Protocol J2A-MC-GZGM(a)

A Phase 1, Open-label, Drug Interaction Study to Investigate the Effect of Multiple Doses of Clarithromycin on the Pharmacokinetics of LY3502970 in Healthy Participants

NCT05469126

Approval Date: 24-Jun-2022

Title Page

Protocol Title: A Phase 1, Open-label, Drug Interaction Study to Investigate the Effect of Multiple Doses of Clarithromycin on the Pharmacokinetics of LY3502970 in Healthy Participants

Protocol Number: J2A-MC-GZGM

Amendment Number: GZGM (a)

Compound: LY3502970

Brief Title: A drug interaction study investigating the effect of clarithromycin on the pharmacokinetics of LY3502970

Study Phase: 1

Acronym: GZGM

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana 46285, USA

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

Document ID: VV-CLIN-065880

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol J2A-MC-GZGM	*06- May-2022*

Amendment (a)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

This protocol has been amended in response to comment from DSRB Submission (Domain Specific Review Board) to incorporate additional ECG assessments. In addition, a few minor editorial changes have also been made. The following table describes the changes made in the amendment (a).

Section # and Name	Description of Change	Brief Rationale
Section 1.2: Schema	Made editorial changes	Made consistent with section 1.3
Section 1.3: Schedule of Activities (SoA)	Added body temperature under vital signs	Added as per the request from the site to make consistent with section 8.2.2
Section 1.3: Schedule of Activities (SoA)	Added single 12-lead ECG assessments on day 15 (baseline) and day 22 (upon administration of LY3502970 and clarithromycin).	Added as per the request from DSRB and clarified ECG language as single 12-lead ECG
Section 8.2.3: Electrocardiograms	Additional language added to □z□“□(□All single 12-lead ECGs recorded should be stored at the investigational site. All single 12-lead ECGs will be performed locally and will not be transmitted to a central laboratory□	Modified language for better clarity.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 1, Open-label, Drug Interaction Study to Investigate the Effect of Multiple Doses of Clarithromycin on the Pharmacokinetics of LY3502970 in Healthy Participants.

Brief Title:

A drug interaction study investigating the effect of **c**larithromycin on the pharmacokinetics of LY3502970.

Rationale:

Study J2A-MC-GZGM (GZGM) will investigate a potential drug-drug interaction (DDI) by evaluating the pharmacokinetics (PK) of LY3502970 in the absence and presence of clarithromycin.

Clarithromycin is being used as an inhibitor of CYP3A4 and P-glycoprotein (P-gp), to understand the effect of inhibition on the pharmacokinetics of LY3502970.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
□ To evaluate the effect of clarithromycin on the PK of LY3502970 in healthy participants	□ PK of LY3502970 (AUC and C_{max})
Secondary	
□ To evaluate the safety and tolerability of LY3502970 dosed alone and concomitantly with clarithromycin	□ Incidence of TEAEs and SAEs

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SAE = serious adverse events; TEAE = treatment-emergent adverse event.

Overall Design

Study GZGM is a phase 1, open-label, 2-period, fixed sequence single-arm study in healthy participants that will investigate the effect of multiple doses of clarithromycin on the pharmacokinetics (PK) of LY3502970. The study consists of a screening period, a treatment period, and a safety follow-up visit.

Brief Summary:

The purpose of this study is to investigate a potential drug-drug interaction (DDI) by evaluating the PK of LY3502970 in the absence and presence of clarithromycin.

Study details include:

- The study duration will be up to 85 days.
- The treatment duration will be 1 day (Period 1) and 17 days (Period 2)
  - Period 1: Participants will be admitted to the clinical research unit (CRU) on Day -2 for an inpatient treatment period of approximately 4 days
  - Period 2: Participants will be admitted to the CRU on Day 14 for an inpatient treatment period of approximately 18 days
- The follow-up visit will be from Day 37 to 43.

Number of Participants:

Approximately 24 participants will be enrolled to ensure that at least 20 evaluable participants complete the study.

Intervention Groups and Duration:

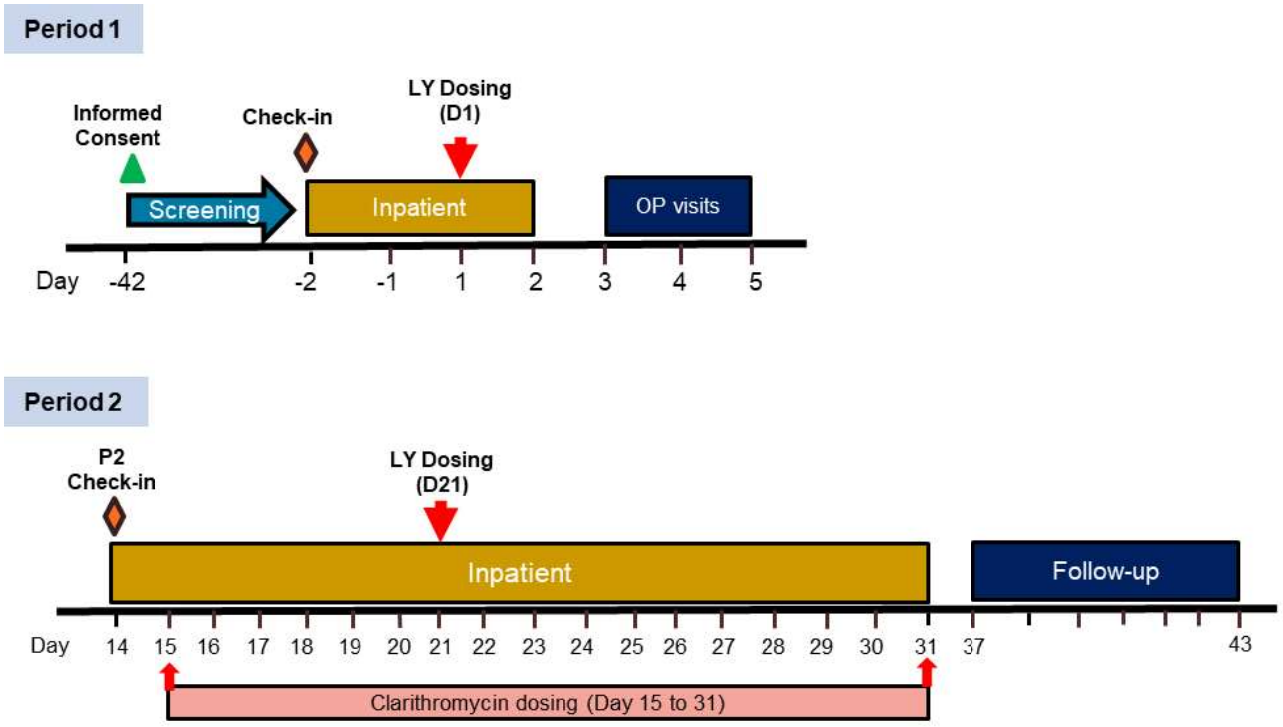
All participants will be screened within 42 days prior to enrollment. Eligible participants will be admitted to the CRU on Day -2 and remain resident in the CRU until discharge on Day 2. After a washout period of at least 14 days, participants will be admitted to CRU on Day 14 and remain resident in the CRU until discharge on Day 31. A follow-up visit will be performed on Day 37 to 43.

