

Protocol J2A-JE-GZGB (b)

A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability,
Pharmacokinetics, and Pharmacodynamics of LY3502970 in Japanese Participants with Type 2
Diabetes Mellitus

NCT05086445

Approval Date: 19-Oct-2021

Title Page

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Protocol Title:

A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Japanese Participants with Type 2 Diabetes Mellitus

Protocol Number: J2A-JE-GZGB

Amendment Number: (b)

Compound: LY3502970

Brief Title: A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Japanese Participants with Type 2 Diabetes Mellitus

Study Phase: Phase 1

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana 46285, USA

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 19-Oct-2021 GMT

Medical Monitor Name and Contact Information will be provided separately

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Original Protocol	15-August-2021
Amendment (a)	28-September-2021

Amendment (b)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

To make the following clarifications and minor consistency updates:

Section # and Name	Description of Change	Brief Rationale
1.2 Schema (Figure GZGB.2.)	Footnote added to state that participants in Cohort 1a may be discharged, at the investigator's discretion, 48 hours after administration of a new dose level if there are no scheduled assessments.	To allow flexibility in the amount of time participants in Cohort 1a need to be resident in the clinical research unit.
Study Schedule: Part B - All Cohorts: Treatment Period (Weeks 1 to 8)	End of table note updated to specify that Days 50, 64, and 78 will only be conducted for Cohorts 2a and 2b whereas Days 59 and 73 will only be conducted for Cohort 2a.	Updated for clarity.
Study Schedule: Part B - All Cohorts: Treatment Period (Weeks 9 to 13)	Same as above.	Same as above.
Study Schedule: Part B - All Cohorts: Treatment	Fasting plasma glucose assessment row removed from the Glucose Management assessments category and moved to the Laboratory tests	Updated for clarity.

Section # and Name	Description of Change	Brief Rationale
Period (Weeks 1 to 8)	assessments category. Additionally, added that these measurements will be conducted at the central laboratory.	
Study Schedule: Part B - All Cohorts: Treatment Period (Weeks 9 to 13)	Same as above.	Same as above.
Study Schedule: Early Termination and Follow-Up for All Cohorts	Same as above.	Same as above.
Study Schedule: Part B - All Cohorts: Treatment Period (Weeks 1 to 8)	End of table note added to state that participants in Cohort 1a may be discharged, at the investigator's discretion, 48 hours after administration of a new dose level if there are no scheduled assessments.	To allow flexibility in the amount of time participants in Cohort 1a need to be resident in the clinical research unit.
4.1.2 Lead-in and Treatment Periods	Removed that the lead-in period for Part B will occur 1 to 2 weeks following the completion of Part A.	This timescale was removed to allow for flexibility.
4.1.2 Lead-in and Treatment Periods	Added that participants in Cohort 1a may be discharged, at the investigator's discretion, 48 hours after administration of a new dose level if there are no scheduled assessments.	To allow flexibility in the amount of time participants in Cohort 1a need to be resident in the clinical research unit.
10.2.1 Blood Sampling Summary	Fasting plasma glucose samples added and total blood collected	Added for completeness, to account for all samples scheduled to be collected during the course of the study.

Section # and Name	Description of Change	Brief Rationale
	blood volume updated accordingly.	
Multiple sections	Minor typographical errors corrected.	Updated for accuracy.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Japanese Participants with Type 2 Diabetes Mellitus

Brief Title: A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Japanese Participants with Type 2 Diabetes Mellitus

Rationale:

Study J2A-JE-GZGB (GZGB) is a Phase 1, single-ascending dose (SAD) and multiple-ascending dose (MAD) study designed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3502970 following oral administration of single dose or multiple once daily (QD) doses for 12 weeks in Japanese participants with type 2 diabetes mellitus (T2DM).

Pharmacokinetic data from previous Phase 1 clinical studies supported QD administration of LY3502970 and found LY3502970 to be safe and well tolerated. The current study is intended to obtain sufficient safety, tolerability, PK, and PD data with preliminary efficacy measurements to support identification of an appropriate dose range for subsequent clinical studies of LY3502970 in Japanese patients with T2DM.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To investigate the safety and tolerability of LY3502970 following single and multiple oral QD doses for 12 weeks in Japanese participants with T2DM.	- TEAEs - SAEs
Secondary	
To characterize the PK profile of LY3502970 following single and multiple oral QD doses for 12 weeks in Japanese participants with T2DM.	$C_{\max}$ and AUC
To characterize the PD effects of LY3502970 following multiple oral QD doses for 12 weeks in Japanese participants with T2DM.	- Changes from baseline in: - fasting glucose - HbA1c - body weight

Abbreviations: AUC = area under the concentration versus time curve; $C_{\max}$ = maximum observed drug concentration; HbA1c = glycated hemoglobin; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; SAE = serious adverse event; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.

