Protocol Amendment J2A-MC-GZGD (c)

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

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Approval Date: 31-Jan-2022

Title Page

Protocol Title:

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

Protocol Number: J2A-MC-GZGD

Amendment Number: c

Quotient Study Number: QSC202755

Compound: LY3502970

Study Phase: Phase 1

Short Title: A Multiple Dose Study of LY3502970 in Healthy Participants

Sponsor Name: Eli Lilly and Company

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

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment b	*16-Dec-2021*
Amendment a	*07-Jun-2021*
Original Protocol	*18-Dec-2020*

Amendment c

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

This amendment was made to more appropriately describe the amount of meal to be consumed on Day 30 (Day 6 of High-Fat meal), for participants to be eligible for dosing.

Section # and Name	Description of Change	Brief Rationale
Section 5.3.1 Meals and Dietary Restrictions	It has been clarified that "Participants should try to consume at least 90% of the predose breakfast on Day 30 (Day 6 of High-Fat meal) in order to be eligible for dosing" instead of "Participants must consume at least 90% of the predose breakfast in order to be eligible for dosing".	This change was done to more appropriately describe the amount of meal to be consumed on Day 30 (Day 6 of High-Fat meal), for participants to be eligible for dosing.

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1. Protocol Summary

1.1. Synopsis

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

Short Title: A Multiple Dose Study of LY3502970 in Healthy Participants

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

Study GZGD will investigate the safety, tolerability, and pharmacokinetics (PK) of multiple oral doses of LY3502970 formulation prototypes in healthy participants.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize and compare the PK of different prototype formulations of LY3502970 after multiple oral doses in healthy participants compared to the reference formulation	• Primary PK parameters for analysis will include C_{max}, AUC, and t_{max}
Secondary	
• To assess the safety and tolerability of prototype formulations in healthy participants • For options 1 and 2 of Part B, to characterize and compare the PK of 1 prototype formulation of LY3502970 under different administration conditions (fasted, fed, PPI) after multiple oral doses in healthy participants	• Incidence of TEAEs and SAEs • Primary PK parameters for analysis will include C_{max}, AUC, and t_{max}

Abbreviations: AUC = area under the curve; C_{max} = maximum observed concentration; PK = pharmacokinetics; PPI = proton pump inhibitor; SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{max} = time to maximum observed concentration.

Overall Design

Study GZGD is a Phase 1, single-site, randomized, partially participant-blind, crossover study in healthy participants to be conducted in 2 parts as presented in the Schema (Section 1.2).

Part A (Initial Formulation Evaluation): Part A will evaluate the safety, tolerability, and PK of multiple oral doses of LY3502970 formulation prototypes in healthy participants. There will be a dose titration period from Day 1 through Day 18, where participants will receive increasing doses of LY3502970 capsule for dose titration. Within-treatment dose escalation will be every 6 days and will reach a maximum dose of CCI once daily (QD) on Day 19. On Days 19 to 24, participants will receive LY3502970 reference capsule (CCI QD) before entering the test phase, from Day 25 to Day 36. During the test phase, the participants will be administered LY3502970 prototype tablet (CCI QD) formulations as per their randomization. The participants will crossover on Day 31 and receive the other prototype formulation through Day 36. Pharmacokinetic and safety assessments will be performed according to the Schedule of Activities (SoA) (Section 1.3).

Following the final dose on Day 36, a terminal PK period will be used to collect additional PK samples through the morning of Day 41. Participants should follow local guidance and clinical research unit (CRU) precautions to minimize risk for Coronavirus Disease 2019 (COVID-19) infection. On Day 41, the investigator or qualified designee will review all available inpatient safety data before discharging participants from the CRU after the morning procedures are completed, provided they are deemed medically fit by the investigator. Participants will complete the study after the safety follow-up visit, which will occur between 7 and 17 days after last dose.

Part B (Secondary Evaluation): Depending on the results of Part A, Part B may further evaluate 1 of the formulations used in Part A with regard food and proton pump inhibitor (PPI) or Part B may be used to evaluate additional prototype formulations.

As in Part A, treatment escalation will occur every 6 days during a titration period and will reach a maximum dose of CCI QD on Day 19. Based on the results of Part A, the sponsor will identify which 1 of 5 interventions (options) may be used for secondary evaluation of LY3502970 (CCI QD) from Day 19 to 36. These options include treatment with LY3502970 in a fasted or fed state and a fasted state with a coadministered PPI or evaluation of additional formulation(s). Each option will begin with a 6-day reference period (CCI QD), followed by two 6-day test periods (CCI QD) as presented in the Schema (Section 1.2). Pharmacokinetic and safety assessments will be performed according to the SoA (Section 1.3).

Following the final dose (CCI QD) on Day 36, a terminal PK period will be used to collect additional PK samples. Participants will remain at the CRU for the entire study. On Day 41, the investigator or qualified designee will review all available inpatient safety data before discharging participants from the CRU after the morning procedures are completed, provided they are deemed medically fit by the investigator. Participants will complete the study after the safety follow-up visit, which will occur between 7 and 17 days after last dose.

Disclosure Statement: This is a participant-blind study consisting of 2 parts testing up to 4 prototype formulations.

Number of Participants:

It is planned that 26 participants (12 for Part A and 14 for Part B), will be assigned, randomly where applicable, to study intervention such that approximately 10 evaluable participants in each part complete the study.

Intervention Groups and Duration:

Part A (Initial Formulation Evaluation): Daily doses of LY3502970 will escalate over the first 19 days of the study, with the maximal dose of CCI given as the reference formulation from Day 19 to 24, followed by 2 test periods of 6 days each.

Part B (Secondary Evaluation): As in Part A, treatment escalation will be every 6 days and will reach a maximum dose of CCI on Days 19 to 24. Based on the results of Part A, the sponsor will identify 1 of 5 options for secondary evaluation of LY3502970 from Day 19 to 36. Each option will begin with a 6-day reference period, followed by two 6-day test periods.

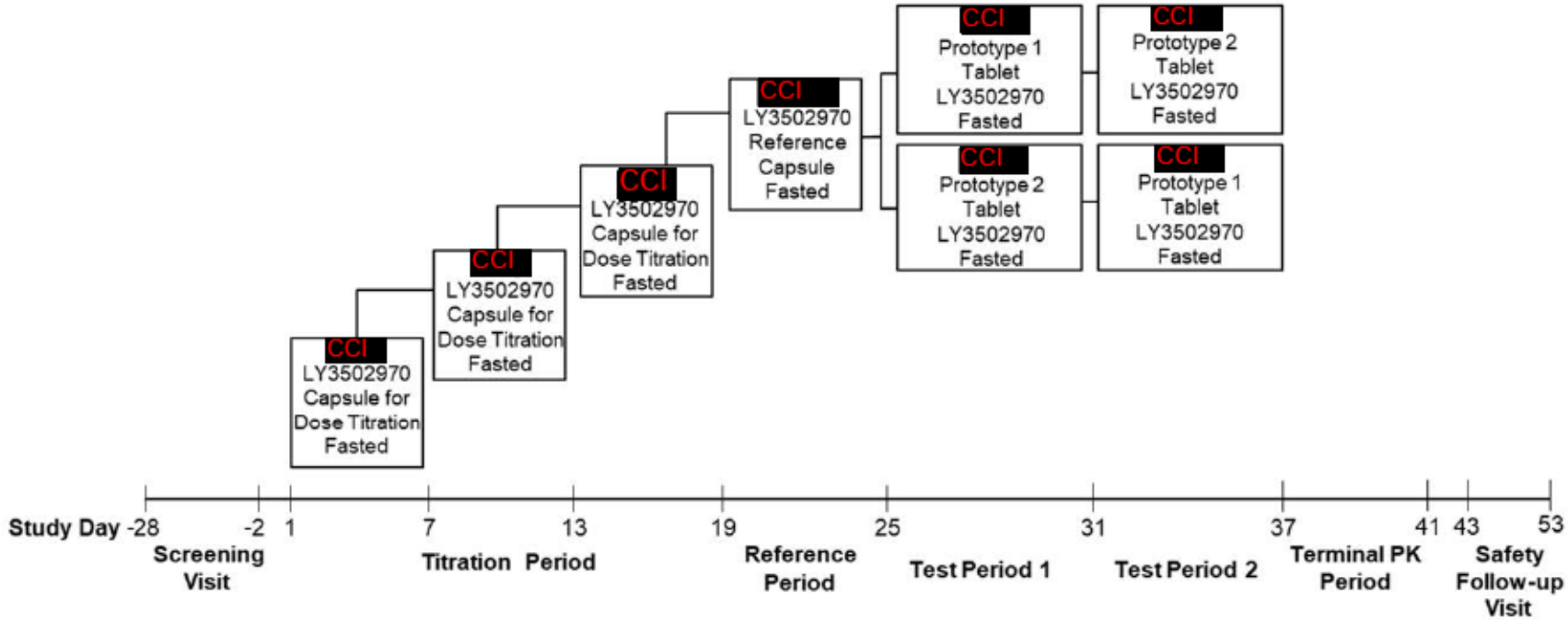
For Part A and B, the maximum duration of study participation for each participant will be up to 13 weeks across the following study intervals:

- screening and baseline, approximately 4 weeks
- treatment period (titration period, reference period, test periods 1 and 2, and the terminal PK period), 6 weeks
- safety follow-up, 7 to 17 days