Participants will receive the following study intervention while resident in the CRU:

- Day 1: [redacted] mg LY3502970 alone
- Day 15 to 20: [redacted] mg clarithromycin every 12 hours (Q12H)
- Day 21: [redacted] mg clarithromycin followed by [redacted] mg LY3502970. Clarithromycin should be administered 1 hour prior to LY3502970 dose administration and a subsequent clarithromycin dose administered 12 hours later
- Day 22 to 31: Clarithromycin dosing (Q12H) will be continued until the morning of Day 31.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: D = day; LY = LY3502970; OP = outpatient; P = period.

1.3. Schedule of Activities (SoA)

Procedure	Screening	Baseline		On study							Follow -up	ET	Comments
				Period 1			Period 2						
Day	-42 to -3	-2	-1	1	2	3-5	14	15-20	21	22-31	37-43 days		
Out-patient visit	X					X					X		
Clinic admission		X					X						
Clinic discharge					X					D31			
Weight	X												
Height	X												
Vital signs and body temperature	X			P							X	X	
Clinical laboratory tests: □ Hematology □ Clinical chemistry □ Urinalysis	X			P							X	X	Local safety only. Refer Section 10.2 for details
Serum Calcitonin	X										X		
Serum Pregnancy	X												
Urine Pregnancy		X					X						

Procedure	**Screening**	**Baseline**		**On study**							**Follow -up**	**ET**	**Comments**
				Period 1			**Period 2**						
Day	**-42 to -3**	**-2**	**-1**	**1**	**2**	**3-5**	**14**	**15-20**	**21**	**22-31**	**37-43 days**		
Medical Assessment	X			P				X (Day 15)	P		X	X	Screening: full physical examination Other timepoints: targeted physical examination
Single 12-lead ECG	X			P				X		X	X	X	ECG will be performed on Day 15 and Day 22
Genetics sample			X										
LY3502970 dose				X					X				1 hr after clarithromycin AM dose in Period 2
Plasma PK samples for LY				P, 0.5, 1, 2, 4, 6, 8, 12, 16	24 (D2), 36 (D2)	48 (D3), 72 (D4), 96 (D5)			P, 0.5, 1, 2, 4, 6, 8, 12, 16	24, 36 (D22), 48 (D23), 72 (D24), 96(D25), 120 (D26)			Times are relative to LY dosing

Procedure	Screening	Baseline		On study							Follow -up	ET	Comments
				Period 1			Period 2						
Day	-42 to -3	-2	-1	1	2	3-5	14	15-20	21	22-31	37-43 days		
										168 (D28) 240 (D31)			
Clarithromycin dose ([redacted] mg Q12H)								X	X	X			On Day 21, dose AM clarithromycin 1 hr prior to LY dose.
Coproporphyrin plasma samples			0, 0.5, 1, 2, 4, 6, 8, 12, 16 hr	P (24 hr)				P, 0.5, 1, 2, 4, 6, 8, 12, 16 hr (D20)	P (24 hr)				0 hr sample at approximately 8 am. Note: Predose sample on Days 20 and 21 will be taken prior to clarithromycin administration
AE assessment and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: ECG = electrocardiogram; ET = early termination; LY = LY3502970; P = predose; PK = pharmacokinetics; Q12H = every 12 hours.

Note: If multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and blood samples (at the scheduled time).

2. Introduction

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

LY3502970 is being developed as a daily oral adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Clarithromycin is an antibiotic **used** to treat bacterial infections including pneumonia, Helicobacter pylori, and as an alternative to penicillin **for treating** strep throat. In the context of this study, it is being used as an inhibitor of CYP3A4 and P-glycoprotein (P-gp) to understand the effect of inhibition on the pharmacokinetics of LY3502970.

2.1. Study Rationale

The Study J2A-MC-GZGM (GZGM) will investigate a potential drug-drug interaction (DDI) by evaluating the pharmacokinetics (PK) of LY3502970 in the absence and presence of clarithromycin. In vitro, LY3502970 is a substrate of CYP3A4 and P-gp.

2.2. Background

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

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

Therefore, the development of additional oral GLP-1RA therapies with improved ease of use remains an unmet need. LY3502970 is an oral GLP-1RA that exhibits the antihyperglycemic 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 investigator's brochure (IB).