Overall Design

Study GZGB is a Phase 1, multicenter, participant- and investigator-blinded, parallel, placebo-controlled, randomized, SAD (Part A), and a 12-week MAD (Part B) study in Japanese participants with T2DM to investigate the safety, tolerability, PK, and PD of LY3502970 administered as a single oral dose or multiple CCI [REDACTED] for 12 weeks. In Part A, single-ascending doses of LY3502970 will be administered in 2 subgroups (1a and 2a). After completing Part A, participants will subsequently be enrolled in Part B (12-week MAD). The safety data through Day 8 from each SAD cohort in Part A will be reviewed prior to initiation of the corresponding dose group in Part B.

Disclosure Statement:

This is a sequential group treatment study investigating single and multiple doses that is participant and investigator-blinded.

Number of Participants:

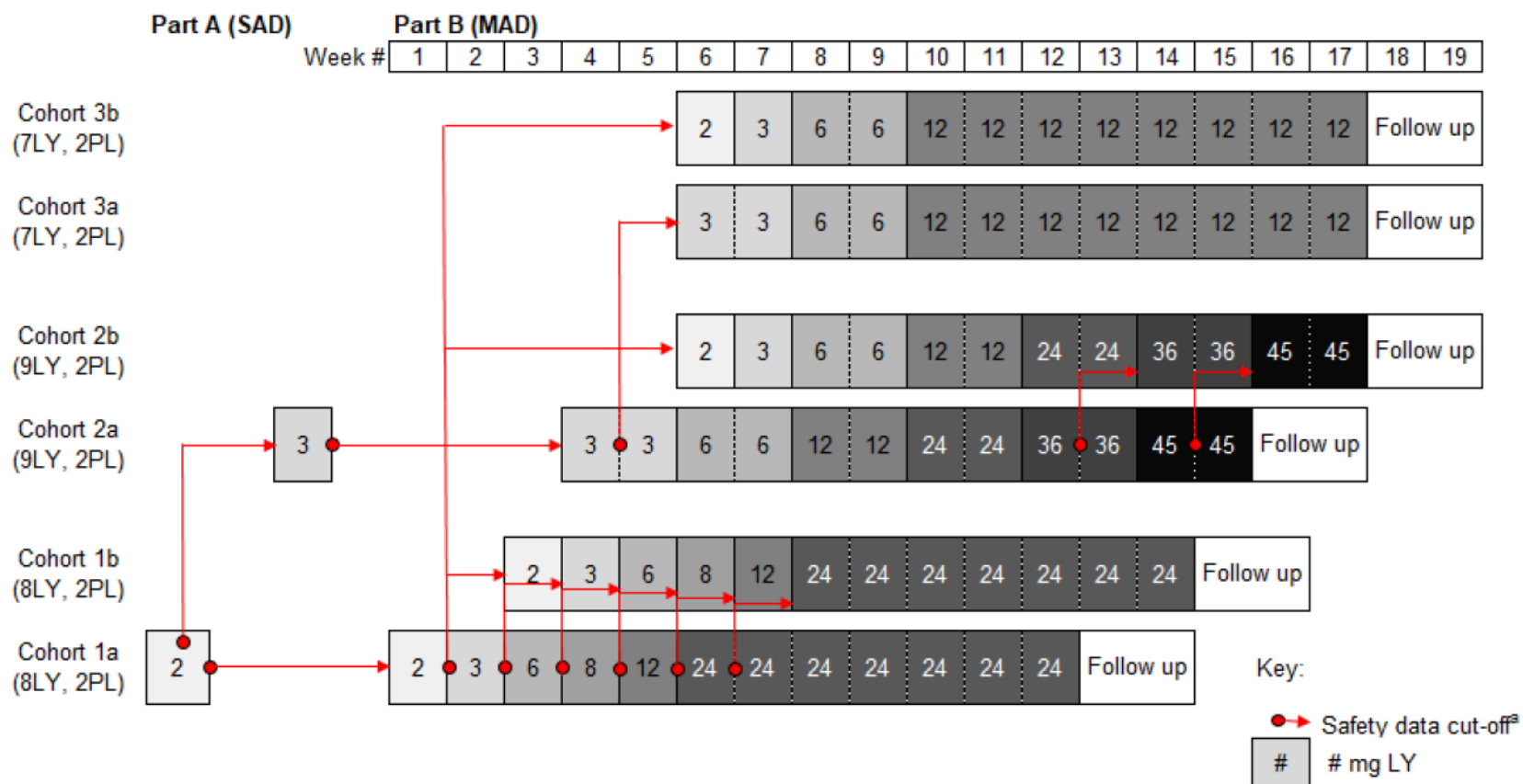
Up to 65 participants may be enrolled so that approximately 15 evaluable participants in each cohort (1, 2, and 3; Groups a and b combined) complete Part B of the study.