Data Monitoring Committee: No

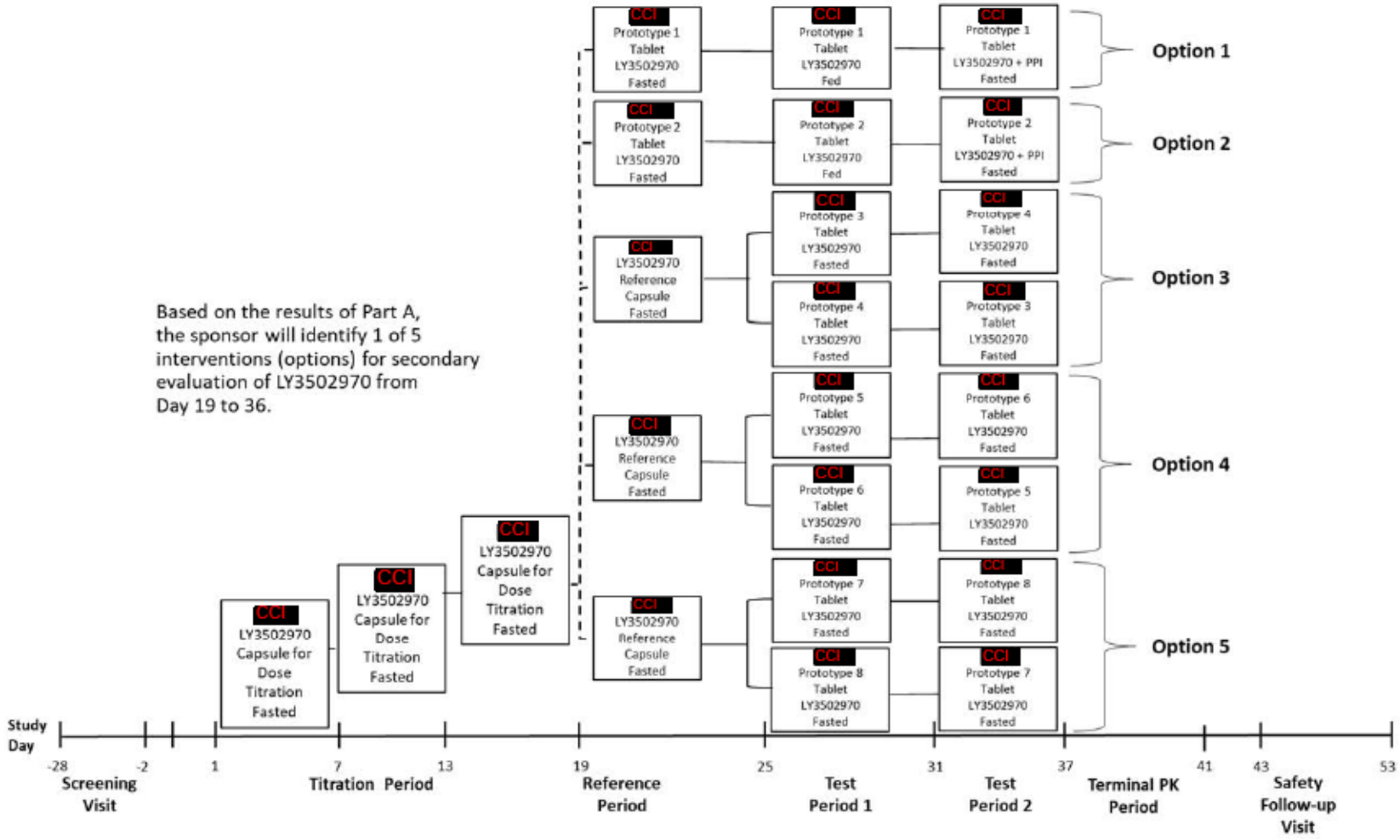
1.2. Schema

Part A



Abbreviations: PK = pharmacokinetics.

Part B



Abbreviations: PK = pharmacokinetics.

Note: Interventions outlined under Options 1 to 5 are subject to change based on interim data review to meet study objectives and endpoints. See Section 6.6.1 for further details.

1.3. Schedule of Activities

1.3.1. Part A

Study Schedule for Part A Screening, Baseline, Early Termination and Follow-up Procedures

Procedure	Screening Visit	Preadmission	Baseline	Safety Follow-up Visit[a]	Comments
Day	**-28 to -2**	**-2**	**-1**	**43 to 53**	The Screening Visit and Safety Follow-up Visit may occur anytime during the specified window.
Informed consent	X				
Outpatient visit	X			X	
CRU admission			X		
Medical history and physical exam	X				Full physical at screening to include vein assessment. Symptom-directed physical assessment at all other timepoints.
Height/weight	X		X	X	Height at screening only. Weight will be measured in a consistent way (see Section 8.2.3).
Body temperature	X				
Vital signs (supine)	X			X	Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.
Safety laboratory tests	X			X	Participants will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 (Section 10.2) for details.
Point of care safety glucose samples	X			X	Samples will be taken with a capillary blood glucose monitor.
Pregnancy test	X		X	X	Females only. Serum pregnancy test at screening. Urine pregnancy test at all other times.
Genetic sample			X		See Appendix 5 (Section 10.5) for details.
Follicle-stimulating hormone	X				For females with a history of spontaneous amenorrhea for 6 to 12 months.
Serum calcitonin	X				
Serology tests	X				See Appendix 2 (Section 10.2) for details.

Procedure	Screening Visit	Preadmission	Baseline	Safety Follow-up Visit[a]	Comments
Day	**-28 to -2**	**-2**	**-1**	**43 to 53**	The Screening Visit and Safety Follow-up Visit may occur anytime during the specified window.
SARS-CoV-2 Antibody[b]	X				
SARS-CoV-2 Antigen[b]	X	X			
Urine drug screen and ethanol breath test	X		X		See Appendix 2 (Section 10.2) for details.
Medical Assessment				X	A symptom-directed physical assessment
AE/medication review	X		X	X	
Single 12-lead ECG	X		X	X	ECGs must be recorded before collecting any vital signs or blood samples. Participants must be supine for approximately 5 minutes before ECG collection and remain supine but awake during ECG collection.

Abbreviations: AE = adverse event; COVID-19 = Coronavirus Disease 2019; CRU = clinical research unit; ECG = electrocardiogram; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

[a] Participants who discontinue early will undergo safety follow-up procedures approximately 120 hours post final dose.

[b] Testing for SARS-CoV-2 may be performed based on current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening and an antigen PCR test performed at screening, the day before admission, and discharge or the day before discharge. The decision on COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the investigator site files via the clinical kick-off meeting minutes.

Study Schedule for Part A Treatment Period Procedures

Procedure	Titration Period[a]			Reference Period[a]	Test Period 1[a]	Test Period 2[a]	Terminal PK Period (Day 37 to 41) & Discharge (Day 41[b])
Day	**1 to 6**	**7 to 12**	**13 to 18**	**19 to 24**	**25 to 30**	**31 to 36**	**37 to 41**
CRU discharge							Day 41
Weight (predose)	Day 1	Day 7	Day 13	Day 19	Day 25	Day 31	Day 41
Vital signs (≤2 hours predose; supine)[c]	Day 1	Day 7	Day 13	Day 19	Day 25	Day 31	Day 41
Safety laboratory tests (predose)[d]	Day 1			Day 19	Day 25	Day 31	Day 37 Day 41
Point of care safety glucose samples (predose)[e]	Day 1	Day 7	Day 13	Day 19	Day 25	Day 31	Day 41
SARS-CoV-2 Antigen							X[f]
Medical Assessment (symptom driven)	Day 1	Day 7	Day 13	Day 19	Day 25	Day 31	Day 41
AE/medication review	→						
Single 12-lead ECG (≤2 hours predose; supine)	Day 1		Day 13	Day 19	Day 25	Day 31	Day 41
Administer study intervention (QD)	→						
Randomization (predose)					Day 25		
LY3502970 PK samples (hour)[c,g]	Day 1: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16 Day 2: Predose	Day 7: Predose	Day 13: Predose	Day 19: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16 Day 20: Predose Day 24: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16	Day 25: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16 Day 26 Predose Day 30: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16	Day 31: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16 Day 32: Predose Day 36: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16	Day 37[g]: 24, 36 Day38[g]: 48 Day 39[g]: 72 Day 40[g]: 96 Day 41[g]: 120

Abbreviations: AE = adverse event; COVID-19 = Coronavirus Disease 2019; CRU = clinical research unit; ECG = electrocardiogram; PCR = polymerase chain reaction; PK = pharmacokinetics; QD = once daily; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

[a] Participants who discontinue early will undergo safety follow-up procedures approximately 120 hours post final dose.

[b] Day 41 procedures begin approximately 120 hours post final dose.

[c] Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.

[d] Sampling times are relative to the time of study intervention administration each day (0 hour). Sampling times may be adjusted after review of preliminary data.

[e] Samples will be taken with a capillary blood glucose monitor.

[f] Testing for SARS-CoV-2 may be performed based on current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening and an antigen PCR test performed at screening, the day before admission, and discharge or the day before discharge. The decision on COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the investigator site files via the clinical kick-off meeting minutes.

[g] Sampling times in the terminal PK period are relative to the time of the final dose of study intervention received (0 hour) and may be adjusted after review of preliminary data.

1.3.2. Part B

Study Schedule for Part B Screening, Baseline, Early Termination and Follow-up

Procedure	Screening Visit	Preadmission	Baseline	Safety Follow-up Visit[a]	Comments
Day	**-28 to -2**	**-2**	**-1**	**43 to 53**	The Screening Visit and Safety Follow-up Visit may occur anytime during the specified window.
Informed consent	X				
Outpatient visit	X			X	
CRU admission			X		
Medical history and physical exam	X				Full physical at screening to include vein assessment. Symptom-directed physical assessment at all other timepoints.
Height/weight	X		X	X	Height at screening only. Weight will be measured in a consistent way (see Section 8.2.3).
Body temperature	X				
Vital signs (supine)	X			X	Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.
Safety laboratory tests	X			X	Participants will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 (Section 10.2) for details.
Point of care safety glucose samples	X			X	Samples will be taken with a capillary blood glucose monitor.
Pregnancy test	X		X	X	Females only. Serum pregnancy test at screening. Urine pregnancy test at all other times.
Genetic sample			X		See Appendix 5 (Section 10.5) for details
Follicle-stimulating hormone	X				For females with spontaneous amenorrhea for 6 to 12 months.
Serum calcitonin	X				
Serology tests	X				See Appendix 2 (Section 10.2) for details.

