Protocol J2A-MC-GZGL(a)

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

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Approval Date:13-Sep-2022

Title Page

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

Protocol Number: J2A-MC-GZGL

Amendment Number: (a)

Compound: LY3502970

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

Study Phase: 1

Acronym: GZGL

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-074384

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	27-Jul-2022

Amendment (a)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

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

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

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria	Exclusion Criterion [13] updated to not include participants 'who used' the medication listed.	Assessment of participants who used OTC and prescription medication within 14 days of dosing and for the duration of the study cannot be assessed during screening, only the 'intention to use' can be assessed.
Section 5.2 Exclusion Criteria	Exclusion Criterion [23] changed from 12 weeks prior to 'dosing' to 'screening'.	This criterion cannot be assessed on the screening day, therefore the timing was changed so that assessment did not occur on Day -2 (prior enrollment).
Section 5.2 Exclusion Criteria	New Exclusion Criterion [35] added to update exclusion criteria related to QT prolongation.	Non-clinical studies of LY3502970 and other GLP-1 receptors have observed cardiovascular effects in humans. Therefore, QT exclusion criteria have been added, and align with the protocol for the prior Study J2A-MC-GZGM.
Section 5.2 Exclusion Criteria Section 6.8 Concomitant Therapy	Details of concomitant therapy restrictions detailed in the previous Exclusion Criteria [14], [15], [16], and [17] moved to Section 6.8 and wording clarified.	Descriptions of concomitant therapy restrictions and exclusions are better described in the Concomitant Therapy section.

Section # and Name	Description of Change	Brief Rationale
Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments	All tests that were to be performed by the local laboratory, except for Microbiology tests, will instead be tested by the central laboratory.	Through discussion with the Clinical Laboratory Services, it has become clear that the central laboratory will provide full hepatic kits to the site that will cover the tests that have shifted from local to central laboratory in Appendix 6 (Section 10.6).

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

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

Brief Title:

A drug interaction study investigating the effect of cyclosporine on the pharmacokinetics of LY3502970.

Rationale:

LY3502970 is a chemically synthesized, oral glucagon-like peptide-1 receptor agonist that exhibits the antihyperglycemic actions of glucagon-like peptide-1. Study J2A-MC-GZGL (GZGL) will investigate a potential drug-drug interaction by evaluating the pharmacokinetics (PK) of LY3502970 in the absence and presence of cyclosporine. Cyclosporine is being used as an inhibitor of hepatic organic anion-transporting polypeptides (OATPs). CCI [redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of multiple oral doses of cyclosporine on the PK of a single oral dose of LY3502970 in healthy participants	• PK of LY3502970 (AUC and C_{max})
Secondary	
• To evaluate the safety and tolerability of a single oral dose of LY3502970 dosed alone and concomitantly with multiple oral doses of cyclosporine in healthy participants	• 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 event; TEAE = treatment-emergent adverse event.

Overall Design

Study GZGL 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 cyclosporine on the PK of LY3502970. The study consists of a screening period, 2 treatment periods, and a safety follow-up visit.

Brief Summary:

Study details include:

- The study duration will be up to 76 days.
- The treatment duration will be 2 days in Period 1 and 6 days in 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 8 days.
- The follow-up visit will occur between Days 27 and 34.

Study Population:

Females not of childbearing potential and male participants who are overtly healthy, aged 21 to 70 years inclusive, with a body weight of 45 kg or more, and body mass index within the range 18.5 to 35.0 kg/m^2 (inclusive).

Number of Participants:

Approximately 30 participants will be enrolled to ensure that approximately 20 evaluable participants complete the study.

Intervention Groups and Duration:

All participants will be screened for study inclusion within 41 days prior to enrollment (Day -2). Participants will be admitted into the CRU on Day -2 and will remain resident in the CRU until discharge on Day 2. Participants will attend outpatient visits for study procedures on Days 3 to 5. After a washout period of at least 14 days, participants will be admitted to the CRU on Day 14 and remain resident in the CRU until discharge on Day 21. A follow-up visit will be performed on Days 27 to 34. While resident at the CRU, all participants will receive study intervention as follows:

- Period 1:
    - On Day -1, midazolam will be administered as a single 200 µg oral dose.
    - On Day 1, LY3502970 will be administered as a single 3 mg oral dose.
- Period 2:
    - On Days 15 to 19, cyclosporine will be administered twice daily as a 200 mg oral dose. On Day 20, cyclosporine will be administered once in the morning as a single 200 mg oral dose.
    - On Days 16 and 19, midazolam will be administered as a single 200 µg oral dose concurrently with the morning dose of cyclosporine.
    - On Day 17, LY3502970 will be administered as a single 3 mg oral dose, 4 hours after the morning dose of cyclosporine.

Ethical Considerations of Benefit/Risk:

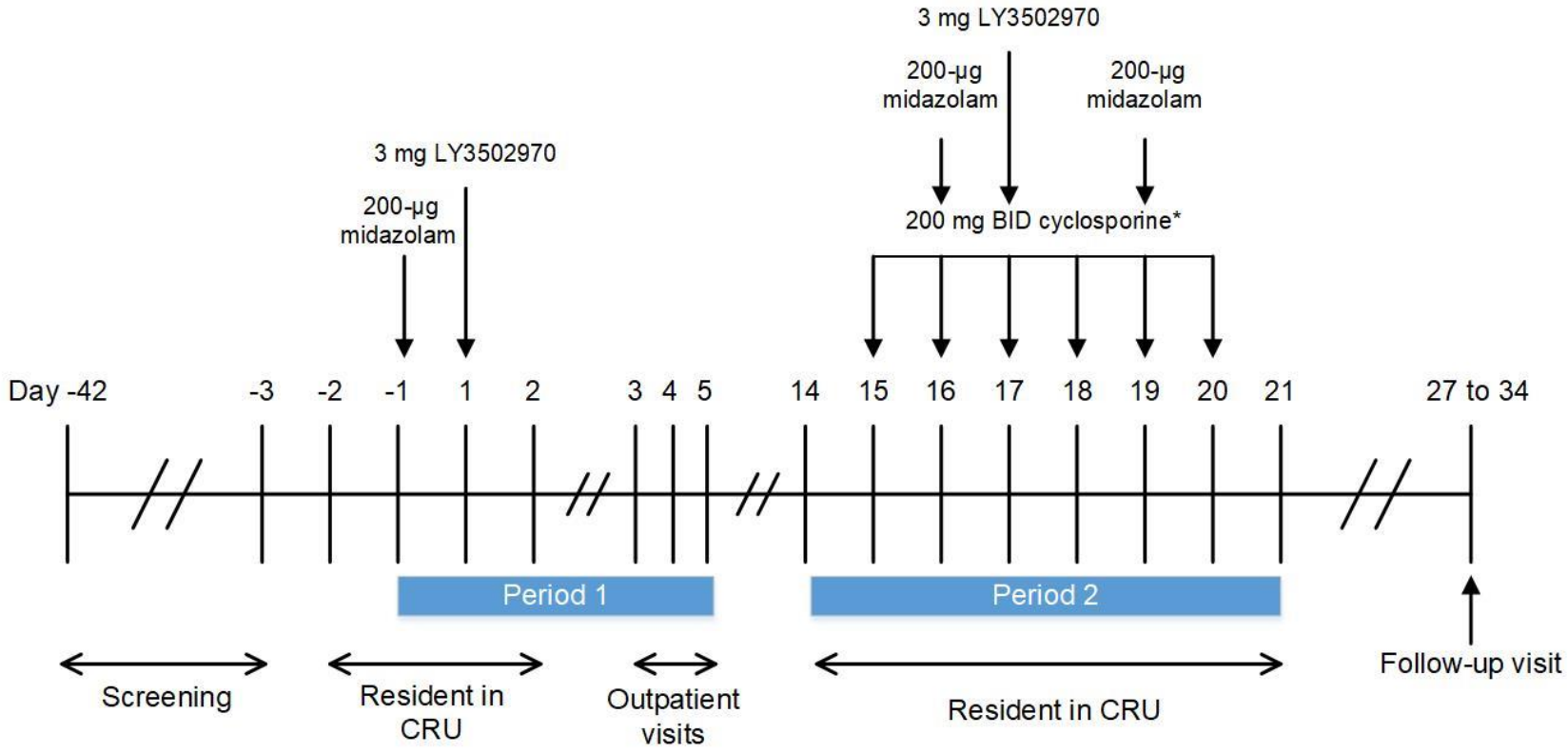
No unexpected safety or tolerability concerns have been identified to date in participants administered LY3502970 up to the highest single dose of 6 mg and multiple doses of 45 mg for a maximum of 49 days.

The most frequent adverse events (AEs) were gastrointestinal AEs. This included nausea, decreased appetite, vomiting, and constipation. These were mostly mild in severity and the majority resolved without treatment.

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.

Data Monitoring Committee: No.

1.2. Schema



Abbreviations: BID = twice daily; CRU – clinical research unit.

1.3. Schedule of Activities

Procedure	Scr	B	On Study									Follow-up	ET	Comments
			Period 1				Period 2							
Day	**-42 to -3**	**-2**	**-1**	**1**	**2**	**3-5**	**14**	**15**	**16**	**17**	**18-21**	**27-34**		
Outpatient visit	X					X						X		
Clinic admission		X					X							
Clinic discharge					X						D21			
Medical history	X													
Weight	X													
Height	X													
Vital signs	X		2h	P				P	X	X	X	X	X	On Day -1, 2h time point relative to midazolam dosing.
Body Temperature			X				X							
Clinical laboratory tests (hematology, clinical chemistry,	X			P				P		X	D21	X	X	Local safety laboratory tests. Refer to Section 8.2.4 for details. Glucose should be measured fasted. On

Procedure	Scr	B	On Study									Follow-up	ET	Comments
			Period 1				Period 2							
Day	-42 to -3	-2	-1	1	2	3-5	14	15	16	17	18-21	27-34		
and urinalysis)														Day 21, only clinical chemistry assessed.
Serum calcitonin	X										D21	X	X	
Serum pregnancy	X													
Urine pregnancy			X				X							
Medical assessment	X		P					P			D21	X	X	Screening: full physical examination. Other time points: Targeted physical examination.
Single-lead ECG	X			P						P	D21	X	X	
Genetic sample				P										
Midazolam dose			X						X		D19			On Days 16 and 19, midazolam dosed concurrently with the morning dose of cyclosporine.

Procedure	Scr	B	On Study									Follow-up	ET	Comments
			Period 1				Period 2							
Day	**-42 to -3**	**-2**	**-1**	**1**	**2**	**3-5**	**14**	**15**	**16**	**17**	**18-21**	**27-34**		
LY3502970 dose				X						X				On Day 17, 4 hours after cyclosporine morning dose.
Cyclosporine BID dosing								X	X	X	D18, D19, D20			On Day 20, only the morning dose of cyclosporine will be administered.
Midazolam PK			P, 0.5, 1, 2, 4, 6, 8, 12h	24h (P)					P, 0.5, 1, 2, 4, 6, 8, 12h	24h (P)	D19 (P), 0.5, 1, 2, 4, 6, 8, 12h, D20 (24h)			Sample time relative to midazolam dose. The 24h sample collected before LY3502970 on Days 1 and 17.
LY3502970 PK				P, 0.5, 1, 2, 4, 6, 8, 12, 16h	24h	48 (D3), 72 (D4), 96h (D5)				P, 0.5, 1, 2, 4, 6, 8, 12, 16h	24 (D18), 48 (D19), 72 (D20), 96h (D21)			Sample time relative to LY3502970 dose.
Coproporphyrin 1 plasma samples			P, 0.5, 1, 2, 4, 6, 8, 12h	24h					P, 0.5, 1, 2, 4, 6, 8, 12h	24h/P, 0.5, 1, 2, 4, 6, 8, 12h	24h (D18)			Sample time relative to midazolam/ cyclosporin morning dose.