Intervention Groups and Duration:

Up to 3 cohorts, each split into 2 subgroups of between 9 and 11 participants per cohort subgroup, randomized as 7 to 9 LY3502970 and 2 placebo in each subgroup. Participants will be screened within 28 or 42 days prior to enrollment, depending on their need to withdraw from oral antidiabetic medication. Part A includes 2 subgroups (1a and 2a); participants in these subgroups will each receive a single oral dose of LY3502970 or placebo. Part B includes all 6 subgroups (1a, 1b, 2a, 2b, 3a, and 3b); participants will receive multiple-ascending oral doses of LY3502970 or placebo daily for up to 12 weeks, with a follow-up visit approximately 2 weeks after the last dose of study intervention.

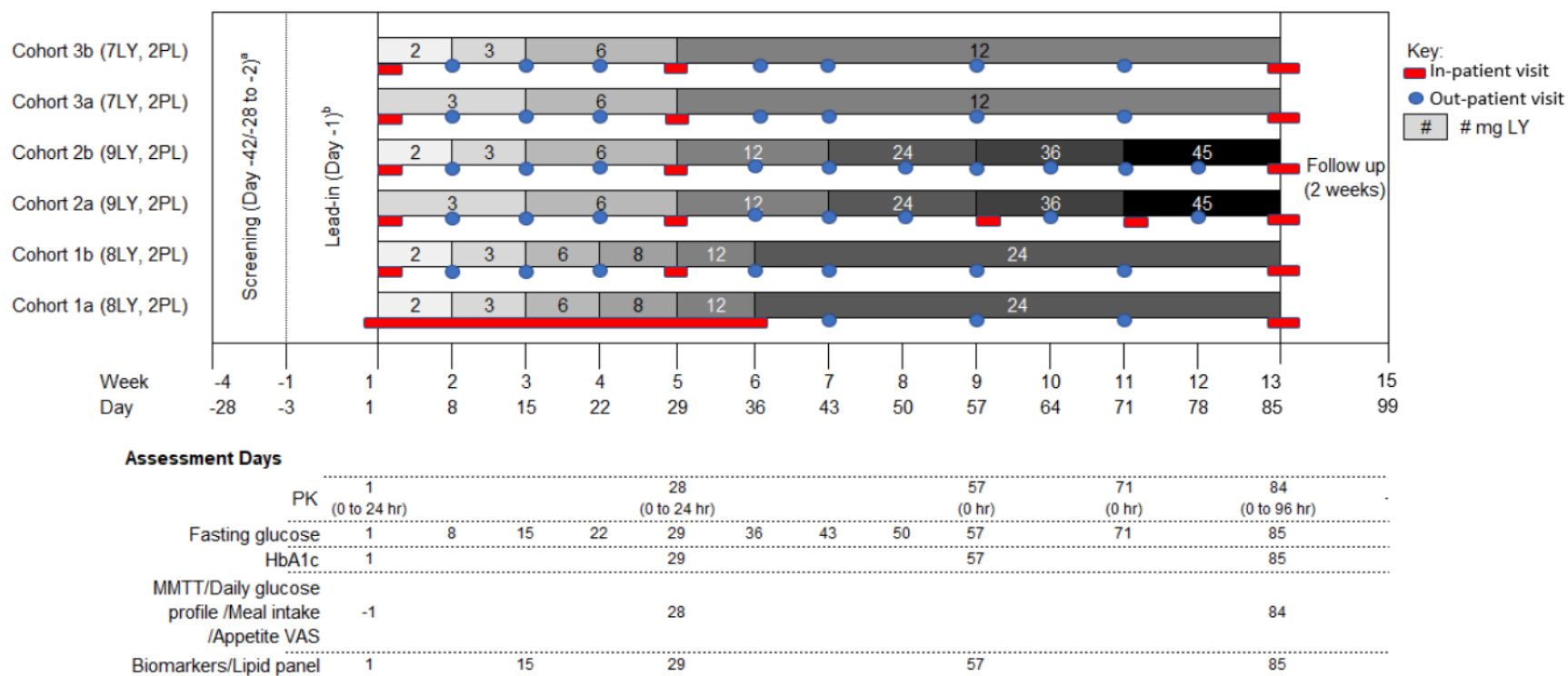
Data Monitoring Committee: No

1.2. Schema



CCI

Figure GZGB.1. Dose-escalation plan for Study GZGB



CCI

Figure GZGB.2. Visit plan for Part B of Study GZGB

1.3. Schedule of Activities (SoA)

Study Schedule for Protocol J2A-JE-GZGB: Cohorts 1a and 2a – Part A: Screening and Lead-in

Procedure	Screening ^a	Lead-in	Comments
Week	-6/-4 to -1	-1	
Day	-42/-28 to -2	-1	
IWRS Visit	0		
Clinical Procedures			
Admission to CRU		X	Participants may be admitted to the CRU on Day -2 at the discretion of the investigator. Once admitted, participants must observe an overnight fast (at least 8 hours) on the evenings of Day -2 (as applicable) and Day -1. The following Day -1 assessments or procedures may be performed on Day -2 at the discretion of the investigator: 1. medical history, 2. physical examination and medical assessment, 3. urine drug screen and ethanol test.
Informed consent	X		
IWRS	X		Participant numbers will be assigned through IWRS at screening (Section 6.3).
Medical history	X	X	Includes demographics, previous and concomitant medication.
Physical examination/ Medical assessment	X	X	Complete physical examination at screening. After screening, medical assessment is performed to include medical review and targeted examination, as appropriate.
Vital signs	X	X	Vital signs must be measured before any blood sample collection.
Body temperature	X		Additional measures should be obtained as clinically indicated.