Procedure	Screening Visit	Preadmission	Baseline	Safety Follow-up Visit[a]	Comments
Day	**-28 to -2**	**-2**	**-1**	**43 to 53**	The Screening Visit and Safety Follow-up Visit may occur anytime during the specified window.
SARS-CoV-2 Antibody[b]	X				
SARS-CoV-2 Antigen[b]	X	X			
Urine drug screen and ethanol breath test	X		X		See Appendix 2 (Section 10.2) for details.
Medical Assessment				X	A symptom-directed physical assessment.
AE/medication review	X		X	X	
Single 12-lead ECG	X		X	X	ECGs must be recorded before collecting any vital signs or blood samples. Participants must be supine for approximately 5 minutes before ECG collection and remain supine but awake during ECG collection.

Abbreviations: AE = adverse event; COVID-19 = Coronavirus Disease 2019; CRU = clinical research unit; ECG = electrocardiogram; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

[a] Participants who discontinue early will undergo safety follow-up procedures.

[b] Testing for SARS-CoV-2 may be performed based on current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening, and an antigen PCR test performed at screening, the day before admission, and discharge or the day before discharge. The decision on COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the investigator site files via the clinical kick-off meeting minutes.

Study Schedule for Treatment Period Procedures in Part B

Procedure	Titration Period[a]			Reference Period[a]	Test Period 1[a]	Test Period 2[a]	Terminal PK Period (Day 37 to 41) & Discharge (Day 41[b])
Day	**1 to 6**	**7 to 12**	**13 to 18**	**19 to 24**	**25 to 30**	**31 to 36**	**37 to 41**
CRU discharge							Day 41
Weight (predose)	Day 1	Day 7	Day 13	Day 19	Day 25	Day 31	Day 41
Vital signs (≤2 hours predose; supine)[c]	Day 1	Day 7	Day 13	Day 19	Day 25	Day 31	Day 41
Safety laboratory tests (predose)[d]	Day 1			Day 19	Day 25	Day 31	Day 37 Day 41
Point of care safety glucose samples (predose)[e]	Day 1	Day 7	Day 13	Day 19	Day 25	Day 31	Day 41
SARS-CoV-2 Antigen							X[f]
Medical Assessment	Day 1	Day 7	Day 13	Day 19	Day 25	Day 31	Day 41
AE/medication review	→						
Single 12-lead ECG (≤2 hours predose)	Day 1		Day 13	Day 19	Day 25	Day 31	Day 41
Administer study intervention (QD)	→						
Administer PPI (PPI options only)[g]						X	
LY3502970 PK samples trough (predose; PPI options only)						Day 33 Day 34 Day 35	
High-fat meal (food effect options only)[g]					X		

Procedure	Titration Period[a]			Reference Period[a]	Test Period 1[a]	Test Period 2[a]	Terminal PK Period (Day 37 to 41) & Discharge (Day 41[b])
Day	**1 to 6**	**7 to 12**	**13 to 18**	**19 to 24**	**25 to 30**	**31 to 36**	**37 to 41**
Randomization (predose)[h]					Day 25		
LY3502970 PK samples (hour)[d,i]	Day 1: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16 Day 2: Predose	Day 7: Predose	Day 13: Predose	Day 19: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16 Day 20: Predose Day 24: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16	Day 25: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16 Day 26 Predose Day 30: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16	Day 31: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16 Day 32: Predose Day 36: Predose, 0.5, 1, 2, 4, 6, 8, 12, 16	Day 37[i]: 24, 36 Day38[i]: 48 Day 39[i]: 72 Day 40[i]: 96 Day 41[i]: 120

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; PK = pharmacokinetics; PPI = proton pump inhibitor; QD = once daily.

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

a Participants who discontinue early will undergo safety follow-up procedures.

b Day 41 procedures begin approximately 120 hours post final dose.

c Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.

d Sampling times are relative to the time of study intervention administration each day (0 hour). Sampling times may be adjusted after review of preliminary data.

e Samples taken with a capillary blood glucose monitor.

f Testing for SARS-CoV-2 may be performed based on current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening and an antigen PCR test performed at screening, the day before admission, and discharge or the day before discharge. The decision on COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the investigator site files via the clinical kick-off meeting minutes.

g Administration of PPI and a high-fat meal will take place only if treatment option 1 or 2 is chosen by the sponsor.

h Randomization at Day 25 will take place only if treatment option 3, 4, or 5 is chosen by the sponsor.

i Sampling times in the terminal PK period are relative to the time of the final dose of study intervention received (0 hour) and may be adjusted after review of preliminary data.

2. Introduction

2.1. Study Rationale

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

Study GZGD will investigate the safety, tolerability, and pharmacokinetics (PK) of multiple oral doses of LY3502970 formulation prototypes in healthy participants.

2.2. Background

Multiple GLP-1RA therapies are approved, the most commonly prescribed being administered once daily (QD) or once weekly by subcutaneous injection. Even with several different GLP-1RAs approved for use in T2DM, the injection remains a barrier for many patients to initiate and to adhere to therapy long-term. The recently approved oral semaglutide (Rybelsus®, Novo Nordisk) is expected to provide patients with a viable alternative to subcutaneous injection delivery. However, its administration requires the patient to adhere to a number of steps to improve bioavailability including:

- fasting for ≥6 hours,
- no more than approximately 120 mL of water at administration, and
- no food or fluid for at least 30 minutes after taking the medication (Hedrington and Davis 2019; Rybelsus package insert, 2019).

Therefore, providing additional oral GLP-1RA therapies remains an unmet need. LY3502970 is an oral GLP-1RA that exhibits the antihyperglycemic actions of GLP-1, acting as an insulin secretagogue and increasing glucose-dependent insulin secretion after a glucose challenge.

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

2.3. Benefit/Risk Assessment

No safety or tolerability concerns that may preclude further investigation of LY3502970 have been identified in 100 healthy participants to date, up to the highest single dose given (CCI) and multiple doses given (CCI).

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

The nonclinical safety profile of LY3502970 included negative genetic toxicity and a range of target organ effects that were generally associated with pharmacologic and class-effect activity in monkeys, the only pharmacologically-sensitive species, which included increased heart rate (GLP-1 class effect), decreased GI motility, vomiting, decreased food consumption, and body weight loss. These effects were reversible and monitorable. In both rats and monkeys, increased

serum bilirubin and/or serum bile acid concentrations were observed and were likely associated with properties of LY3502970 as a known inhibitor of liver transporters including OATP, BSEP, and MRP2. These serum chemistry changes in both species were not associated with concurrent indicators of liver injury and were reversible. Additionally, a potential off-target embryo-fetal developmental effect was identified in a pilot study in pregnant rabbits. Women of childbearing potential will not be included in the proposed clinical trial. No observed adverse effect dose levels (NOAELs) were identified in both rats and monkeys. Exposure multiples in male and female rats at the NOAEL (200 mg/kg) are 18x and 38x, respectively, to the highest planned dose of CCI. Exposure multiples in monkeys at the NOAELs in males (4 mg/kg) and females (0.45 mg/kg), defined by effects that were consistent with class effects or exaggerated pharmacology, are 1.5x and 0.15x, respectively, to the planned highest dose of CCI. However, since the effects are considered monitorable and reversible in the clinic, an exposure multiple of 1.5x to the lowest observed adverse effect level (LOAEL) (4.0 mg/kg) in female monkeys is also observed. Overall, the exposure multiples and the monitorability of the effects are considered sufficient to enable further safe clinical investigation of LY3502970 in the proposed dose range.

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

Esomeprazole is a marketed proton pump inhibitor (PPI) commonly used chronically to treat GI disorders such as gastroesophageal reflux disease. Short term courses are also used to treat patients with H. pylori infection and duodenal ulcer disease. The short course of therapy in this trial at the approved dosage is expected to have minimal risk to participants. The safety profile of the drug is well known and described in the prescribing information (Nexium summary of product characteristics).

2.3.1. COVID-19 Related Risks and Risk Mitigation Measures

The following risks and risk mitigating measures apply to the parts of the study that are conducted during the Coronavirus Disease 2019 (COVID-19) pandemic. See Appendix 9 (Section 10.9) for provisions for changes in study conduct during exceptional circumstances.

2.3.1.1. Investigational Medicinal Product Related Risk

Against the background of the COVID-19 pandemic, the potential risk of a participant developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of the investigational medicinal product (IMP) – oral GLP-1RA – has been considered alongside available preclinical and clinical data (including class effects) and it is considered that a participant would not be at increased risk of either becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) or experiencing a more severe illness. That is, the IMP has no known immunomodulatory effect that would confer an increased risk to healthy participants enrolled in the study.

2.3.1.2. General COVID-19 Related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with Quotient Sciences' monitoring and prevention control measures.

Coronavirus Disease 2019 testing may be performed based on current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening, and an antigen polymerase chain reaction test or other antigen test performed at

screening, the day before admission, and discharge or the day before discharge. Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the investigator site file via the clinical kick-off meeting minutes.

The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

2.3.1.3. COVID-19 Vaccine-Related Risk

Approved COVID-19 vaccines, including killed, inactivated, peptide, DNA, and RNA vaccines, may be permitted at the investigator's discretion and as per local guidance. This also includes health authority conditional marketing authorization.

Based on the mechanism of action of the IMP, as an oral GLP-1RA, there is no perceived impact on the safety of the study participants or on the study objectives for participants who may receive these vaccines (either first or second dose). It is also very unlikely that administration of the IMP would interfere with COVID-19 vaccination response; however, no specific preclinical or clinical investigations have been conducted at this point with the IMP.