Procedure	Scr	B	On Study									Follow-up	ET	Comments
			Period 1				Period 2							
Day	**-42 to -3**	**-2**	**-1**	**1**	**2**	**3-5**	**14**	**15**	**16**	**17**	**18-21**	**27-34**		
Cyclosporine PK								P, 2, 4, 12h (P)	P, 2, 4, 12h (P)	P, 2, 4, 12h (P)				Sample time relative to morning dose.
AE assessment and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; B = baseline; BID = twice daily; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; D = Day; P = predose; PK = pharmacokinetic; Scr = screening.

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

2. Introduction

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

LY3502970 is being developed as a daily oral adjunct therapy to diet and exercise to improve glycemic control in adults with T2D.

Cyclosporine is an immunosuppressant used to prevent organ transplantation rejection and treat inflammatory diseases such as rheumatoid arthritis and psoriasis. In the context of this study, it is being used as an inhibitor of hepatic OATPs, to understand the effect of inhibition on the PK of LY3502970.

2.1. Study Rationale

Study J2A-MC-GZGL (GZGL) will investigate a potential DDI by evaluating the PK of LY3502970 in the absence and presence of cyclosporine. Cyclosporine is being used as an inhibitor of hepatic OATPs. CCI [redacted]

2.2. Background

Multiple GLP-1RA therapies are approved. These are most commonly administered either once daily or once weekly through subcutaneous injection. Even with several different GLP-1RAs approved for use in T2D mellitus, the injection remains a barrier for many patients to initiate and to 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 at least 6 hours,
- no more than approximately 120 mL of water at administration, and
- no food or fluid for at least 30 minutes after taking the medication.

Therefore, development of additional oral GLP-1RA therapies with improved ease of use remains an unmet need. LY3502970 is an oral GLP-1RA that exhibits the antihyperglycemic actions of GLP-1. It acts as an insulin secretagogue and increases glucose-dependent insulin secretion after a glucose challenge.

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

2.3. Benefit/Risk Assessment

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

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

- doses up to 6 mg in the first-in-human single-ascending dose and up to 24 mg in the multiple-ascending dose study (J2A-MC-GZGA [GZGA])
- doses up to 45 mg in the multiple-dose study (J2A-MC-GZGC [GZGC]) in participants with T2D
- a 3-mg dose in an open-label study (J2A-MC-GZGF) to determine the disposition of radioactivity in healthy male participants following administration of LY3502970, and
- doses up to 16 mg in the multiple-dose study (J2A-MC-GZGJ [GZGJ]) in fed and fasted healthy participants.

The most frequent AEs were 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 multiple oral doses of cyclosporine on the PK of a single oral dose of LY3502970 in healthy participants	• PK of LY3502970 (AUC and C_{max})
Secondary	
• To evaluate the safety and tolerability of a single oral dose of LY3502970 dosed alone and concomitantly with multiple oral doses of cyclosporine in healthy participants	• Incidence of TEAEs and SAEs
Exploratory	
• To evaluate the exposure of cyclosporine following single and multiple oral doses in healthy participants	• Blood concentrations of cyclosporine
• To evaluate the effect of multiple oral doses of cyclosporine on CYP3A activity in healthy participants	• PK of midazolam and 1'-hydroxymidazolam (AUC and C_{max})
• To evaluate the effect of multiple oral doses of cyclosporine on endogenous OATP biomarker in healthy participants	• Concentrations of biomarker coproporphyrin 1

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; CYP = cytochrome P450; OATP = organic anion-transporting polypeptides; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study GZGL 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 cyclosporine on the PK of LY3502970.

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

Screening

All participants will be screened for study inclusion within 41 days prior to enrollment (Day -2).

Treatment and Assessment Period

Participants will be admitted into CRU on Day -2 and Day 14 for an inpatient treatment period. Approximately 30 participants will be enrolled to ensure that approximately 20 evaluable participants complete the study.

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

Period 1:

On Day -1, midazolam will be administered as a single 200 µg oral dose with approximately 240 mL of water. Participants will be fasted overnight and remain fasted for approximately 2 hours after receiving midazolam (see Section 5.3.1 for more details). Water is permitted ad libitum during the fasting period, except for 1 hour before and after midazolam dose administration.

On Day 1, LY3502970 will be administered as a single 3 mg oral dose with approximately 240 mL of water. Participants will be fasted overnight and remain fasted for approximately 2 hours after receiving LY3502970. Water is permitted ad libitum during the fasting period, except for 1 hour before and after LY3502970 dose administration.

Washout period:

Participants will be discharged from the CRU on Day 2 following completion of study procedures. Participants will attend outpatient visits for study procedures on Days 3 to 5. There will be a washout period of at least 14 days between LY3502970 doses before Period 2.

Period 2:

On Days 15 to 19, cyclosporine will be administered BID as a 200 mg oral dose with approximately 240 mL of water. On Day 20, cyclosporine will be administered once in the morning as a single 200 mg oral dose with approximately 240 mL of water.