2.3. Benefit/Risk Assessment

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

The available safety data to date are from ongoing 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 study (J2A-MC-GZGA [GZGA])
- Doses up to [redacted] mg in the multiple-dose study (J2A-MC-GZGC [GZGC]) in participants with T2D
- A [redacted] mg dose in an open-label study (J2A-MC-GZGF) to determine the disposition of radioactivity in healthy male participants following administration of LY3502970
- Doses up to [redacted] mg in the multiple-dose study (J2A-MC-GZGJ) in fed and fasted healthy participants.

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

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

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

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of clarithromycin on the PK of LY3502970 in healthy participants	PK of LY3502970 (AUC and C_{max})
Secondary	
To evaluate the safety and tolerability of LY3502970 dosed alone and concomitantly with clarithromycin	Incidence of TEAEs and SAEs
Exploratory	
Effect of clarithromycin on endogenous OATP biomarker	Concentrations of biomarker coproporphyrin 1

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; OATP = □‘z□„–(z□„□□□z□□□□„‘ (□□-□‘□„—□; PK = pharmacokinetics; SAE = serious adverse events; TEAE = treatment-emergent adverse events.

4. Study Design

4.1. Overall Design

Study GZGM is a phase 1, open-label, 2-period, fixed sequence single-arm study in healthy participants that will investigate the effect of multiple doses of clarithromycin on the PK of LY3502970.

The schema in Section 1.2 illustrates the study design.

Screening

All participants will be screened for study inclusion within 42 days prior to enrollment (Day -2).

Treatment and Assessment Period

Participants will be admitted into the clinical research unit (CRU) on Day -2 and Day 14 for an inpatient treatment period. Approximately 24 participants will be enrolled to ensure that at least 20 evaluable participants complete the study.

While resident at the CRU, all participants will receive study intervention as follows:

Period 1:

On Day 1, LY3502970 will be administered orally as a single [redacted] mg dose with approximately 240 mL of water. Participants will be fasted overnight and remain fasted with no access to food for 4 hours after taking the study drug (see Section 5.3.1 for more details). Water is permitted ad libitum during the fasting period, except for 1 hour before and after dose administration.

Washout period:

Participants will be discharged from the CRU on Day 2 following the completion of study procedures. There will be a washout period of at least 14 days before period 2.

Period 2:

- Days 15 to 31: Clarithromycin will be administered orally as [redacted]-mg doses ([redacted]-mg tablet) every 12 hours (Q12H) with approximately 240 mL of water beginning on Day 15 to Day 31
- Day 21: LY3502970 will be administered orally as a [redacted] mg dose. Participants will be fasted overnight and remain fasted for 4 hours after taking the study drug. Clarithromycin should be administered 1 hour prior to LY3502970 dose administration.

Note: Clarithromycin should be taken at approximately the same times each day (Day 15 to 31) and may be taken with or without food, except for the morning dose on the day of LY3502970 dosing (Day 21) when it should be taken in the fasted state. Participants should remain fasted on this dosing day for 4 hours after the LY3502970 dose (see Section 5.3.1 for details).

PK blood sampling and safety assessments, including vital signs measurements, physical examinations, clinical laboratory tests, electrocardiograms (ECGs), and AE recording will be performed according to the Schedule of Activities (SoA; Section 1.3).

Participants will be discharged from the CRU on Day 31 following completion of study procedures, provided they are deemed medically fit by the investigator or designee.

Follow-Up

Participants will attend an outpatient follow-up visit from Day 37 to Day 43 after the final dose of study intervention. If participants are not able to attend the CRU for this visit, the CRU should contact the participant via phone call to conduct AE and concomitant medication review.

4.2. Scientific Rationale for Study Design

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

Clarithromycin is a time-dependent (irreversible) inhibitor of CYP3A4 and reversible inhibitor of P-gp. Due to the half-life of CYP3A4 enzyme, 6 days of continuous clarithromycin dosing is necessary for maximal effect on CYP3A4 activity (Ke et al. 2014). Accordingly, CYP3A4 activity takes days to recover after stopping clarithromycin dosing, hence the currently recommended dosing regimen and fixed sequence design.

The mean half-life of LY3502970 ranges from 24.6 to 35.3 hours across the doses in phase 1 study. LY3502970 is a substrate of CYP3A4, therefore, clarithromycin may increase the exposure and half-life of LY3502970. Hence, PK sampling for LY3502970 will be extended in period 2 compared to period 1. Clarithromycin will continue to be dosed until the last PK sample to ensure consistent complete CYP3A4 inhibition during the LY3502970 PK assessment.

In vitro, LY3502970 is a substrate of CYP3A4 and Pgp. It is also a substrate of hepatic organic anion-transporting polypeptides (OATPs). Along with inhibiting CYP3A4 and Pgp, clarithromycin is a weak inhibitor of hepatic OATPs in vitro (Prueksaritanont et al. 2017). Measurement of the endogenous OATP biomarker, coproporphyrin 1, is included to assess in vivo OATP inhibition by clarithromycin.

4.3. Justification for Dose

A dose of [redacted] mg clarithromycin administered every 12 hours for 6 days is known to fully inhibit CYP3A4 and inhibit intestinal P-gp (Ke et al. 2014; Prueksaritanont et al. 2017).

The dose of [redacted] mg of LY3502970 has been selected for this study based on tolerability in healthy volunteers. In the absence of dose titration, doses greater than [redacted] mg in healthy volunteers pose an increased risk of emesis. Depending on the time of occurrence of emesis relative to dosing, this can result in partial or complete loss of administered drug before it is absorbed, thereby compromising the results of the study.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled procedure shown in the SoA for the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

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 single 12-lead ECG. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

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

Screening will occur up to 42 days prior to enrollment. Participants who are not enrolled within 42 days of screening may undergo an additional medical assessment, clinical measurements, or both to confirm their eligibility. In such instances, repeat the following screening tests and procedures: medical assessment, vital signs, clinical laboratory tests, and single 12-lead ECG.