The emerging safety and efficacy data from millions of vaccinated people, many of whom are elderly and with underlying health conditions and taking multiple concomitant medications, indicate that these vaccines have an excellent safety and efficacy record. In the broader interests of society and to limit the extent of the global pandemic, it is important that participants should receive a vaccine when it is offered to them.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize and compare the PK of different prototype formulations of LY3502970 after multiple oral doses in healthy participants compared to the reference formulation	• Primary PK parameters for analysis will include C_{max}, AUC, and t_{max}
Secondary	
• To assess the safety and tolerability of prototype formulations in healthy participants • For options 1 and 2 of Part B, to characterize and compare the PK of 1 prototype formulation of LY3502970 under different administration conditions (fasted, fed, PPI) after multiple oral doses in healthy participants	• Incidence of TEAEs and SAEs • Primary PK parameters for analysis will include C_{max}, AUC, and t_{max}

Abbreviations: AUC = area under the curve; C_{max} = maximum observed concentration; PK = pharmacokinetics; PPI = proton pump inhibitor; SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{max} = time to maximum observed concentration.

4. Study Design

4.1. Overall Design

Study GZGD is a Phase 1, single site, randomized, partially participant-blind, crossover study in healthy participants to be conducted in 2 parts as presented in the Schema (Section 1.2).

Part A (Initial Formulation Evaluation): Part A will evaluate the safety, tolerability, and PK of multiple oral doses of LY3502970 formulation prototypes in healthy participants. There will be a dose titration period from Day 1 through Day 18, where participants will receive increasing doses of LY3502970 capsule for dose titration. Within-treatment dose escalation will be every 6 days and will reach a maximum dose of CCI QD on Day 19. On Days 19 to 24, participants will receive LY3502970 reference capsule (CCI QD) before entering the test phase, from Day 25 to Day 36. During the test phase, the participants will be administered LY3502970 prototype tablet (CCI QD) formulations as per their randomization. The participants will crossover on Day 31 and receive the other prototype formulation through Day 36. Pharmacokinetic and safety assessments will be performed according to the SoA (Section 1.3).

Following the final dose on Day 36, a terminal PK period will be used to collect additional PK samples through the morning of Day 41. Participants should follow local guidance and CRU precautions to minimize risk for COVID-19 infection. On Day 41, the investigator or qualified designee will review all available inpatient safety data before discharging participants from the CRU after the morning procedures are completed, provided they are deemed medically fit by the investigator. Participants will complete the study after the safety follow-up visit, which will occur between 7 and 17 days after last dose.

Refer to Section 5.3.1 for fasting restrictions. The PK and safety assessments will be performed according to the Schedule of Activities (SoA; Section 1.3). The PK sampling schedules may be modified based on the available safety and PK data.

Part B (Secondary Evaluation): Depending on the results of Part A, Part B may further evaluate 1 of the formulations used in Part A with regard to food and proton pump inhibitor (PPI) or Part B may be used to evaluate additional prototype formulations.

As in Part A, treatment escalation will occur every 6 days during a titration period and will reach a maximum dose of CCI QD on Day 19. Based on the results of Part A, the sponsor will identify which 1 of 5 interventions (options) may be used for secondary evaluation of LY3502970 (CCI QD) from Day 19 to 36. These options include treatment with LY3502970 in a fasted or fed state and a fasted state with a coadministered PPI or evaluation of additional formulation(s). Each option will begin with a 6-day reference period (CCI QD), followed by two 6-day test periods (CCI QD) as presented in the Schema (Section 1.2). Pharmacokinetic and safety assessments will be performed according to the SoA (Section 1.3).

Following the final dose (CCI QD) on Day 36, a terminal PK period will be used to collect additional PK samples. Participants will remain at the CRU for the entire study. On Day 41, the investigator or qualified designee will review all available inpatient safety data before discharging participants from the CRU after the morning procedures are completed, provided they are deemed medically fit by the investigator. Participants will complete the study after the safety follow-up visit, which will occur between 7 and 17 days after last dose.

4.2. Scientific Rationale for Study Design

This study will evaluate at least 2 prototype formulations of LY3502970 in healthy participants, compared to a reference formulation. Based on the PK of the prototype formulations employed in Part A, Part B may either assess 1 of the formulations from Part A with food and a PPI or Part B may be used to explore additional formulations.

Each period of each part of the study will last 6 days to allow each patient to reach a PK steady state (based on half-life as discussed in Section 4.3. below) for the formulation. This steady state evaluation of relative bioavailability is required because of the need for a titration period to dose high enough for the formulation to be expected to impact exposure. This design also allows each individual subject to be used as their own control to limit the number of healthy volunteers needed for the assessment. PK profiles are being collected on the first day of the reference and test periods for prototype variability and performance assessment and will not be used for statistical comparison. Each part of the study contains a reference period starting on Day 19 to serve as a constant dose reference exposure followed by 2 test periods that commence on Days 25 and 31 to assess either prototype formulations or the effect of a high-fat meal and PPI.

As this is a Phase 1 study assessing the PK, relative bioavailability, and safety of LY3502970, the most relevant population is healthy participants. Participants without a history of alcohol or drug abuse or regular co-medication are proposed to avoid interaction on drug metabolism and to avoid non-compliance.

Developmental and reproductive toxicology studies have not been completed. Therefore, females of childbearing potential will not be allowed to participate in the study.

Based on the above considerations and target population, healthy surgically sterilized or postmenopausal female participants and healthy male participants, aged 18 to 65 years, inclusive, are considered suitable for this study.

The Clinical Trial Authorisation (CTA) application for this study describes a flexible protocol design using the concept of formulation design space to allow decision-making in response to interim PK observations. The principles of a flexible protocol were discussed and agreed with the Medicines and Healthcare products Regulatory Agency (MHRA) at a Scientific Advice Meeting between the MHRA and Quotient Sciences (formerly Pharmaceutical Profiles).

Based upon the concept of formulation design space, specific IMPs are not detailed within the Investigational Medicinal Product Dossier (IMPD) but rather a defined dose range of formulation inputs and corresponding performance outputs are described and justified based on in vitro studies. The chosen formulation from within the approved design space for the first prototype to be dosed will be documented in a decision document and approved by the sponsor and a Quotient Sciences representative ahead of manufacture.

4.3. Justification for Dose

The planned LY3502970 doses (CCI) will allow characterization of PK in healthy participants, which will support selection of the best formulation for future clinical trials.

These planned doses were selected based on the following:

- The nonclinical safety profile of LY3502970 as described in Section 2.3

- Following weekly within-treatment dose escalation, doses up to and including CCI were tolerated in the multiple dose part of study GZGA. The mean half-life ($t_{1/2}$) ranging from 32.1 to 36.5 hours supports a QD dosing regimen. Therefore, the proposed dosing regimen in this study (CCI QD dosing with within-treatment dose escalation every 6 days) is similar to the dosing regimens that have been previously administered and tolerated in the multiple ascending dose (MAD) study. There were no discontinuations due to tolerability of participants dosed up to CCI of LY3502970 in Study GZGA of 37 participants.
- LY3502970 has both low solubility and permeability and therefore, formulation could impact the absorption of the drug especially at higher doses due to supersaturation. To date, the reference capsule formulation has demonstrated linear PK through CCI.

Safety of study participants will be closely monitored during the early stages of dose escalation and participants that are unable to tolerate the dose regimen will be discontinued as described in Section 7.1.3. As additional data emerges, dose levels and escalation schemes may be modified but dose will not be increased.

For more details of the tolerability profile of participants in Study GZGA see the IB for LY3502970.

Esomeprazole

The 40-mg dose of esomeprazole is the highest recommended therapeutic dose. Therefore, it is associated with the most sustained elevation of gastric pH (Nexium summary of product characteristics).

4.4. End of Study Definition

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

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

5. Study Population

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

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests and electrocardiogram (ECG). The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented. The inclusion and exclusion criteria used to determine eligibility should be applied at screening only, and not continuously throughout the trial.

Screening may occur up to 28 days prior to enrollment. Participants who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent and of an acceptable age to provide informed consent according to local law.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history and physical examination.
3. Participants who have safety laboratory test results within normal reference ranges for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator
4. Participants who have venous access sufficient to allow for blood sampling as per the protocol
5. Participants who are reliable, willing to make themselves available for the duration of the study, willing to follow study procedures, and willing to remain in the CRU

Weight

6. Body mass index (BMI) within the range 18.5 to 35.0 kg/m^2 (inclusive)

Sex

7. Male or female

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants: For contraceptive guidance for men, refer to Appendix 4 (Section 10.4).

b. Female participants: Women of childbearing potential (WOCBP) as defined in Section 10.4 are excluded from the trial.

Informed Consent

8. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

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

Medical Conditions

1. have known allergies to LY3502970, GLP-1 analogs, related compounds or any components of the formulation, or history of significant atopy
2. have an abnormal blood pressure and/or pulse rate as determined by the investigator – minor deviations acceptable to investigator are allowed
3. have a significant history of or current cardiovascular (e.g., myocardial infarction, congestive heart failure, cerebrovascular accident, venous thromboembolism), respiratory, hepatic, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study intervention; or of interfering with the interpretation of data
4. have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis), elevation in serum amylase or lipase (>1.5-fold upper limit of normal [ULN]) or GI disorder (e.g., relevant esophageal reflux or gall bladder disease) or any GI disease which impacts gastric emptying (e.g., gastric bypass surgery, pyloric stenosis, with the exception of appendectomy) or could be aggravated by GLP-1 analogs
5. have a personal or family history of medullary thyroid carcinoma or have multiple endocrine neoplasia syndrome type 2
6. have a history of malignancy within 5 years prior to screening
7. have known liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or have elevations in aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) greater than 2X ULN
8. have evidence of significant psychiatric disorder(s) as determined by the investigator
9. have obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis
10. evidence of current SARS-CoV-2 infection
11. presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active.

Prior/Concomitant Therapy

12. use over-the-counter, prescription, herbal, or traditional medicines 14 days before planned dosing. This includes the occasional intake of vitamin/mineral supplements. Any

medications that maintain elevated gastric pH, including but not limited to H_2-receptor blockers and PPIs, are specifically excluded for 14 days prior to dosing and for the duration of the study. Refer to Section 6.5 for additional concomitant therapy restrictions regarding acetaminophen. If this situation arises, inclusion of an otherwise suitable participant may be at the discretion of the investigator. COVID-19 vaccines are accepted concomitant medications; however, it is not advised that participants receive a COVID-19 vaccine within 72 hours of dosing due to the potential vaccine-related AEs. Exceptions may apply on a case-by-case basis, if considered not to interfere with the objectives of the study, as determined by the investigator.