On Days 16 and 19, midazolam will be administered as a single 200 µg oral dose concurrently with the morning dose of cyclosporine with approximately 240 mL of water. Participants will be fasted overnight and remain fasted for approximately 2 hours after receiving midazolam. Water is permitted ad libitum during the fasting period, except for 1 hour before and after midazolam dose administration.

On Day 17, LY3502970 will be administered as a single 3 mg oral dose, 4 hours after the morning dose of cyclosporine. LY3502970 will be administered with approximately 240 mL of water after an overnight fast and participants will remain fasted for approximately 2 hours after receiving LY3502970. Water is permitted ad libitum during the fasting period, except for 1 hour before and after LY3502970 dose administration.

Participants will be discharged from the CRU on Day 21 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 between Days 27 to 34. 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, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable responses in safety based on race or ethnicity. This question can be answered only if all the relevant data are collected.

CCI [redacted]

The mean $t_{1/2}$ of LY3502970 ranges from 24.6 to 35.3 hours; therefore, PK sampling up to 96 hours and a washout period of 14 days between doses is considered sufficient. Clinically, cyclosporine administration increases the overall exposure of hepatic OATP substrates generally without an increase in the substrate $t_{1/2}$; therefore, LY3502970 PK sampling up to 96 hours is considered sufficient in the presence of cyclosporine. The t_{max} of LY3502970 ranges from 4 to 12 hours. The t_{max} of cyclosporine is approximately 2 hours. As cyclosporine may inhibit enzymes/transporters in the intestine, LY3502970 is to be dosed 4 hours after cyclosporine to minimize interaction between cyclosporine and LY3502970 in the intestine. The t_{max} of the evening dose of cyclosporine is expected to occur within the range of LY3502970 t_{max}.

Measurement of the endogenous OATP biomarker, coproporphyrin 1, is included to selectively assess in vivo hepatic OATP inhibition by cyclosporine.

Clinical data suggest cyclosporine weakly inhibits CYP3A, when assessed at an average dose of 203 mg per day in renal allograft patients (de Jonge et al. 2011). Assessment of CYP3A index substrate midazolam is included to determine the effect of the current cyclosporine regimen on CYP3A activity in healthy volunteers. Additionally, inhibition of CYP3A can be time dependent, which has not been clinically assessed for cyclosporine; therefore, effect of cyclosporine on midazolam PK will be assessed on Days 16 and 19. Due to expression of CYP3A in the intestine, midazolam will be administered simultaneously with cyclosporine in Period 2.

While cyclosporine is extensively metabolized by CYP3A (Neoral, United States Prescribing Information, 2009), it was shown in Study GZGA that LY3502970 does not affect CYP3A activity up to 24 mg daily. Cyclosporine is also a substrate of P-glycoprotein; however, staggered dosing of LY3502970 and cyclosporine is planned to minimize any interactions at intestinal

enzymes/transporters. Therefore, no effect of a single 3-mg dose of LY3502970 on cyclosporine PK is anticipated. However, cyclosporine blood concentrations will be assessed in the study, as data on multiple-dose cyclosporine PK in healthy volunteers is currently limited, to determine achievement of steady-state.

4.3. Justification for Dose

The dose of 3 mg of LY3502970 has been selected for this study as it is expected to be reasonably well tolerated in healthy volunteers without dose titration. The selection of this dose is also supported by linear PK to the efficacious doses (based on data for 0.3 to 24 mg dose range in Study GZGA).

Similar dosing regimens for cyclosporine have been evaluated clinically to assess drug interactions in healthy volunteers, for example 175 to 200-mg BID for 4.5 to 5.5 days (Weiss et al. 2020; tofacitinib FDA Clinical Pharmacology Review, 2011), leading to altered PK of OATP substrates. The reports indicated the regimen was well tolerated with no serious or novel safety signals. Weiss et al. reported that of the AEs suspected to be related to cyclosporine, all AEs were mild, except for 1 moderate AE (pharyngitis). The 200-mg dose is within the therapeutic range for cyclosporine, and BID administration is indicated due to a $t_{1/2}$ of approximately 8 hours (Neoral, United States Prescribing Information, 2009).

For assessment of the effect of cyclosporine on CYP3A activity, a 200 μg dose of midazolam was chosen. This subtherapeutic dose is sufficiently measurable in plasma but should avoid the sedative effect of midazolam (Cannady et al. 2015).

4.4. End of Study Definition

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

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 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 41 days prior to enrollment. Participants who are not enrolled within 41 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 ECG.

5.1. Inclusion Criteria

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

Age

1. Participants 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 12-lead ECGs that are within normal reference range for the population or investigator site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
3. Participants who 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. Body weight of 45 kg or more and body mass index within the range 18.5 to 35.0 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

7. Males who agree to use highly effective/effective methods of contraception may participate in this study.
8. WNOCBP may participate in this study. 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 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 ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Participants who have significant history of or current cardiovascular, respiratory, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting risk when taking LY3502970; or of interfering with the interpretation of data.
2. Participants who have any abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study.
3. Participants who have abnormal blood pressure, pulse rate, or both, deemed to be clinically significant by the investigator at screening.
4. Fasting serum triglyceride level of greater than 5.65 mmol/L.
5. Participants who have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis), elevation in serum amylase or lipase (greater than 1.5-fold ULN), GI disorder (for example relevant esophageal reflux or gall bladder disease), or any GI disease, which impacts gastric emptying (for example gastric bypass surgery, pyloric stenosis, with the exception of appendectomy) or could be aggravated by GLP-1 analogs.
6. Participants who currently have clinically significant atopy or have a history of clinically significant multiple or severe drug allergies or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).
7. Participants who have liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or have elevations in aminotransferase levels (ALT and AST) greater than 2×ULN and total bilirubin greater than 1×ULN at screening.
8. Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years prior to screening.
9. Participants who have a history of or current psychiatric disorders that in the opinion of the investigator would adversely affect participant safety or compliance.
10. Participants who regularly use known drugs of abuse.
11. Have a history of renal impairment with an estimated glomerular filtration rate less than 90 mL/min/1.73 m^2.