5.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, clinical laboratory tests, vital signs, and single 12-lead ECGs that are within the normal reference range for the population or investigator site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
3. Participants who have a hemoglobin level of at least 11.4 g/dL for female participants and at least 12.5 g/dL for male participants.
4. Participants who are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures including dietary requirements.
5. Participants who have venous access sufficient to allow for blood sampling as per the protocol.

Weight

6. Participants with a body weight of 45 kg or more and body mass index (BMI) within the range of 18.5 to 35.0 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

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

8. Women not of childbearing potential (WNOCBP) may participate in this study. Women of childbearing potential (WOCBP) will not be allowed to participate in the study

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol see Appendix 4 (Section 10.4).

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

10. Participants who have a significant history of or current cardiovascular, respiratory, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting risk when taking LY3502970; or of interfering with the interpretation of data.
11. Participants who have any abnormality in the single 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study.
12. Participants who have an abnormal blood pressure and/or pulse rate (seated systolic BP ≥160 mm Hg or seated diastolic BP ≥100 mm Hg), or otherwise deemed to be clinically significant by the investigator at screening.
13. Participants who have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis), elevation in serum amylase or lipase (>1.5-fold upper limit of normal [ULN]), or GI disorder (relevant esophageal reflux or gall bladder disease) or any GI disease, which impacts gastric emptying (gastric bypass surgery, pyloric stenosis, with the exception of appendectomy) or could be aggravated by GLP-1 analogs.
14. Participants who currently have clinically significant atopy or have a history of clinically significant multiple or severe drug allergies or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).
15. Participants who have liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or have elevations in aminotransferase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) greater than 2x ULN at screening.
16. Participants who have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
17. Participants who have a history of or current psychiatric disorders that in the opinion of the investigator would adversely affect patient safety or compliance.

18. Participants who regularly use known drugs of abuse.

Prior/Concomitant Therapy

19. Participants who have known allergies to LY3502970, related compounds, or any components of the formulation.
20. Participants who used or intend to use over the counter (OTC) or prescription medication and/or herbal/vitamin/traditional medicines or mineral supplements that may affect the safety or objectives of the study, as considered by the investigator after discussion with the sponsor if required, within 14 days (or 5 half-lives, whichever is longest) prior to dosing and for the duration of the study. Paracetamol and Covid-19 vaccinations are permitted.
21. Use of any drugs or substances that are known strong inducers, inhibitors or substrates of CYP3A are specifically excluded within 2 weeks prior to the first administration of study drug and during the study. The use of CYP3A drugs, substrates or inhibitors is excluded for 2 weeks following the last dose of clarithromycin.
22. Use of any drugs or substances that are known strong inducers or inhibitors of P-glycoprotein are specifically excluded within 14 days prior to the first administration of study drug and during the study.

Prior/Concurrent Clinical Study Experience

23. Participants who are currently enrolled in a clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study.
24. Participants who have participated, within the last 3 months, in a clinical study involving an IP. If the previous IP has a long $t_{1/2}$, 5 half-lives or 3 months (whichever is longer) should have passed since the last dosing, prior to check-in.

Diagnostic Assessments

25. Participants who show evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies. A negative test within 6 months of screening would not need to be repeated.
26. Participants who show evidence of hepatitis C and/or positive hepatitis C antibody. A negative test within 6 months of screening would not need to be repeated.
27. Participants who show evidence of hepatitis B, positive hepatitis B surface antigen, and/or positive hepatitis B core antibody. A negative test within 6 months of screening would not need to be repeated.
28. i z□□,–,,□z□□□(□’ □(’ z□“(□“□□□(–z–,,□□□,,□(-“□“-(□’(□A; (ng/L at screening visit.

Other Exclusions

29. Women who are lactating.
30. Women of child-bearing potential.
31. Participants who are unwilling to comply with the dietary restrictions required for this study.

32. Participants who have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) or are unwilling to stop alcohol consumption 24 hours prior to dosing until discharged from the CRU (1 unit = 12 oz or 360 mL of beer, 5 oz or 150 mL of wine, and 1.5 oz or 45 mL of distilled spirits.
33. Participants who smoke more than 10 cigarettes or e-cigarettes, 3 cigars, or 3 pipes per day and are unable or unwilling to refrain from smoking while resident at the CRU.
34. Participants who have donated blood of 450 mL or more, or participated in a clinical study that required a blood volume of 400 mL or more since the last study visit within the past 3 calendar months.
35. Participants who are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
36. Participants who are employees of Eli Lilly and Company or the CRU.
37. Participants who, in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.
38. Have history of renal impairment with estimated glomerular filtration rate < 90 ml/min/1.73 m^2.
39. Known QT prolongation or receiving drugs known to prolong the QT interval, ventricular arrhythmia (torsades de pointes), hypokalemia, significant bradycardia, or taking Class IA or III antiarrhythmics.
40. Have any medical conditions, medical history, or are taking any medications that are contraindicated in the clarithromycin prescribing information, such as prior history of hypersensitivity to clarithromycin.

5.3. Lifestyle Considerations

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

5.3.1. Meals and Dietary Restrictions

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.

LY3502970 will be administered after an overnight fast of at least 8 hours on Days 1 and 21. On these days, participants will remain fasted for approximately 4 hours postdose, at which time a meal will be served. Water is permitted ad libitum during the fasting period, except for 1 hour before and after dose administration (other than the water provided during dosing). On all other dosing days (i.e., clarithromycin alone on Days 15 to 20 and 22 to 31), there are no fasting requirements for dosing.

Clarithromycin can be taken with or without food, with the exception of the morning dose on the day of LY3502970 dosing (Day 21), in which it should be taken 1 hour prior to the LY3502970 dose in the fasted state.

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 abstain from ingesting caffeine- or xanthine-containing products (for example, coffee, tea, cola drinks, and chocolate) on Day 1 and Day 21.
- The participants should not consume alcohol for at least 24 hours before CRU admission and throughout the duration of the stay in the CRU.
- 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 clinical unit.