Prior/Concurrent Clinical Study Experience

13. 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
14. have participated, within 90 days of screening, in a clinical study involving an investigational product. If the previous product has a long half-life, 5 half-lives or 90 days (whichever is longer) should have passed
15. have previously completed or withdrawn from this study

Diagnostic assessments

16. have an abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study
17. show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies
18. show evidence of hepatitis C and/or positive hepatitis C antibody
19. show evidence of hepatitis B and/or positive hepatitis B surface antigen and/or hepatitis B core antibody
20. have a serum calcitonin level of:
    a. ≥20 ng/L at screening visit, if estimated glomerular filtration rate ≥60 mL/min/1.73m^2
    b. ≥60 ng/L at screening visit, if estimated glomerular filtration rate <60 mL/min/1.73m^2
21. have serum triglyceride ≥5 mmol/L (442.5 mg/dL) at screening
22. have hemoglobin below the lower limit of normal at screening
23. have fasting blood glucose level of <3.9 mmol/L at screening

Other Exclusions

24. are women of child-bearing potential
25. are women who are lactating
26. males with pregnant or lactating partners
27. have donated blood of more than 450 mL or more in the last 3 months or any blood or plasma donation within the last month from screening and check-in on Day -1.

Participants must be willing to refrain from donating blood or plasma throughout the study duration and for at least 90 days following last dose of study drug.

28. regularly use known drugs of abuse and/or show positive findings on drug screening
29. have a history of alcohol abuse in the past 2 years
30. have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (females up to 65), or are unwilling to stop alcohol consumption 24 hours prior to dosing until discharge from the CRU (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits). Participants with a positive alcohol breath test at screening or admission will be excluded.
31. smoke >10 cigarettes per day or the equivalent or are unable to abide by CRU smoking restrictions
32. are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
33. are Lilly employees
34. in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

5.3. Lifestyle Considerations

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

5.3.1. Meals and Dietary Restrictions

1. Participants will be required to refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, cranberries, pomelos, exotic citrus fruits, grapefruit hybrids, or apple and orange juices from 7 days before the start of study intervention until after the final PK sampling.
2. For the food effect study (Part B), no water is allowed until 2 hours after dosing, after which time, water is allowed ad libitum.

Meals will be provided as appropriate in the CRU. Participants will be required to fast overnight for at least 8 hours before:

- Taking an oral dose of LY3502970
- Collection of safety laboratory samples.

Participants will be provided with a light snack in the evening and then fast from all food and drink (except water) for a minimum of 8 hours on the day prior to dosing and to continue to fast for at least 4 hours postdose on days when PK samples will be collected, and from Days 19 to 36, at which time a meal will be provided. It is planned an evening meal will be provided at approximately 10 hours postdose and an evening snack at approximately 14 hours postdose. Meals after the lunch time may be time shifted as required or additional meals may be provided if deemed appropriate or necessary to ensure that the participants have adequate daily caloric intake.

On Days 1 to 18, when postdose PK samples are not being collected, meals will be provided at appropriate times, that is, a light breakfast at 2 hours postdose, lunch at approximately 4 hours postdose, dinner at approximately 10 hours postdose and an evening snack at approximately 14 hours postdose.

Participants will be administered LY3502970 with approximately 240 mL of room temperature water. Fluids will be restricted from 1 hour prior to and until 1 hour after LY3502970 dosing, except for the water required for dose administration. Fluids may be consumed freely at all other times, except those described above.

High-Fat Meal in Food Effect Option

If the food effect option is chosen by the sponsor, participants will receive a high-fat meal prior to each dose during the 6-day test period. The standardized high-fat, high-calorie meal (fat comprises approximately 50% of total caloric content of the meal) should consist of approximately 1000 calories. No additional food or substitute is allowed. A typical test meal consists of 1 hash brown, 2 rashers of Sainsbury's streaky bacon – grilled,1 small (45 g) egg fried in 10 g butter, 2 slices of white medium sliced bread with 20 g of butter, and 240 mL of full-fat milk. This test meal derives approximately 150, 250, and 500 to 600 calories from protein, carbohydrates, and fat, respectively.

Participants will be provided with a light snack and will fast from all food and drink (except water) until the following morning, when they will be provided with a high-fat breakfast. The breakfast should be consumed over a maximum period of 25 minutes, with dosing occurring 30 minutes after the start of breakfast. Participants should be encouraged to eat their meal evenly over the 25-minute period. It is acknowledged that some participants will take less time to eat, but dosing should still occur 30 minutes after the start of breakfast. Participants should try to consume at least 90% of the predose breakfast on Day 30 (Day 6 of High-Fat meal) in order to be eligible for dosing. The start and stop times and percentage of the breakfast consumed must be recorded in the source documents.

The acceptable deviation for the predose meal from the nominal time point is:

- Participants will be dosed with LY3502970 30 minutes ± 5 minutes after the start of breakfast

5.3.2. Caffeine, Alcohol, and Tobacco

No alcohol will be allowed at least 24 hours before CRU admission, including screening, and throughout the duration of the stay in the CRU. No nicotine use will be permitted while at the CRU.

5.3.3. Activity

Participants will be advised to maintain levels of physical activity/exercise per CRU guidelines during the study. When certain study procedures are in progress at the site, participants may be required to remain recumbent or sitting.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened. Vital signs and laboratory values may be repeated up to 2 times as part of the screening assessment at the discretion of the investigator. Participants who were eligible for inclusion in a previous part, but who were not randomized, may be included in a subsequent part.

Admission/predose safety procedures such as safety blood, ECGs, vital signs, urinalysis and drugs of abuse tests can be repeated as clinically indicated under the discretion of investigator or sub-investigator if there is a concern regarding a participant's safety or eligibility to participate in the clinical trial.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

Treatments Administered

Intervention Name	LY3502970 Capsule for Dose Titration, CCI	LY3502970 Reference Capsule, CCI	LY3502970 Prototype X Tablet, CCI (where X will denote the prototype number for the chosen formulation)	Proton Pump Inhibitor (esomeprazole) in Part B Only
Dose Formulation	Capsule	Capsule	Tablet	Tablet
Unit Dose Strength(s)	CCI			40 mg
Dosage Level(s)	CCI QD (as 1 capsule)	CCI QD	CCI QD	40 mg QD
Route of Administration	Oral	Oral	Oral	Oral
Use	Titration	Reference	Experimental	Comedication
IMP and NIMP	IMP	IMP	IMP	NIMP

Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational medicinal product; QD = once daily.

The dose of prototype formulations of LY3502970 will remain constant; however, the specific formulation used may differ across treatment sequences. Prototype formulations will be selected from a 2-dimensional design space of formulation component levels.

Where Quotient Sciences is manufacturing the IMP(s), suitability of the manufacturing process will be documented in a Pharmaceutical Development and Control Strategy Report.

All IMPs will be reconciled and destroyed in accordance with the study-specific quality agreement and technical addendum.

6.1.1. Administration Details

Participants will fast overnight for at least 8 hours prior to LY3502970 administration during the study except for during the food-effect option of Part B. LY3502970 will be administered orally with 240 mL of room temperature water in the morning of each dosing day in a sitting position and should be taken within approximately 3 minutes. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

In Part B, a high-fat meal (described in Section 5.3.1) may be administered. For the 6 days of the food-effect test period, participants will fast overnight for at least 8 hours prior to consuming the high-fat meal. LY3502970 will then be administered orally with 240 mL of room temperature water, 30 minutes after the start of the meal.

For the evaluation of LY3502970 with a PPI, doses of esomeprazole will be administered for each of the 6 days following an overnight fast of at least 8 hours and at least 1 hour prior to administration of LY3502970 and the morning meal.

On multiple dosing days (i.e., Days 2 to 36) dosing will be performed within ±1 hour of the nominal timepoint, where nominal time is the time of dosing from Day 1. Should the window be utilized (e.g., for logistical reasons) then dosing will revert back to nominal time at the next dosing occasion.

6.2. Preparation/Handling/Storage/Accountability

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants will be blinded (e.g., with a blindfold or similar method) to the various LY3502970 formulations in Parts A and B (Options 3, 4, and 5) from Days 25 to 37. For Options 1 and 2 in Part B, participants will not be blinded.

Parts A and B (Options 3, 4, and 5) of the study are randomized wherever possible in instances where 2 prototypes are being evaluated simultaneously under the option; therefore, in such

instances, a randomization schedule will be produced for each part. The original randomization schedules and proof of quality control procedures will be held by the Data Sciences department at Quotient Sciences until the study is archived, at which time the randomization materials will be retained in the ISF.

When randomization is employed, participants will be randomized immediately prior to dosing on Day 25. Participant numbers will be randomized to a study intervention sequence so that 12 participants for Part A and 14 participants for Part B are assigned to 1 of 2 sequences. The assignment will be balanced with 6 participants for Part A and 7 participants for Part B assigned to each treatment sequence.

Participant numbers will be allocated on the morning of dosing according to the code 001 to 024 using the lowest number available. Replacement participants will be allocated participant numbers 901 to 924, where the last 2 digits are the same as those of the original participant (e.g., if Participant 005 withdraws, the replacement will have participant number 905 and will receive any regimens which Participant 005 did not receive in addition to any regimens which are required to make the required comparison of interest).

Study intervention will be dispensed as summarized in SoA (Section 1.3).

Returned study intervention should not be re-dispensed to the participants.

Blinding will be maintained throughout the conduct of the study as described in the separate study-specific Blinding Plan.

If a participant becomes unblinded to their treatment assignment, the participant must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist (CP), clinical research physician (CRP) or scientist (CRS) for the study participant to continue in the study.

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

6.3.1. Package and Labeling

The drug product is supplied for clinical trial use as capsules or tablets for oral administration. Each dosage unit contains LY3502970 as a spray dried dispersion equivalent to CCI of the LY3502970 drug substance. The investigational product should be stored according to instructions on the label. All study treatments will be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigational product will be labeled according to the country's regulatory requirements. The NIMP (esomeprazole) are marketed in the United Kingdom (UK). They are to be used in the clinical trial within the terms of the marketing authorization.