ECG (single)	X		Single ECGs will be collected locally and will not be transmitted/stored.
Height	X		
Weight and waist circumference	X		Weight will be measured twice for each participant in a consistent way using a calibrated scale (Section 8.5.2.3).
Laboratory Tests			
Clinical laboratory tests: • hematology • clinical chemistry • urinalysis	X		Samples are analyzed at local laboratory for screening. Samples are to be collected after a fast of at least 8 hours. See Appendix 2, Section 10.2. Estimated glomerular filtration rate will be assessed at screening for eligibility.
HbA1c	X		Performed at the central laboratory.

Procedure	Screening ^a	Lead-in	Comments
Week	-6/-4 to -1	-1	
Day	-42/-28 to -2	-1	
IWRS Visit	0		
Calcitonin	X		Performed at local laboratory.
Serology: • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody • HIV	X		Performed at local laboratory.
Syphilis test	X		Performed at local laboratory.
Serum pregnancy test	X		Performed at local laboratory. Females only.
Follicle-stimulating hormone	X		Performed at local laboratory. Females only.
Thyroid-stimulating hormone	X		Performed at local laboratory.
Ethanol test and urine drug screen	X	X	Performed at local laboratory. May be repeated at the discretion of the investigator.
Glucose Management			
Training on SMPG, participant diary issued		X	Training may be completed at any time up until discharge from the CRU on Day 5 during the treatment period.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; HbA1c = glycated hemoglobin; HIV = human immunodeficiency virus; IWRS = interactive web response system; OAM = oral antidiabetic medication; SMPG = self-monitored plasma glucose.

- ^a Screening may occur up to 28 days prior to enrollment for participants who do not require withdrawal from OAM. However, screening may occur up to 42 days prior to enrollment for participants who are required to withdraw from OAM in order to meet inclusion criterion #4 (that is, withdrawal of OAM for at least 28 days prior to dosing).

Note: If multiple procedures take place at the same time point, vital signs and ECG should be measured before collection of blood samples at nominal time points.