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 and reading).

5.3.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Repeating laboratory tests during the screening period or repeating screening tests to comply with the protocol designated screening period does not constitute rescreening.

5.4. Criteria for Temporarily Delaying Enrollment of a Participant

Not applicable

6. Study Intervention 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 Interventions Administered

This study involves the comparison of clarithromycin administered alone and clarithromycin co-administered with LY3502970. Table GZGM.1 shows the study interventions to be administered.

Table GZGM.1 Study Interventions Administered

Intervention Name	Clarithromycin	LY3502970
Type	drug	drug
Dose Formulation	tablet	capsule
Unit Dose Strength(s)	[redacted] mg IR tablet	[redacted] mg
Dosage Level(s)	[redacted] mg Q12H on Days 15 to 31	[redacted] mg on Day 1 and 21
Route of Administration	oral	oral
Use	perpetrator	experimental
IMP and NIMP	NIMP	IMP
Sourcing	Purchased locally by the trial site	Provided centrally by the Sponsor
Packaging and Labeling	Commercially available clarithromycin will be used	Study intervention will be provided in a container. Each container will be labeled as required per the country requirement

Abbreviations: IMP = investigational medicinal product; IR = immediate release; NA = not applicable; NIMP = non-investigational medicinal products; SC = subcutaneous; Q12H = every 12 hours.

6.2. Administration Details

Each dose of clarithromycin and LY3502970 will be administered orally with approximately 240 mL of room temperature water in the morning of each dosing day (see Section 1.3) in a sitting position. When clarithromycin and LY3502970 are administered on Day 21, 240 mL of room temperature water will be used for dosing of both products and clarithromycin should be administered 1 hour prior to LY3502970 dosing. If required to complete dosing, additional water

may be given in 50 mL aliquots and will be recorded in the source but will not be considered as a protocol deviation.

Participants will not be allowed to lie supine for 2 hours after LY3502970 dosing unless clinically indicated or for study procedures.

Doses of LY3502970 on Days 1 and 21 will be administered after an overnight fast of at least 8 hours and participants will remain fasting for approximately 4 hours postdose. Water is permitted ad libitum during the fasting period, except for 1 hour before and after dose administration. As mentioned previously, on Day 21, the administration of clarithromycin will occur one hour before the administration of LY3502970. On all other dosing days (i.e., clarithromycin alone on Days 15 to 20 and 22 to 31), there are no fasting requirements for dosing.

6.3. 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 Study Reference Manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

This is a non-randomized, open-label study.

6.5. 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.

6.6. Dose Modification

Dose modification will not be permitted in this study.

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

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

6.8. Treatment of Overdose

For this study, any dose of LY3502970 greater than [redacted] mg or clarithromycin greater than [redacted] mg within a 24-hour time period +/- 2 hours will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/serious adverse event (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 from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.9. Concomitant Therapy

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

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

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 14 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator preferably after discussion with the Sponsor, the medication will not interfere with the study.

CYP3A substrates, inhibitors, and inducers that are listed in the clarithromycin label as concomitant medicines of concern cannot be used 14 days prior to the first dose of study intervention nor for 14 days after the last dose of clarithromycin.

Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use during the study at the discretion of the investigator. Other concomitant medication may be considered on a case-by-case basis up on approval by the investigator in consultation with the sponsor if required.

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 (Section 10.1.7).

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study to complete procedures for an early discontinuation visit and posttreatment follow-up, if applicable, as shown in the SoA.

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons
- an AE that is considered to be intolerable
- an abnormal safety laboratory test result determined to be clinically significant by the Investigator.

7.1.1. Liver Chemistry Stopping Criteria

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

Elevation	Exception
ALT or AST >5x ULN	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	[illegible] doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL>2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN (when the source of increased ALP is the liver)	
ALP >2.5x ULN and TBL > 2x ULN	In participants [illegible] doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL>2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines with minor modifications	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FDA = Food and Drug Administration; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

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

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using [□,—“□,–,z□□(”□□□ □-z(tj m–[ν(after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the single 12-lead ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

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

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

Enrolled participants who discontinue without study intervention will not be required to attend the early termination visit.

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 the 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

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure as applicable.
- 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.
- If multiple procedures take place at the same time point, the following order of the procedure should be used: single 12-lead ECG, vital signs, and blood samples (at the scheduled time).
- Appendix 2 (Section 10.2) lists the laboratory tests that will be performed for this study.
- Appendix 2 (Section 10.2.1) provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.
- Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

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

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

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

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

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the Schedule of Activities (Section 1.3) and following the study-specific recommendations included in the eCRF
  - Vital sign measurements should be obtained before the collection of blood samples.
  - Additional vital signs may be measured during each study period if warranted.
  - Blood pressure and pulse rate should be measured after resting for at least five minutes in a supine position.
  - Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participant should be supine for approximately 5 minutes and stand for at least three minutes. If the participant feels unable to stand, supine vital signs only will be recorded.
  - Body temperature will be measured, as specified in the SoA, and as clinically indicated.

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcFintervals. Refer to Section 7.1.2 for QTcF withdrawal criteria and any additional QTcF readings that may be necessary.

Electrocardiograms must be recorded before collecting any vital signs or blood samples. Participants must be supine for 5 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high-quality records.

All single 12-lead ECGs recorded should be stored at the investigational site. All single 12-lead ECGs will be performed locally and will not be transmitted to a central laboratory.