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 in the eCRF.

The study intervention will be administered at the clinical site, and documentation of treatment administration will occur at the site.

A record of the number of capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

Participants who are significantly noncompliant will be discontinued from the study. The assessment of study intervention compliance will be determined by the following:

- Information about the participant's adherence to the SoA
- Information about the participant's compliance with concomitant medications
- Information about any other parameters the investigator considers necessary

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) 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
- Dosage information including dose and frequency for concomitant therapy of special interest

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 14 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study. Medications that alter gastric pH may be contraindicated during this study. Any medications that transiently affect gastric pH (antacids, milk of magnesia, etc.) should not be used on the days of LY3502970 administration. Any medications that maintain elevated gastric pH, including but not limited to H_2-receptor blockers and PPIs, are specifically excluded for 7 days prior to dosing and for the duration of the study (aside from potentially esomeprazole in Part B). Acetaminophen, at doses of ≤3 grams/day, is permitted for use during the study at the discretion of the investigator. This will be recorded in the electronic case report form (eCRF).

Nausea and/or vomiting during this study may be treated with antiemetics but these medications should not be used prophylactically. Nonsteroidal anti-inflammatory medications (including ibuprofen, aspirin), acetaminophen, cough suppressants, antihistamines, vitamin/mineral supplements, antibiotics, and topical ointments may be used on an as-needed basis. These and other concomitant medication may be considered on a case-by-case basis by the investigator preferably in consultation with the medical monitor.

COVID-19 vaccines are accepted concomitant medications; however, it is not advised that participants receive a COVID-19 vaccine within 72 hours of dosing due to the potential vaccine-related AEs. Exceptions may apply on a case-by-case basis, if considered not to interfere with the objectives of the study, as determined by the investigator.

Any additional medication used during the study (including those not requiring sponsor notifications) must be documented on the appropriate eCRF.

6.6. Dose Modification

The participants should follow the planned dosing regimen. In the case of poor tolerability at any time during the study, dosing may be interrupted temporarily (Section 7.1.3).

6.6.1. Data Review during the Study

Access to safety, tolerability, and PK data is scheduled to occur once approximately 10 evaluable participants have completed Part A of the study. The purpose of this review is to guide optimal formulation selection for Part B.

In-study decisions for formulation to be dosed will be made by the project team, and will always include the investigator, the sponsor's medical monitor or the sponsor's medically qualified designee who is familiar with the study protocol and IB, and a PK expert, where appropriate.

The following in-study decisions will be made during this study:

- Formulation selection for Part B
- Whether to dose PPI
- Selection of prandial status

The decision made regarding the intervention in Part B is planned to be based on the interventions (options) presented in the schema for Part B in Section 1.2. Based on data observations and to meet with study objectives and endpoints, it may instead be decided to dose a single new prototype in the fasted state or a single new prototype in the fasted and fed state.

The decisions for Part B will only be made after a review of the available data collected from Part A. For the Part B decisions to occur, data should be available from approximately 10 participants who have received both prototype formulations and completed the planned safety assessments up to Day 40. If data are not available for 10 participants, the principal investigator, scientific lead and sponsor will make a decision as to whether the data available are sufficient to support the formulation selection decision.

The following data are required:

- demography

- adverse events
- plasma concentrations of LY3502970
- pharmacokinetic parameter estimates

Within-cohort dose escalations during the titration phase will be driven by emerging real-time safety data and assessed by the investigator on an individual participant basis. The decision to proceed with the next incremental dose will be documented in the source.

6.7. Intervention after the End of the Study

Investigators will continue to follow the SoA (Section 1.3) for all participants until notified by Lilly that study completion has occurred.

The study intervention will not be made available to participants after conclusion of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

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

Discontinuation of the study intervention should be considered by the investigator if any of the following occur in a participant:

- an AE that is considered to be intolerable,
- an abnormal safety laboratory test result, determined to be clinically significant by the investigator, or
- QTcF >500 msec and an increase from baseline in QTcF >60 msec, from at least 2 consecutive readings.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula (QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Early Termination of the Study

The investigator will thoroughly review the tolerability of the study intervention for each participant prior to each dose titration and decide if they should continue with the assigned treatment regimen. No formal dose escalation is planned for this study. A safety investigation will be triggered to determine if the study intervention should be terminated early based on the following criteria:

- Three study participants develop the same TEAE or SAE considered possibly or probably related to the study intervention that is severe or medically significant, but not immediately life-threatening; or where hospitalization or prolongation of hospitalization is indicated; or is disabling; or limits self-care activities of daily living.

- Two study participants develop any TEAE or SAE regardless of attribution to the study intervention that has life-threatening consequences or requires urgent intervention.
- Death of any study participant at any time related to AE.

7.1.2. Hepatic and Pancreatic Criteria for Discontinuation

Discontinuation of the study intervention for abnormal liver tests **should be considered** by the investigator when a participant meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or AST >5X ULN
- ALT or AST >3X ULN sustained for more than 2 weeks or
- ALT or AST >3X ULN and TBL >2X ULN or INR >1.5 or
- ALT or AST >3X ULN the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3X ULN
- ALP>2.5X ULN and TBL >2X ULN
- ALP>2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Lipase and/or amylase ≥3X ULN (Appendix 7 [Section 10.7] should be considered by the investigator)

Participants who discontinue from study intervention due to the abnormal liver tests will undergo monitoring as described in Appendix 6 (Section10.6) and in Appendix 7 (Section 10.7).

7.1.3. Intolerable Gastrointestinal Events

In the presence of persistent GI events, participants who are unable to tolerate their assigned dose level for ≥3 days (have persistent vomiting or moderate to severe nausea) should be discontinued from using the study intervention. A participant may skip up to 2 doses in succession during the titration phase due to intolerable GI events.

7.1.4. Hypoglycemia

Discontinuation of the study intervention should be considered by the investigator for participants with severe hypoglycemia (Level 3 according to Section 8.2.6.3) or persistent hypoglycemic events (Levels 1 and 2).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)

- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

Participants will be discontinued under the following circumstances:

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

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time. Participants withdrawn from the study due to safety reasons will not be replaced.

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

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

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she fails to return for safety follow-up visit 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 the follow-up visit or were otherwise unable to be followed up by the site.

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

8. Study Assessments and Procedures

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

- Study procedures and their timing are summarized in the SoA.
- 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 has to be correctly recorded in the eCRF. Failure or being late (i.e., outside stipulated time allowances as detailed per Quotient Science's standards) to perform procedures or obtain samples will be considered as protocol deviations and the CRU will be required to notify the sponsor.

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

Appendix 2 (Section 10.2.1) provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Samples will be retained in compliance with applicable laws, regulations, and 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.

8.2.1. Physical Examinations

- A complete physical examination at screening will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded according to the SoA (Section 1.3).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

Medical assessments are a symptom-directed physical assessment and will be conducted according to the SoA (Section 1.3) and as clinically indicated.

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3) and each measurement recorded in the eCRF.
- Vital sign measurements should be obtained before collection of blood samples.
- Additional vital signs may be measured during each study period if warranted.
- Blood pressure and pulse rate should be measured after resting for at least 5 minutes in a supine position.
- Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participant should be supine for approximately 5 minutes and stand for at least 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. Body Weight

Weight will be measured as indicated in the SoA (Section 1.3) and all measurements will be recorded in the eCRF. Participants will be weighed in light clothing at approximately the same time in the morning before dosing and after an overnight fast and evacuation of bowel and the bladder, if possible.

During the treatment period, weight will be measured twice on each scheduled occasion, with the participant stepping off the scale between measurements. Both weight measurements will be recorded in the source document and the eCRF. Wherever possible, the same scale will be used for all weight measurements throughout the study and the scale will not be moved or recalibrated.

8.2.4. Electrocardiograms

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

Single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

Electrocardiograms must be recorded before collecting any vital signs or blood samples. Participants must be supine for approximately 5 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All single ECGs recorded should be stored at the investigational site.

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

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

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the participant for symptoms (e.g., palpitations, near syncope, syncope) to determine whether the participant can continue in the study. The investigator or qualified designee is responsible for determining if any change in participant management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point. Any new clinically relevant finding should be reported as an AE.

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

8.2.5. Clinical Safety Laboratory Assessments

Participants will be required to fast for at least 8 hours before each blood sample is drawn. Clinical laboratory tests include hematology, clinical chemistry, and urinalysis.

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA, standard collection requirements, and the laboratory manual.

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

8.2.6. Safety Monitoring

The Lilly CP or CRP will monitor safety data throughout the course of the study.

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

- trends in safety data
- laboratory analytes including ALT, AST, TBL, amylase, and lipase
- adverse events, including AEs of special interest (nausea, vomiting, and diarrhea) and
- reported pancreatitis

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

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the personnel included in the unblinding/blinding plan.

8.2.6.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests in Appendix 6 (Section 10.6), including ALT, AST, ALP, TBL, direct bilirubin (D. Bil), gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated 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 <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with

the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

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

Comprehensive hepatic evaluation

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

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

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

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

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

Additional hepatic data collection (hepatic safety case report forms [CRFs]) in study participants who have abnormal liver tests during the study

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

1. Elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests (if baseline ALT <1.5X ULN)
   - In participants with baseline ALT ≥1.5X ULN, the threshold is ALT ≥3X baseline on 2 or more consecutive tests
2. Elevated TBL to ≥ 2X ULN (if baseline TBL <1.5X ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5X ULN, the threshold should be TBL ≥2X baseline
3. Elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests (if baseline ALP <1.5X ULN)
   - In participants with baseline ALP ≥1.5X ULN, the threshold is ALP ≥2X baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be a serious adverse event (SAE)
5. Discontinuation of study drug due to a hepatic event

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

8.2.6.2. Pancreatic Safety

Serum amylase and lipase measurements will be collected as part of the clinical laboratory testing at time points specified in the SoA (Section 1.3). Additional measurements may be performed at the investigator's discretion.