Prior/Concomitant Therapy

12. Participants who have known allergies to LY3502970, related compounds, or any components of the formulation.
13. Participants who intend to use OTC or prescription medication, herbal/vitamin/traditional medicines, or mineral supplements that may affect the safety or objectives of the study, as considered by the investigator after discussion with the sponsor if required, within 14 days (or 5 half-lives, whichever is longest) prior to dosing and for the duration of the study. Acetaminophen or acetaminophen-containing products at doses less than or equal to 3 grams per day and coronavirus disease 2019 vaccinations are permitted.
14. Exclusion Criterion [14] has been deleted.
15. Exclusion Criterion [15] has been deleted.
16. Exclusion Criterion [16] has been deleted.
17. Exclusion Criterion [17] has been deleted.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

20. Participants who show evidence of HIV infection or positive HIV antibodies. A negative test within 6 months of screening would not need to be repeated.
21. Participants who show evidence of hepatitis C or positive hepatitis C antibody. A negative test within 6 months of screening would not need to be repeated.
22. Participants who show evidence of hepatitis B, positive hepatitis B surface antigen, or positive hepatitis B core antibody. A negative test within 6 months of screening would not need to be repeated.
23. Participants who have had a recent infection or been exposed to a live vaccine within 12 weeks prior to screening, or expected to need or receive a live vaccine (including herpes zoster vaccination) during the course of the study.
24. Participants who have serum calcitonin levels greater than or equal to 20 ng/L at screening visit.

Other Exclusions

25. Women who are lactating.
26. WOCBP.
27. Participants who are unwilling to comply with the dietary restrictions required for this study.
28. Participants who have an average weekly alcohol intake that exceeds 21 units per week (males of 65 years or less) and 14 units per week (all females and males over 65 years) or

are unwilling to stop alcohol consumption 24 hours prior to dosing until discharged from the CRU (number of units = [total volume of drink (mL) x alcohol by volume (%)]/1000).
29. Participants who smoke more than 10 cigarettes (or the equivalent in the form of e-cigarettes), 3 cigars, or 3 pipes per day and are unable or unwilling to refrain from smoking while resident at the CRU.
30. 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.
31. 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.
32. Participants who are employees of Eli Lilly and Company or the CRU.
33. Participants who, in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.
34. Have any medical conditions, medical history, or are taking any medications that are contraindicated in the cyclosporine or midazolam prescribing information, such as prior history of hypersensitivity to cyclosporine or midazolam.
35. Participants who have known QT prolongation or are receiving drugs known to prolong the QT interval, ventricular arrhythmia (torsades de pointes), hypokalemia, significant bradycardia, or taking Class IA or III antiarrhythmics.

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 17 and participants will remain fasted for approximately 2 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 LY3502970 dose administration (other than the water provided during dosing).

Midazolam will be administered after an overnight fast of at least 8 hours on Days -1, 16, and 19 and participants will remain fasting for approximately 2 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 midazolam dose administration (other than the water provided during dosing).

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 Days -1, 1, 15, 16, 17, and 19.

Participants should not consume alcohol for at least 24 hours before CRU admission and throughout the duration of their 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 CRU.

5.3.3. Activity

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

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. However, if individuals meet the criteria but are unable to enroll due to nonmedical reasons, they may be enrolled in a later cohort. Repeating laboratory tests during the screening period or repeating screening tests to comply with protocol designated screening period does not constitute rescreening.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

Not applicable.

6. Study Interventions 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 table lists the interventions used in this clinical study.

Table GZGL.1 Study Interventions Administered

Intervention Name	Cyclosporine (Neoral)	Midazolam	LY3502970
Type	Drug	Drug	Drug
Dose Formulation	100 mg capsule	5 mg/5 mL solution ampoule	3 mg capsule
Dosage Level(s)	200 mg twice daily on Days 15 to 19 200 mg once in the morning on Day 20	200 µg on Days -1, 16, and 19	3 mg on Days 1 and 17
Route of Administration	Oral	Oral	Oral
Use	Perpetrator	Victim	Experimental
IMP and NIMP	NIMP	NIMP	IMP
Sourcing	Provided by the site	Provided by the site	Provided centrally by the sponsor in accordance with current GMP
Packaging and Labeling	Commercially available cyclosporine will be used (no modification will be made to packaging with the exception of labeling for clinical use only)	Commercially available midazolam will be used (no modification will be made to packaging with the exception of labeling for clinical use only)	Study intervention will be provided in containers. Each container will be labeled as required per country requirement

Abbreviations: GMP = Good Manufacturing Practice; IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

6.1.1. Administration Details

Each dose of LY3502970, midazolam, and cyclosporine will be administered orally with approximately 240 mL of room temperature water (see Section 1.3). LY3502970, midazolam,

and cyclosporine should be administered in a sitting position. On Days 16 and 19, cyclosporine and midazolam should be administered concurrently, with approximately 240 mL of room temperature water. On Day 17, LY3502970 should be administered 4 hours after the cyclosporine morning dose. If required to complete LY3502970, midazolam, and cyclosporine 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 17 will be administered after an overnight fast of at least 8 hours and participants will remain fasting for approximately 2 hours postdose. Water is permitted ad libitum during the fasting period, except for 1 hour before and after LY3502970 dose administration.