ECGs will be interpreted by a qualified physician, the investigator, or a qualified designee at the site as soon after the time of ECG collection as possible. Ideally, the participant should be present

- to determine whether the participant meets entry criteria at the relevant visit, 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 evaluation. Any new clinically relevant finding should be reported as an adverse event.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

8.2.4. Clinical Safety Laboratory Tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. U-,,□,–z--□(□,‘ □,”,,–z□(z≥□□□□z-(
-z≥□□z□□□□(”,,□–,,□’ □(z□“(□’ □□“(□’ ,,–’ (z□“(□□□(z□□□–,,z□“–(□.,,□’ (□’“(□□–“-□.,,□’ (—,,□“z□“6(
□□-“□□(○–‘“–(≥□(□’“(,,□□“□,,‘ z□□□(□□(≥“(□ □□“(□“□“□“(□’z□(“□□“–□–(”□□(□’“(
□z□,,–,,□z□□1(–□□–,,,□□8
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.5. Pregnancy Testing

In this study, WOCBP will be excluded. In WNOCBP, serum or urine pregnancy test will be conducted as indicated in the SoA (Section 1.3).

8.2.6. Safety Monitoring

The Lilly clinical pharmacologist (CP) or clinical research physician (CRP) will monitor safety data throughout the course of the study.

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

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

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

8.2.6.1. Hepatic Monitoring

[illegible]

[illegible]

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	[illegible]
ALP <1.5x ULN	[illegible]
TBL <1.5x ULN	[illegible]
[illegible]	
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]

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

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	[illegible] oms[a], or [illegible]
ALP <1.5x ULN	[illegible]
TBL <1.5x ULN	[illegible]
[illegible]	[illegible][a], or [illegible]
[illegible]	ALP [illegible]
[illegible]	[illegible]

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

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

[illegible]

[illegible] consultation with the Lilly designated medical monitor, including tests for

- hepatitis D virus (HDV),
- cytomegalovirus (CMV),
- Epstein-Barr virus (EBV),
- acetaminophen levels,
- acetaminophen protein adducts,
- urine toxicology screen,
- [illegible],
- blood alcohol levels,
- urinary ethyl glucuronide, and
- blood phosphatidyl ethanol.

[illegible] condition, the investigator should consider referring the participant for a

- hepatologist or gastroenterologist consultation,

- magnetic resonance cholangiopancreatography (MRCP),
- endoscopic retrograde cholangiopancreatography (ERCP),
- cardiac echocardiogram, or
- liver biopsy

[illegible]

[illegible]

1. [illegible]
    - [illegible] on 2 or more consecutive tests
2. [illegible]
    - [illegible]
3. [illegible]
    - [illegible]
4. [illegible]
5. [illegible]

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

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

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

- AEs
- SAEs
- Product complaints (PCs)

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

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

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

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

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	signing of the informed consent form (ICF)	Until AE has resolved.	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					
SAE and SAE updates prior to start of study intervention **and** deemed reasonably possibly related to study procedures	signing of ICF	Until AE has resolved.	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates after start of study intervention	start of intervention	Until event has resolved	Within 24 hours of awareness	SAE paper form	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE* □after □z□□,–,, □z□□□(study participation has ended **and** the investigator becomes aware	After □z□□,–,, □z□□□(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	90 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	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	□	□	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

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

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male [illegible] 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 A; weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study be withdrawn from the study If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Events of Special Interest

Nausea, vomiting, and diarrhea events are considered adverse events of special interest (AESI) and will be recorded as AEs in the eCRF. For each event, assessment of severity, duration (start z□+(+□□□(–z“ □36(z□+(,,□□“□,,; z□□□□(□□,,,□□(□’(□“-z□“—□“□(□□(□□□–y intervention and protocol procedure will be captured.

Other AESI for this program include:

- cardiovascular events
- hypoglycemia
- hepatic events, and
- pancreatic events.

8.3.4. Pharmacokinetics

- Whole blood samples will be collected for measurement of plasma concentrations of LY3502970 as specified in the SoA.
- A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (for example, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of LY3502970. Samples collected for analyses of LY3502970 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.3.5. 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 (LC-MS/MS) method.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following the last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism and/or protein-binding work.

8.4. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.5. Genetics

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

See Appendix 5 (Section 10.5) for Information regarding genetic research and Appendix 1 (Section 10.1.9) for details about sample retention and custody.

8.6. Biomarkers

8.6.1. Coproporphyrin 1

At the visits and times specified in the Schedule of Activities, venous blood samples 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. Refer SoA (Section 1.3) for Coproporphyrin sampling timepoints.

Concentrations of coproporphyrin will be assayed using a validated LC-MS/MS method.

8.7. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8. Health Economics

This section is not applicable to this study.

9. Statistical Considerations

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

9.1. Statistical Hypotheses

The primary study objective is to evaluate the effect of clarithromycin on the PK of LY3502970 in healthy participants. The secondary objective is to evaluate the safety and tolerability of LY3502970 dosed alone and concomitantly with clarithromycin.

9.1.1. Multiplicity Adjustment

The effect of clarithromycin on the PK parameters of LY3502970 will be assessed through the 90% CIs for the geometric mean ratios of LY3502970 co-administered with clarithromycin relative to LY3502970 alone. Any statistical tests of treatment effects, if applicable, will be conducted at a 2-sided alpha level of 0.1.

No multiplicity adjustments will be made in this study.

9.2. Analyses Sets

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

Participant Analysis Population	Description
Entered	All participants who sign the ICF.
Enrolled	All participants assigned to study intervention, regardless of whether they take any doses.
Safety	All participants who receive at least 1 dose of study intervention. whether or not they completed all protocol requirements. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic	All participants who receive at least 1 dose of study drug and have evaluable PK data.
Coproporphyrin Biomarker	All participants who receive at least 1 period of evaluable coproporphyrin data.

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

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 Characteristics

m’ “(□z□□,,–,,□z□□□(z‘ “6(□“6(□“,,‘ ’ □6’ “,,‘ ’ □6race, ethnicity, and other demographic characteristics will be recorded and may be used in the PK and safety analyses as quantitative or classification variables.

