer) prior to dosing ….	However, if the participant is unable to wash out these drugs because of an underlying condition, then if appropriate, the participant could switch to:
ketoconazole	miconazole
itraconazole	
voriconazole	
posaconazole	

Antibiotics

If a participant is taking the following antibiotics…	The following may be substituted 14 days prior to dosing:
clarithromycin	azithromycin
telithromycin	

Note: Topical antifungals and antibiotics are allowed. Exclusion of the above antifungals and antibiotics does not apply to use of topical products.

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
Ab	antibody
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from time 0 extrapolated to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time 0 to time t, where t is the last time point with a measurable concentration
BP	blood pressure
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
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.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRU	clinical research unit
CYP	cytochrome P450
DNA	deoxyribonucleic acid

ECG	electrocardiogram
EDC	electronic data capture system
eGFR	estimated glomerular filtration rate.
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.
FDA	Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

IP	investigational product; A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB	Institutional Review Board
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
OATP	organic anion-transporting polypeptides
participant	Equivalent to CDISC term "participant": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
QTc	corrected QT interval
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
T2DM	Type 2 diabetes mellitus
TBL	total bilirubin level
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

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