Doses of midazolam on Days -1, 16, and 19 will be administered after an overnight fast of at least 8 hours and participants will remain fasting for approximately 2 hours postdose. Water is permitted ad libitum during the fasting period, except for 1 hour before and after midazolam dose administration.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a nonrandomized, open-label study.

6.4. Study Intervention Compliance

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

6.5. Dose Modification

Dose modification will not be permitted in this study.

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

Cyclosporine, midazolam, or LY3502970 will not be made available to participants after completion of the study.

6.7. Treatment of Overdose

For this study, any dose of LY3502970 greater than 3 mg, midazolam greater than 200 μg, or cyclosporine greater than 200 mg 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/SAE and laboratory abnormalities until LY3502970, cyclosporine, or midazolam 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), and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.8. Concomitant Therapy

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

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

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

Participants must abstain from taking prescription or nonprescription drugs, specifically drugs or substances that are known substrates, inducers, or inhibitors of CYP3A, and substrates or inhibitors of OATP and/or P-glycoprotein. In addition, potassium-sparing medications (diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists) or

potassium-containing supplements, herbal/vitamin/traditional medicines or mineral supplements must be excluded 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 and preferably after discussion with the sponsor, the medication will not interfere with the study (see Section 5.2).

Acetaminophen and acetaminophen-containing products, at doses of less than or equal to 3 grams per 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 by the investigator in consultation with the sponsor.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1 (Section 10.1.8).

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 (Section 1.3).

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,
- the participant has an AE that is considered to be intolerable, or
- an abnormal safety laboratory test result is determined to be clinically significant by the investigator.

A participant who has emesis that may interfere with the interpretation of the primary endpoint may be replaced, after discussion between the sponsor and the investigator.

7.1.1. Liver Chemistry Stopping Criteria

The study intervention should be interrupted or discontinued if 1 or more of these conditions occur:

Elevation	Exception
ALT or AST >5×ULN	
ALT or AST >3×ULN and either TBL >2×ULN or INR >1.5	In participants with Gilbert's syndrome: if baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL >2×ULN.
ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)	
ALP >3×ULN (when the source of increased ALP is the liver)	
ALP >2.5×ULN and TBL >2×ULN	In participants with Gilbert's syndrome: if baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL >2×ULN.

ALP >2.5×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, 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 intervention 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 nondrug etiology is identified.

Participants who discontinue from study intervention due to the abnormal liver tests will undergo monitoring as described in Appendix 10.6 (Section 10.6).

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

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

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and posttreatment follow-up, 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 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. Failure or being late (in other words outside stipulated time allowances) to perform procedures or obtain samples due to legitimate clinical issues (for example equipment technical problems, venous access difficulty, or subject defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations but the CRU will still be required to notify the sponsor in writing via a file note. If multiple procedures take place at the same time point, the following order of procedures should be used: ECG, vital signs, blood samples (at the scheduled times).

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

Efficacy is not evaluated in this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems.

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

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

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3) and following the study-specific recommendations included in the eCRF.

If multiple procedures take place at the same time point, the following order of procedures should be used: ECG, vital signs, blood samples (at the scheduled times). Additional vital signs may be measured during each study period if warranted.

Blood pressure and pulse rate should be measured after at least 5 minutes supine.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes. If the participant feels unable to stand, supine vital signs only will be recorded.

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 QTcF intervals.

For each participant, a single 12-lead digital ECG will be collected according to the SoA. If multiple procedures take place at the same time point, the following order of procedures should be used: ECG, vital signs, blood samples (at the scheduled times). Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary.

All ECGs recorded should be stored at the investigational site. 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 qualified designee as soon after the time of ECG collection as possible, and ideally while the participant is still present

- to determine whether the participant meets entry criteria at the relevant visit(s), and
- for immediate participant management, should any clinically relevant findings be identified.

The investigator, or qualified designee, is responsible for determining if any change in participant management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2 (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.

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 Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

If laboratory values from nonprotocol 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, a 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 or clinical research physician or scientist will monitor safety data throughout the course of the study.

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

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

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

8.2.6.1. Hepatic Monitoring

Close hepatic monitoring

Laboratory tests (Appendix 6. Section 10.6), including ALT, AST, ALP, TBL, direct bilirubin, and gamma-glutamyl transferase should be repeated, with additional tests for creatine kinase within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

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

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

Comprehensive hepatic evaluation

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

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

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time, international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computerized tomography scan).

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

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

- urinary ethyl glucuronide, and
- blood phosphatidylethanol.

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

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

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

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

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

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

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

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

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 AESIs (as defined in Section 8.3.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature, causality, or both. Further information on follow-up procedures is provided in Appendix 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 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 the ICF	Until AE has resolved.	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Until event has resolved	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A; continues indefinitely	Within 24 hours of awareness	SAE paper form	N/A

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

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

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

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

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

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

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

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

Female participants who become pregnant

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

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

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

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

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

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

8.3.3. Adverse Events of Special Interest

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

Other AESI for this program include

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

8.4. Pharmacokinetics

Whole-blood samples will be collected for measurement of blood concentrations of cyclosporine and plasma concentrations of LY3502970 and midazolam (including 1'-hydroxymidazolam) as specified in the SoA (Section 1.3).

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, cyclosporine, and midazolam (including 1'-hydroxymidazolam). Samples collected for analyses of LY3502970, cyclosporine, and midazolam (including 1'-hydroxymidazolam) concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.

8.4.1. Bioanalysis

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

Concentrations of LY3502970 and midazolam (including 1'-hydroxymidazolam) will be assayed using a validated liquid chromatography tandem mass spectrometry method.

Blood concentrations of cyclosporine will be assayed locally.