Further diagnostic assessments will be recommended whenever lipase and/or amylase are confirmed to be ≥3X ULN at any visit posttreatment sequence allocation even if the participant is asymptomatic (as per the algorithm for the monitoring of pancreatic events in Appendix 7, Section 10.7) and, if pancreatitis is suspected, the case will be further defined during an adjudication process.

To ensure participant safety and compliance with regulatory guidance, the investigator is to consult with the Lilly CP/CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests.

8.2.6.3. Hypoglycemia

Blood glucose will be monitored for safety throughout the study according to the SoA (Section 1.3; point of care safety glucose samples) using a capillary blood glucose monitor. Participants will be trained by site personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia. Investigators should use the following classification of hypoglycemia:

- Level 1 hypoglycemia-Glucose <70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L):

Level 1 hypoglycemia can alert a person to take action, such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

- Level 2 hypoglycemia-Glucose <54 mg/dL (3.0 mmol/L):

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

- Level 3 hypoglycemia-Severe hypoglycemia (in adults):

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

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

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

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

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

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints (PCs)

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest as defined in Section 8.3.2 will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

AEs considered by the investigator to be related to COVID-19 vaccines will be reported to the MHRA via the Yellow Card system.

8.3.1. Timing and Mechanism for Collecting Events

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

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	11 days after the last of study intervention	Within 24 hours of learning of the pregnancy	SAE paper form	N/A
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

8.3.2. Adverse Events of Special Interest

Nausea, vomiting, and diarrhea events are considered AEs of special interest and will be recorded as AEs in the eCRF. For each event assessment of severity, duration (start and stop

dates) and investigator's opinion of relatedness to study intervention and protocol procedure will be captured.

Other AESIs (Section 8.2) for this program include:

- Cardiovascular events
- Hypoglycemia
- Hepatic events
- Pancreatic events

8.4. Treatment of Overdose

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

In the event of an overdose, the investigator should:

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

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

8.5. Pharmacokinetics

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

- During the treatment period, all predose PK samples are intended to be collected 24 hours (±10 minutes) from the prior day's administration of study intervention.
- A maximum of 3 samples for LY3502970 concentrations may be collected at additional time points during the study for additional trough PK samples on Day 33 to Day 35 if option 1 or 2 is selected for Part B or if warranted and agreed upon between both the investigator and sponsor. The timing of sampling may be altered during the course of the study based on newly available data to ensure appropriate monitoring.
- Samples will be used to evaluate the PK of LY3502970. Genetic analyses will not be performed on these blood samples. Participant confidentiality will be maintained. On days during which blood samples for the determination of multiple aspects of study intervention will be taken, 1 sample of sufficient volume can be used.

8.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3502970 will be assayed using a validated liquid chromatography tandem mass spectrometry method. Bioanalytical samples collected to measure 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 and/or protein-binding work or for analysis of esomeprazole concentrations, if options 1 or 2 of Part B are conducted.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

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

See Appendix 5 (Section 10.5) for information regarding genetic research and Appendix 1 (Section 10.1.11) for details about sample retention and custody.

8.8. Biomarkers

This section is not applicable.

8.9. Immunogenicity Assessments

This section is not applicable.

8.10. Medical Resource Utilization and Health Economics

This section is not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The study will compare different formulations of LY3502970 against a reference formulation. The primary study objective is to characterize and compare the PK of different prototype formulations of LY3502970. The secondary objectives are to assess the safety and tolerability of prototype formulations and, for options 1 and 2, to characterize and compare the PK of 1 prototype formulation of LY3502970 under different administration conditions (fasted, fed, PPI) .

9.2. Sample Size Determination

It is planned that 26 participants (12 for Part A and 14 for Part B), will be assigned, randomly where applicable, to study intervention such that approximately 10 evaluable participants in each part complete the study. The sample size for the study was chosen to provide sufficient data for evaluating safety and/or PK parameters.

To enable the minimum number of evaluable participants to be met, participants who discontinue early may be replaced after consultation with the investigator and sponsor. The replacement participant will be assigned to the same treatment as the discontinued participant.

Participants withdrawn from the study due to IMP safety reasons will not be replaced.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All participants assigned to study intervention, regardless of whether they take any doses of study intervention, or if they took the correct intervention.
Safety	All participants who took at least 1 dose of study intervention.
Pharmacokinetic Analysis	All randomized participants who received at least 1 full dose of prototype formulation and have a baseline and at least 1 postbaseline evaluable PK sample.

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

9.3.2. Study Participant Characteristics

The participant's age, sex, weight, height, or other demographic characteristics will be recorded and maybe used in the PK and safety analyses as quantitative or classification variables.

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analysis of this study will be the responsibility of 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 confidence intervals (CIs) will be given at a 2-sided 90% level.

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

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

Pharmacokinetic analyses will be conducted on the PK Analysis Set (i.e., using relevant data from participants included in the PK Analysis population). Safety analyses will be conducted on the Safety Analysis Set (i.e., using relevant data from participants included in the Safety Population).

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety and population PK analysis purposes to avoid issues with post hoc analyses and incomplete disclosures of analyses. Analyses will be fully detailed in the SAP.

9.4.2. 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 AEs for each treatment will be presented by severity and by association with the study intervention as perceived by the investigator. Adverse events reported to occur prior to the first study dose will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

The number of SAEs will be reported. Details regarding the analysis of AEs of special interest will be described in the SAP.

9.4.3. Statistical Evaluation of Safety

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 and change from baseline by treatment group, 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 group.

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

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

9.4.4. Pharmacokinetic Analyses

9.4.4.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3502970 will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will include C_{max}, $AUC_{(0\text{-}24)}$, and t_{max}. Other parameters, such as $AUC_{(0\text{-}\infty)}$, $AUC_{(0\text{-}tlast)}$. half-life, apparent clearance, and apparent volume of distribution, may be reported. If deemed necessary, additional model-based analysis may be performed.

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

9.4.4.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters for LY3502970 will be evaluated to estimate relative bioavailability.

Under the crossover design of Part A and option 3, 4, or 5 of Part B, both the actual values and change from baseline of the log-transformed PK parameters will be analyzed using a linear mixed effects model. The model will include baseline, treatment, period and sequence as fixed effects, and subject as a random effect. The log-transformed PK parameters from the reference formulation will be used as baseline. The ratios of the geometric least squares (LS) means between 2 test formulations will be calculated along with the 90% CIs for the ratios.

Under the non-randomized crossover design of option in Part B, the log-transformed PK parameters from each of the 2 treatments (prototype formulation with food or with a PPI) will be compared to the prototype formulation (fasted) using a linear mixed effects model with baseline and treatment as fixed effects and subject as a random effect. The log-transformed PK parameters from the prototype formulation (fasted) will be used as baseline. The ratio of the LS means between each of the 2 treatments and the prototype formation (fasted) will be calculated along with the 90% CI for the ratios.

The t_{max} will be analyzed using a nonparametric method (Kruskal-Wallis test).

9.5. Interim Analyses

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

9.6. Data Monitoring Committee

Not applicable.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by 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.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

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

10.1.4. Data Protection

- Participants will be assigned a unique identifier (in the form of a participant number) by the Quotient Sciences. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her 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 his/her data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

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

Reports

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

Data

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

10.1.6. Data Quality Assurance

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

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

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, or fax.

Data Capture System

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

An electronic data capture system (EDC) will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture 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 entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

10.1.8. Study and Site Start and Closure

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

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

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

10.1.9. Publication Policy

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

10.1.10. Investigator Information

Physicians working in teaching or nonteaching hospitals or outpatient setting will participate as investigators in this clinical trial.

10.1.11. 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 Patient Visit**
Long-term storage samples	Sponsor or Designee	15 years
Biomarkers	Sponsor or Designee	15 years
Pharmacokinetics	Sponsor or Designee	2 years
Genetics/Pharmacodynamics	Sponsor or Designee	15 years
Immunogenicity	Sponsor or Designee	15 years

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed below will be performed by the CRU:

- If laboratory results are used to make a study intervention decision, these results will be provided to the medical monitor via listings provided by the laboratory.
- The local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing will be performed to confirm the absence of pregnancy.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to the investigative site or other blinded personnel.

Safety Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Glucose, fasting
Differential WBC absolute counts of:	Blood urea nitrogen
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Amylase
Eosinophils	Lipase
Basophils	Creatinine
Platelets	
	Lipid Panel[a]
Urinalysis	Total cholesterol
Specific gravity	Triglycerides
pH	Low-density lipoprotein cholesterol
Protein	High-density lipoprotein cholesterol
Glucose	
Ketones	
Bilirubin	Liver Panel
Urobilinogen	Total bilirubin
Blood	Direct bilirubin
	Gamma-glutamyl transferase
Nitrite	Indirect bilirubin
Microscopic examination of sediment[b]	Alkaline phosphatase

	Aspartate aminotransferase
Serology[a]	Alanine aminotransferase
Hepatitis B surface antigen	
Hepatitis B core antibody	Ethanol breath testing[c]
Hepatitis C antibody	Urine drug screen[c]
HIV	Pregnancy test[d]
	Follicle-stimulating hormone[a,e]
	SARS-CoV-2 Ab and SARS-CoV-2 Ag
Calcitonin[a]	

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

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

[a] Performed at screening only.

[b] Test only if dipstick result is abnormal and are further definable by microscopy.

[c] Urine drug screen and ethanol breath level will be performed at screening and may be repeated at admission to the clinical research unit and at other times indicated in the Schedule of Activities (Section 1.3).

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

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

10.2.1. Blood Sampling Summary

This table summarizes the approximate number of blood sample collections based on anticipated timepoints and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. All blood volumes are approximate, however, the total amount of blood drawn will be no more than 550 ml over a period of 4 weeks.