9.3. Statistical Analyses

9.3.1. General Considerations

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

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

9.3.2. Primary Endpoint Analysis

9.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3502970 will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max}, time to reach C_{max} (t_{max}), AUC from time zero to the last time point with a measurable concentration ($AUC_{0\text{-}tlast}$), and AUC from time zero to infinity ($AUC_{0\text{-}inf}$) of LY3502970. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

All PK parameters will be listed and summarized using descriptive statistics.

9.3.2.2. Statistical Methods

Pharmacokinetic parameter estimates will be evaluated to delineate the effects of –z□,,’ □□□ □–,,□□□(interaction with LY3502970. The PK parameters C_{max} and AUC for LY3502970, when administered alone (reference) and in the presence of clarithromycin (test), will be compared using a linear mixed-effect model. The parameters will be log-transformed prior to analysis. The model will include treatment as a fixed effect and subject as a random effect. The least-square means for each treatment, the difference between the treatment least-square means (test□reference), and the associated 90% CIs will be estimated from the model and back-transformed from the log scale to provide estimates of the geometric means for each treatment, geometric mean ratio between test and reference treatments, and corresponding 90% CIs. A DDI will be assessed by examining the 90% CIs for the geometric mean ratios of LY3502970 co-administered with clarithromycin relative to LY3502970 alone.

The t_{max} of LY3502970 for both treatments, test and reference, will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference and approximately 90% CI will be reported.

9.3.3. Secondary Endpoint Analysis

9.3.3.1. Safety Analyses

All IP and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. The incidence of TEAEs and SAEs for each treatment will be presented by severity and by association with IP or study procedure as perceived by the investigator. Adverse events reported to occur prior to the first study dose will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities. The number of IP-related SAEs will be reported.

All safety analyses will be made on the Safety Analysis Set. Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data. Laboratory measurements will be summarized with respect to observed values by treatment, at each time point, using descriptive statistics. In addition, all clinical chemistry, hematology, and urinalysis data outside the reference ranges will be tabulated by parameter and treatment. Vital signs will be summarized with respect to observed values and change from baseline values by treatment at each time point using descriptive statistics.

9.3.4. Exploratory Endpoint Analysis

9.3.4.1. Coproporphyrin Analyses

Plasma concentrations of coproporphyrin 1 will be listed and summarized, using standard descriptive statistics. Parameter estimates for coproporphyrin 1 will be calculated by standard noncompartmental methods. Parameters, including C_{max}, t_{max}, and $AUC_{0\text{-}tlast}$, will be summarized using descriptive statistics.

Additional analysis may be performed, if warranted, upon review of the data.

9.3.4.2. Statistical Methods

The PK parameters C_{max} and AUC for coproporphyrin (test, i.e. after clarithromycin treatment) with the C_{max} and AUC for coproporphyrin (reference, i.e., prior to clarithromycin treatment) will be compared using a linear mixed-effect model. The parameters will be log-transformed prior to analysis. The model will include treatment as a fixed effect and subject as a random effect. The least-square means for each treatment, the difference between the treatment least-square means (test□reference), and the associated 90% CIs will be estimated from the model and back-transformed from the log scale to provide estimates of the geometric means for each treatment, geometric mean ratio between test and reference treatments, and corresponding 90% CIs.

9.3.5. Other Analyses

Details for other analyses may be documented in the SAP.

9.3.6. 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.

9.3.7. Sample Size Determination

Approximately 24 participants will be enrolled to ensure that at least 20 evaluable participants complete the study.

The sample size is calculated to quantify the clarithromycin effect on each PK parameter of interest (AUC and C_{max}) of LY3502970. Assuming an intra-subject coefficient of variation (CV) of 28% and 20% for AUC and Cmax respectively based upon the analyses in a previous study (GZGA), this sample size will provide approximately 90% chance to ensure no more than 2-fold increase on each LY3502970 PK parameter of interest induced by clarithromycin assuming up to 50% increase of a true effect.

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 the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- 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 [illegible] representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 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 ICFs during their participation in the study.
- A copy of the ICFs must be provided to the participant 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 [illegible] 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. 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.

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

Data

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

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source data may include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

- Study monitors will perform ongoing source data verification to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

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

Data managed by a central vendor, such as laboratory test data, will be stored electronically in [illegible] reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

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

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the [illegible]

- Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.5.

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.8. Publication Policy

b(z—z–“(,’(’“(≥-,–z,(-,–6(’“(“-(’’(’,,((—(,–(≥“(≥,‘’–(
for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.9. Long-term Sample Retention

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

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

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

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

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

Sample Retention Period

Sample Type	Custodian	Retention Period After Last Patient Visit*
PK	Sponsor or Designee	1 yr
Genetics	Sponsor or Designee	7 yr
Biomarkers (coproporphyrin)	Sponsor or Designee	1 yr

Abbreviation: PK = pharmacokinetics.

* Retention periods may differ locally

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the local laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- 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	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium (total)
Mean cell hemoglobin concentration	Phosphate
Leukocytes (WBC)	Glucose, fasting
Platelets	Urea
Differential WBC [Absolute counts] of:	Creatinine
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Total bilirubin
Eosinophils	Alkaline phosphatase (ALP)
Basophils	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Urinalysis	Gamma-glutamyl transferase (GGT)
Specific gravity	Amylase
pH	Lipase
Protein	
Glucose	Fasting Lipid Panel[a]
Ketones	Total cholesterol
Bilirubin	Triglycerides
Urobilinogen	LDL
Leukocytes	HDL
Blood	
Nitrite	Hepatitis B surface antigen[a,b]
Microscopic examination of sediment[c]	Hepatitis B core antibody (Total)[a,b]
	Hepatitis C antibody[a,b]
Calcitonin[d]	HIV[a,b]
	Pregnancy test[e]
	FSH[a,f]

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

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

[a] Performed at screening only

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

[c] Test only if dipstick result is abnormal and are further definable by microscopy. Microscopy to be performed at

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

[e] Serum pregnancy test at screening. Urine pregnancy test at all other timepoints

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

10.2.1. Blood Sampling Summary

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

Protocol J2A-MC-GZGM Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a] including serum calcitonin	25	1	25
Clinical laboratory tests[a]	10	2	20
Serum Calcitonin	5	1	5
LY3502970 Pharmacokinetics	2	31	62
Coproporphyrin plasma concentrations	3	20	60
Additional PK (if needed)	3	3	9
Blood discard for cannula patency	0.3	47	14.1
Pharmacogenetics	10	1	10
Total			205.1
Total for clinical purposes [rounded up to nearest 10 mL]			210

Abbreviation: PK = pharmacokinetics.