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

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

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

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

8.7. Biomarkers

8.7.1. Coproporphyrin 1

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

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

8.8. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.9. Health Economics or Medical Resource Utilization and Health Economics

This section is not applicable for this study.

9. Statistical Considerations

The SAP will be finalized prior to the first participant's first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

The primary study objective is to evaluate the effect of cyclosporine on the PK of LY3502970 in healthy participants.

9.1.1. Multiplicity Adjustment

The effect of cyclosporine on the PK parameters of LY3502970 will be assessed through the 90% CIs for the geometric mean ratios of LY3502970 coadministered with cyclosporine 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 purposes of analysis, the following analysis sets are defined:

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

9.2.1. Study Participant Disposition

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

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

9.2.2. Study Participant Characteristics

The participant's age, sex, weight, height, race, 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 SAP or the clinical study report.

Additional exploratory analyses of the data may be conducted as deemed appropriate. PK analyses will be conducted on the Pharmacokinetic Analysis Set. Safety analyses will be conducted on the Safety Analysis Set. Coproporphyrin 1 Biomarker analyses will be conducted on the Coproporphyrin 1 Biomarker Set.

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

9.3.2. Primary Endpoints Analysis

9.3.2.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3502970 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max}, t_{max}, AUC0-tlast, and AUC0-inf of LY3502970. Other noncompartmental parameters, such as $t_{1/2}$, 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

PK parameter estimates will be evaluated to delineate the effects of cyclosporine's interaction with LY3502970. The PK parameters C_{max} and AUC for LY3502970, when administered alone (reference) and in the presence of cyclosporine (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 participant 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 coadministered with cyclosporine 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. Exploratory Endpoint Analysis

9.3.3.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for midazolam and 1'-hydroxymidazolam will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max}, t_{max}, AUC0-tlast, and AUC0-inf of midazolam and 1'-hydroxymidazolam, as well as metabolite ratio based upon AUC. Other noncompartmental parameters, such as $t_{1/2}$, apparent clearance, and apparent volume of distribution may be reported.

Whole-blood concentrations of cyclosporine will be listed and summarized using standard descriptive statistics. 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 concentration predose, C_{max}, t_{max}, and AUC0-tlast, will be summarized using descriptive statistics.

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

9.3.3.2. Statistical Methods

PK parameter estimates will be evaluated to delineate the effects of cyclosporine's interaction with midazolam. The PK parameters C_{max}, AUC, and metabolite ratio of midazolam and 1'-hydroxymetabolism when administered alone (reference) and in the presence of cyclosporine (test), will be compared using a linear mixed-effect model.

The PK parameters C_{max} and AUC for coproporphyrin 1 (test) with the C_{max} and AUC for coproporphyrin 1 (reference) 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 participant 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.

9.3.4. Safety Analyses

9.3.4.1. Clinical Evaluation of Safety

All study intervention and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. The incidence of treatment-emergent AEs and SAEs for each treatment will be presented by severity and by association with study intervention or study procedure as perceived by the investigator. AEs reported to occur prior to the first study dose will be distinguished from those reported as new or

increased in severity during the study. Each AE will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities. The number of investigational product-related SAEs will be reported.

9.3.4.2. Statistical Evaluation of Safety

All safety analyses will be made on the Safety Analysis Set. Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data. Laboratory measurements 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.

9.3.5. Other Analyses

Details for other analyses may be documented in the SAP.

9.4. Interim Analysis

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

9.5. Sample Size Determination

Approximately, 30 participants will be enrolled to ensure that approximately 20 evaluable participants complete the study.

The sample size is calculated to quantify the cyclosporine's effect on each PK parameter of interest (AUC and C_{max}) of LY3502970. Assuming an intraparticipant coefficient of variation of 29% and 20% for AUC and C_{max}, respectively, based upon the analyses in the previous Study GZGA, this sample size will provide an approximately 90% chance to ensure no more than a 2-fold increase on each LY3502970 PK parameter of interest induced by cyclosporine 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 Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable ICH GCP Guidelines, and
- applicable laws and regulations.

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

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

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

The investigator will be responsible for 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, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
- reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

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

10.1.2. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the 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 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.

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

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

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

Participants who are unable to enroll due to nonmedical reasons and are then enrolled in a later cohort outside of the screening window are required to sign a new ICF.

10.1.3. Data Protection

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

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

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

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

10.1.4. Committees Structure

Not applicable.

10.1.5. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

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

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRFs 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 might 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 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 the sponsor or its representatives, regulatory agencies, or both 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 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 electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

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

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

10.1.7. Source Documents

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

Data reported on or entered in the CRF and 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 10.1.6.

10.1.8. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

- For study termination:
    - discontinuation of further study intervention development.
- For site termination:
    - failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
    - inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator, or
    - total number of participants included earlier than expected.

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

10.1.9. Publication Policy

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

10.1.10. Long-Term Sample Retention

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

Sample Type	Custodian	Retention Period After Last Participants Visit*
Pharmacokinetic and Biomarker	Sponsor or Designee	1 year
Genetics	Sponsor or Designee	7 years

*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, response evaluation, or both. 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	
pH	Fasting Lipid Panel [a]
Protein	Total cholesterol
Glucose	Triglycerides
Ketones	Low-density lipoprotein (LDL)
Bilirubin	High-density lipoprotein (HDL)
Urobilinogen	Hepatitis B surface antigen [a,c]
Leukocytes	Hepatitis B core antibody (total) [a,c]
Blood	Hepatitis C antibody [a,c]
Nitrite	HIV [a,c]
Microscopic examination of sediment [b]	Pregnancy test [d]
	FSH [a,f]
Calcitonin [e]	eGFR
Amylase [a]	
Lipase [a]	

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

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

[a] Performed at screening only.