Protocol J2A-MC-GZGD Sampling Summary

Purpose	Approximate Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Screening tests[a]	29.5	1	29.5
Genetic sample	10	1	10
Serum pregnancy test	3.5	1	3.5
Clinical laboratory tests[a]	6.5	16	104
Pharmacokinetics	2	75[b]	150
Blood discard for cannula patency	1	18	18
Total			315[b]
Total for clinical purposes (rounded up to nearest 10 mL)			320

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

[b] If option 1 or 2 is chosen for Part B, 78 blood samples will be drawn for pharmacokinetics. In this case, total blood drawn will be approximately 321 mL.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a 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, 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 and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.

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

- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a 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 (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

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

10.3.3. Definition of Product Complaints

Product Complaint

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

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate eCRF 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 the sponsor or designee in lieu of completion of the eCRF 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 the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

10.3.5. Reporting of SAEs

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

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting
Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met. ● The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators. ● An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and notify the IRB/IEC, if appropriate according to local requirements.

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

Definitions:

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

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

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Determination can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female is defined as, women with:
   - 12 months of amenorrhea for women >55, with no need for FSH
   - Women ≥55, with a diagnosis of menopause prior to starting hormone replacement therapy
   - 12 months of amenorrhea for women >40 years old with an intact uterus, FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g., oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators [SERMs], or chemotherapy that induced amenorrhea)

Contraception Guidance:

Men, regardless of their fertility status, with non-pregnant women of childbearing potential partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or effective method of contraception (such as diaphragms with spermicide or cervical sponge) for the duration of the study and for 3 months following the last dose of the study intervention (i.e., until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus).

Men and their partners may choose to use a double-barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted however that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.)

Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Men with pregnant partners are excluded from participation in this study.

Men should refrain from sperm donation for the duration of the study and for 3 months following the last dose of study intervention (i.e., until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus).

Men who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception

Women of childbearing potential (WOCBP) are excluded from the trial.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of 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 fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at ≤20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in 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 discontinue study intervention or be withdrawn from the study.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to LY3502970, susceptibility to, and severity and progression of disease. Variable response to LY3502970 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 T2DM and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3502970 and/or interventions of this drug class and T2DM. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3502970 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on LY3502970 continues but no longer than 15 years or other period as per local requirements.

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

Hepatic Evaluation Testing

See Section 8.2.6.1 for guidance on appropriate test selection.

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

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

HCV RNA [d]	EBV DNA [d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [d]	HSV (Type 1 and 2) DNA [d]
Microbiology [c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.
[b] Not required if anti-smooth muscle antibody (ASMA) is tested.
[c] Assayed ONLY by investigator-designated local laboratory; no central testing available.
[d] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.7. Appendix 7: Pancreatic Monitoring Tests for Treatment-Emergent Abnormality

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

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

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

Diagnosis of acute pancreatitis

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

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

If acute pancreatitis is suspected, the investigator should:

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

Discontinuation for acute pancreatitis

If acute pancreatitis is diagnosed, the participant must discontinue use of the study intervention.

Asymptomatic elevation of serum amylase and/or lipase

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

10.8. Appendix 8: Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
CI	confidence intervals
CIOMS	Council for International Organizations of Medical Sciences
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
COVID-19	Coronavirus Disease 2019
CP	clinical pharmacologist
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.
CRS	clinical research scientist
CRU	clinical research unit
CTA	Clinical Trial Authorisation
Device Deficiencies	Equivalent to product complaint
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.

Term	Definition
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
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
IRB	Institutional Review Board
LOAEL	lowest observed adverse effect level
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	Non-investigational Medicinal Product
NOAEL	no observed adverse effect dose levels
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
PD	pharmacodynamics
PK	pharmacokinetics/
PPI	proton pump inhibitor
QD	once daily
QTc	corrected QT interval

Term	Definition
RAP	reporting and analysis plan
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
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
T2DM	type 2 diabetes mellitus
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.
UK	United Kingdom
ULN	upper limit of normal

10.9. Appendix 9: 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 circumstances changes will not typically require additional notification to these groups, unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

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

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with 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,"
- a change in the method, location, or both, of study intervention administration,
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and

- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional circumstances

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

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

Remote visits

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

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

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

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.10. Appendix 10: Protocol Amendment History

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

Amendment a: 07 June 2021

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

Overall Rationale for the Amendment:

The protocol is amended to

- update the number of capsules administered to each participant in the titration phase of the study.
- correct inconsistencies
- include COVID-19 vaccine-related information

Section # and Name	Description of Change	Brief Rationale
1.2 Schema for Part A and Part B 1.3 Schedule of Activities for Part A and Part B	Safety follow-up period changed from Day 43 to Day 57 to Day 43 to Day 53	To correct inconsistency because participants are planned to complete the study after the safety follow-up visit, which will occur between 7 and 17 days after last dose, which implies Day 43 to Day 53
2.3.1 COVID-19 Related Risks and Risk Mitigation Measures 5.2 Exclusion Criterion 12 6.5 Concomitant Therapy 8.3 Adverse Events, Serious Adverse Events and Product complaints	Updated these sections to allow use of COVID-19 vaccines	Added as per MHRA guidance
5.2 Exclusion Criteria	Added a new criterion to exclude participants who have a fasting blood glucose level of <3.9 mmol/L at screening	Additional fasting days are introduced in this study.

Section # and Name	Description of Change	Brief Rationale
5.3.1 Meals and Dietary Restrictions	Fasting for 4 hours postdose was added from Days 19 to 36 On fasting days added meals after the lunch time may be time shifted as required or additional meals may be provided if deemed appropriate or necessary to ensure that the participants have adequate daily caloric intake	To get more consistency of the PK profile leading up to the key PK sampling days
6.1 Study Intervention(s) Administered 6.3.1 Package and Labeling	Updated the unit dose strength of the LY3502970 to CCI [redacted] Changed dosage level from 3 capsules to 1 capsule	Per the original Pharmaceutical study plan, the LY3502970 capsule for dose titration was planned to be provided at each dose level (CCI [redacted]) as a presentation of 3 x capsules each with unit dose strength of CCI [redacted] respectively. Following further development work within the CMC phase of the study, this plan was altered to present a dose in a single capsule at each dose strength. Overall dose to be given remains unchanged.
6.1 Study Intervention(s) Administered	Dose formulation of proton pump inhibitor (esomeprazole) in Part B changed from capsule to tablet	Only a tablet form is available in the UK and the capsule and tablet are equivalent.
6.6.1 Data Review During the Study	Review of demography data was added for Part B dosing decisions.	Collection of demography data was inadvertently excluded in the original protocol.

Amendment b: 16 December 2021

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the safety of the study participants or the scientific value of the study.

Overall Rationale for the Amendment:

This amendment was made to: (a) increase the number of participants enrolled in Part B of the study from 12 to 14 to increase the probability of at least 10 participants completing the study in the event of discontinuations and (b) clarify the process of determining the selection of prototypes in Part B.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis and Section 9.2. Sample Size Determination	The number of participants per cohort of the study has been updated to 26 (12 for Part A and 14 for Part B)	The number of participants for Part B has been increased to increase the probability of at least 10 evaluable participants completing the study in the event of discontinuations.
Section 1.2 Schema and 6.6.1. Data Review during the Study	For Part B, it has been clarified that interventions outlined under Options 1 to 5 are subject to change based on interim data review to meet study objectives and endpoints.	This change has been made to better facilitate the iterative process of formulation optimization.
Section 1.3. Schedule of Activities and Section 8.2.1. Physical Examinations	The “symptom-directed physical examination” changed to “symptom-directed physical assessment”.	This is a recent template update.
Section 1.1. Synopsis and Section 4.1 Overall Design	The sentence fragment “in manner similar to Part A” has been deleted	This change was made for beginning the reference and test periods in Part B with any of the prototypes.
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	Options 2, 3, and 4 have been corrected to Options 3, 4, and 5. Also, Option 5 has been corrected to Option 2.	Typographical errors have been corrected.

Section # and Name	Description of Change	Brief Rationale
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	A sentence has been modified as follows: Parts A and B (Options 3, 4, and 5) of the study are randomized wherever possible in instances where 2 prototypes are being evaluated simultaneously under the option; therefore, in such instances, a randomization schedule will be produced for each part.	The sentence has been modified to clarify that randomization schedule will be produced only in instances where 2 prototypes are being evaluated simultaneously under the options specified.
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	The sentence fragment "when randomization is employed" has been added.	The sentence fragment was added to clarify that participants will be randomized only when randomization is used.
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	For Part B, the number of participants has been updated to 14 and assignment to each treatment sequence has been updated to 7 participants.	The number of participants has been increased to increase the probability of at least 10 evaluable participants completing the study in the event of discontinuations.
Section 9.4.4.2. Pharmacokinetic Statistical Inference	Option "1 or 2" has been deleted.	This modification has been done to accommodate both randomized and non-randomized crossover designs depending on the number of prototypes being evaluated.

DOCUMENT HISTORY	
Document	**Date**
Amendment b	*16-Dec-2021*
Amendment a	*07-Jun-2021*
Original Protocol	*18-Dec-2020*

11. References

Banks PA, Freeman ML, Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379-2400. https://doi.org/10.1111/j.1572-0241.2006.00856.x

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

Koizumi M, Takada T, Kawarada Y, et al. JPN guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2006;13(1):25-32. https://doi.org/10.1007/s00534-005-1048-2

Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab*. 2016;18(3):203-216. https://doi.org/10.1111/dom.12591

Nexium [summary of product characteristics]. Luton, United Kingdom: AstraZeneca UK Limited.

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

Steinberg WM, Buse JB, Ghorbani MLM, et al. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: results from the LEADER randomized trial. *Diabetes Care*. 2017a;40(7):966-972. https://doi.org/10.2337/dc16-2747

Steinberg WM, Rosenstock J, Wadden TA, et al. Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: secondary analyses of pooled data from the SCALE clinical development program [published correction in *Diabetes Care*. 2018;41(7):1538. https://doi.org/10.2337/dc18-er07]. *Diabetes Care*. 2017b;40(7):839-848. https://doi.org/10.2337/dc16-2684

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