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

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

10.3.1. Definition of AE

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

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 DDI. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <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 The disease/disorder being studied or expected progression, signs, or symptoms of the condition. Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to a hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have ≥“““□(z□□□□□,z□“(,,□’“(□’□□,–,z□□□(□”,,–“(□(□□□□z,,“□(
setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The t“□(—,,z≥,-,,□(□“z□(z(□≥□z□,,z-(—,,□□□□,,□□(□’(z(□“□□□□□(z≥,-,,□(□(–□□–□–(
normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

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

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information [illegible] clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.

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

- It is **not** z—“z≥-“(”(’“(„“„’ z((“—(’ –„“(”(’“(z„-„z(“—„z-(records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

  S(““(„(—“”„“—(z(“„(’ “(„(““““(z(-“z(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 b□□“ □□,; z□□□□□(T □□–’ □□“(2bT3(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 Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.5. Reporting of SAEs

SAE Reporting via SAE Report

- Facsimile transmission of the SAE Report is the preferred method to transmit this information to the sponsor or designee.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Report within the designated reporting time frames.
- Contacts for SAE reporting can be found in 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the b□□“□,; z□□□□(Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

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, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

10.4.1. Contraception Guidance

10.4.1.1. Female Participants

1. Women of childbearing potential (WOCBP) are excluded from the trial.
2. Women not of childbearing potential (WNOCBP) may participate in this trial.

See Appendix 4 (Section 10.4) above for definitions.

10.4.1.2. Male Participants

The table below describes contraception guidance for men.

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

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

Methods	Examples
Highly effective contraception	• combination of oral contraceptive pill and mini pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic [illegible] susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to LY3502970 orT2D and related diseases. They may also be used to develop tests/assays including diagnostic tests related toLY3502970 and T2D. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- [DNA samples will be analyzed for [describe planned analyses]. [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 toLY3502970 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on LY3502970 continues but no longer than 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 8.2.6.1 for guidance on appropriate test selection.

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

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

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

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)

Hematology	**Clinical Chemistry**
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA[b]	Anti-actin antibody[c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[b]	EBV DNA[b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[b]	HSV (Type 1 and 2) DNA[b]
Microbiology[d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
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 (ASMA) is tested.

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

10.7. Appendix 7: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

[illegible] 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 [illegible] 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, 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, 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.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for plasma PK. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- working with the sponsor to determine how study intervention that is typically administered on site will be administered to the participant; for example, during a mobile healthcare visit or at an alternate location such as an infusion center.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of [illegible] receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, [illegible] "), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).

- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

If study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, this additional requirement must be met:

- Only authorized study personnel may supply, prepare or administer study intervention.

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 „□□“□□„ z□□□□source documentation and should be transferred to the site in a secure and timely manner.

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CI	confidence interval
CLcr	creatinine clearance
CMV	cytomegalovirus
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CT	computed tomography
CTA	Clinical Trial Agreement
CV	coefficient of variation
DDI	drug-drug interaction

Term	Definition
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERCP	endoscopic retrograde cholangiopancreatography
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	b□□“□□„‘ z□□□□□(T□□–’ □□“
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
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 □z□□„–„□z□□□decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board

Term	Definition
LC-MS/MS	liquid chromatography-tandem mass spectrometry
NIMP	Non-investigational Medicinal Product
OATP	organic z□,,□□□□z□□□□□,,□‘ (□□-□□“□,,—“
participant	Equivalent to CDISC term □□□≥ơ‘–□□I(z□(,,□ ,,□,,—□z-(□’ □(□z□□,,–,,□z“□(,,□(z(—,,□,,–z-(□□,z-6(either as recipient of an investigational medicinal product or as a control
PC	product complaint
P-gp	P-glycoprotein
PK/PD	pharmacokinetics/pharmacodynamics
QD	once daily
QW	once weekly
QTc	corrected QT interval
QTcF	j m(,,□“□□z-(–□□□“–□“–(–□□,,□‘ ([□,,–“□,,–,,z□□(”□□□ □-z
Q12H	every 12 hours
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
T2D	type 2 diabetes
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

11. References

Hedrington MS, Davis SN. Oral semaglutide for the treatment of type 2 diabetes. *Expert Opin Pharmacother*. 2019;20(2):133-141. https://doi.org/10.1080/14656566.2018.1552258.

Ke AB, Zamek-Gliszczynski MJ, Higgins JD, Hall SD. Itraconazole and clarithromycin as ketoconazole alternatives for clinical CYP3A inhibition studies. *Clin Pharmacol Ther*. 2014;95(5):473-6.

Prueksaritanont T, Tatosian DA, Chu X, et al. Validation of a microdose probe drug cocktail for clinical drug interaction assessments for drug transporters and CYP3A. *Clin Pharmacol Ther*. 2017;101(4):519-530.

Rybelsus (semaglutide) [package insert]. Bagsvaerd, Denmark: Novo Nordisk; 2019.

Signature Page for VV-CLIN-065880 v1.0

Approval	PPD Statistician 24-Jun-2022 13:45:13 GMT+0000

Approval	PPD Medical Director 24-Jun-2022 14:10:41 GMT+0000

Signature Page for VV-CLIN-065880 v1.0

Approved on 24 Jun 2022 GMT