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

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

[d] Females only. Serum pregnancy test at screening. Urine pregnancy test at all other time points.

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

[f] For females with spontaneous amenorrhea for at least 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-GZGL Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a,c]	25	1	25
Clinical laboratory tests[a]	10	4	40
Clinical chemistry only	7	1	7
Calcitonin	5	2	10
LY3502970 pharmacokinetics	2	26	52
Midazolam pharmacokinetics	2	27	54
Cyclosporine concentrations[b]	3	12	36
Coproporphyrin 1 biomarker	3	26	78
Additional pharmacokinetics, if needed	2	3	6
Blood discard for cannula patency	0.3	25	7.5
Genetics	10	1	10
Total			325.5
Total for clinical purposes			330

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

[b] Blood concentrations of cyclosporine will be assayed locally.

[c] Including screening clinical laboratory tests and calcitonin.

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

10.3.1. Definition of Adverse Event

AE Definition
An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, 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, are 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 preexisting condition including either an increase in frequency, intensity, or both, 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 investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

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

10.3.2. Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation, treatment, or both, which would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

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

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization

but may jeopardize the participant or may require medical or surgical intervention to prevent 1 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 Adverse Event and/or Serious Adverse Event and Product Complaints

AE, SAE, and Product Complaint Recording

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

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

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: 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, significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the IB in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to 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 an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 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, evaluations, or both, as medically indicated or as requested by sponsor or designee to elucidate the nature, causality, or both, 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 Serious Adverse Events

SAE Reporting via SAE Report

- Facsimile transmission of the SAE paper form 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 pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SAE report.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical

investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

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

Abbreviations: WOCBP = women of childbearing potential; WNOCBP = women not of childbearing potential.

10.4.2. Contraception Guidance

10.4.2.1. Female Participants

WOCBP are excluded from the study. WNOCBP may participate in this study.

See Appendix 10.4.1 for definitions.

10.4.2.2. Male Participants

The table below describes contraception guidance for all 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. • must agree to use highly effective/effective methods of contraception.
Contraception for men in exclusively same-sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

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

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and 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
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ 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.

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, or • lactational amenorrhea

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

DNA samples will be used for research related to LY3502970 or T2D and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3502970 or T2D. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

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 multistudy assessment of genetic factors involved in the response to LY3502970 or study interventions of this class to understand study disease or related conditions.

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

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

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

Tests assayed by Lilly-designated central laboratory	
Acetaminophen	**Hepatitis A virus (HAV) testing:**
Acetaminophen protein adducts	HAV total antibody
Alkaline phosphatase isoenzymes	HAV IgM antibody
Caeruloplasmin	**Hepatitis B virus (HBV) testing:**
Copper	Hepatitis B surface antigen (HBsAg)
Ethyl alcohol (EtOH)	Hepatitis B surface antibody (anti-HBs)
Phosphatidylethanol (PEth)	Hepatitis B core total antibody (anti-HBc)
Hepatic Hematology Panel	Hepatitis B core IgM antibody
Hemoglobin	Hepatitis B core IgG antibody
Hematocrit	HBV DNA [b]
Erythrocytes (red blood cells [RBCs])	**Hepatitis C virus (HCV) testing:**
Leukocytes (white blood cells [WBCs])	HCV antibody
Differential:	HCV RNA [b]
Neutrophils, segmented	**Hepatitis D virus (HDV) testing:**
Lymphocytes	HDV antibody
Monocytes	**Hepatitis E virus (HEV) testing:**
Basophils	HEV IgG antibody
Eosinophils	HEV IgM antibody
Platelets	HEV RNA [b]
Cell morphology (RBC and WBC)	**Epstein-Barr virus (EBV) testing:**
Hepatic Clinical Chemistry Panel	EBV antibody
Total bilirubin	EBV DNA [b]
Direct bilirubin	**Cytomegalovirus (CMV) testing:**
Alkaline phosphatase (ALP)	CMV antibody
Alanine aminotransferase (ALT)	CMV DNA [b]

Aspartate aminotransferase (AST)	**Herpes simplex virus (HSV) testing:**
Gamma-glutamyl transferase (GGT)	HSV (Type 1 and 2) antibody
Creatine kinase (CK)	HSV (Type 1 and 2) DNA [b]
Hepatic Coagulation Panel	Liver kidney microsomal type 1 (LKM-1)
Prothrombin time, INR (PT-INR)	Anti-nuclear antibody (ANA)
Urine Chemistry	Anti-smooth muscle antibody (ASMA) [a]
Drug screen	Anti-actin antibody [c]
Haptoglobin	Immunoglobulin IgA (quantitative)
Ethyl glucuronide (EtG)	Immunoglobulin IgG (quantitative)
	Immunoglobulin IgM (quantitative)

Tests assayed ONLY by investigator-designated local laboratory
Microbiology
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 ASMA is tested.

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

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Informed consent

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

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

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

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

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

Other alternative locations

Data capture

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

Safety reporting

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

Return to on-site visits

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

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 and ancillary supplies

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 participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), 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 investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC0-inf	area under the concentration versus time curve from time zero to infinity
AUC0-tlast	area under the concentration versus time curve from time zero to the last time point with a measurable concentration
BID	twice daily
CI	confidence interval
C_{max}	maximum observed concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (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
CYP	cytochrome P450
CV	coefficient of variation
DDI	drug-drug interaction
ECG	electrocardiogram

eCRF	electronic case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB	institutional review board
OATP	organic anion-transporting polypeptides
OTC	over-the-counter
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PK	pharmacokinetics
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
$t_{1/2}$	half-life
T2D	Type 2 diabetes
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time to reach maximum observed concentration
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

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