Study Schedule for Protocol J2A-JE-GZGB: Cohorts 1a and 2a – Part A: Treatment Period

Procedure	Treatment Period						
Day	1	2	3	4	5	8 ± 2	15 ± 2
IWRS Visit	1						
Clinical Procedures							
IWRS ^a	X						
Discharge from CRU					X		
Outpatient visit						X	X
Weight ^b	P						
Waist circumference	P						
Medical assessment ^c	P				X	X	X
Vital signs (hr)	P, 1, 2, 4, 8, 12	24	48	72	96	X	X
Triplicate ECG (hr) ^d	P, 1, 2, 4, 8, 12	24	48	72	96	X	
Single ECG							X
Concomitant medications	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X
Investigational Product							
Dispensing of IP	X						
Laboratory Tests							
Urine pregnancy test (local laboratory)	P						
Clinical laboratory tests ^{e, f} (central laboratory)	P				X	X	X
PGx sample	P						
PK sampling (hr)	P, 0.5, 1, 2, 4, 8, 12, 16	24	48	72	96		
Glucose Management							
Review of participant diary						X	X

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; IP = investigational product; IWRS = interactive web response system; non-PGx = nonpharmacogenetics; P = predose; PGx = pharmacogenetics; PK = pharmacokinetics.

^a Participants will be randomized to treatment on Day 1 using the IWRS.

- b Weight will be measured twice for each participant in a consistent way using a calibrated scale (Section [8.5.1.3](#)).
- c A medical assessment will be performed prior to discharge from the CRU and is to include medical review and targeted examination, as appropriate.
- d Predose ECGs are to be collected prior to blood sampling.
- e Clinical laboratory tests for safety include hematology, clinical chemistry, and urinalysis (see Appendix 2 [Section [10.2](#)]). Blood samples will be taken predose on all dosing days.
- f Participants will be required to fast for at least 8 hours before each blood sample is drawn.

Note: If multiple procedures take place at the same time point, vital signs and ECG should be measured before collection of blood samples at nominal time points.

Study Schedule for Protocol J2A-JE-GZGB: All Cohorts – Part B: Screening and Lead-in

Procedure	Screening ^{a, b}	Lead-in	Comments
Week	-6/-4 to -1	-1	
Day	-42/-28 to -2	-1	
IWRS Visit	1		
Clinical Procedures			
Admission to CRU		X	Admission to the CRU shall occur on Day -1 after an overnight fast of at least 8 hours. Participants may be admitted to the CRU on Day -2 at the discretion of the investigator. Once admitted, participants must observe an overnight fast (at least 8 hours) on the evenings of Day -2 (as applicable) and Day -1. The following Day -1 assessments or procedures may be performed on Day -2 at the discretion of the investigator: 1. medical history, 2. physical examination and medical assessment, 3. urine drug screen and ethanol test.
Informed consent	X		
IWRS	X		Participant numbers will be assigned through IWRS at screening (Section 6.3).
Medical history	X	X	Includes demographics, previous and concomitant medication.
Physical examination/ medical assessment	X	X	Complete physical examination at screening. After screening, medical assessment is performed to include medical review and targeted examination, as appropriate.
Vital signs	X	X	Vital signs must be measured before any blood sample collection.
Body temperature	X		Additional measures should be obtained as clinically indicated.
ECG (single)	X		Single ECGs will be collected locally and will not be transmitted/stored.
Height	X		
Weight and waist circumference	X		Weight will be measured twice for each participant in a consistent way using a calibrated scale (Section 8.5.2.3).
Laboratory Tests			
Clinical laboratory tests: • hematology • clinical chemistry • urinalysis	X		Samples are analyzed at local laboratory for screening. Samples are to be collected after a fast of at least 8 hours. See Appendix 2, Section 10.2. Estimated glomerular filtration rate will be assessed at screening for eligibility.

Procedure	Screening ^{a, b}	Lead-in	Comments
Week	-6/-4 to -1	-1	
Day	-42/-28 to -2	-1	
IWRS Visit	1		
HbA1c	X		Performed at the central laboratory.
Calcitonin	X		Performed at local laboratory.
Serology: • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody • HIV	X		Performed at local laboratory.
Syphilis test	X		Performed at local laboratory.
Serum pregnancy test	X		Performed at local laboratory. Females only.
Follicle-stimulating hormone	X		Performed at local laboratory. Females only.
Thyroid-stimulating hormone	X		Performed at local laboratory.
Ethanol test and urine drug screen	X	X	Performed at local laboratory. May be repeated at the discretion of the investigator.
MMTT (glucose, insulin, C-peptide, and glucagon)		X	Participants should be fasted for at least 10 hours before morning MMTT and will consume the mixed meal in the morning and evening (refer to Section 8.5.2.2). Blood sampling for glucose, insulin, C-peptide, and glucagon: 0 (premeal), 0.5, 1, 1.5, and 2 hours after start of each meal. The start of evening mixed meal should be 10 hours after planned study intervention administration time.
Daily glucose profiles (central laboratory)		X	Blood samples will be collected to measure plasma glucose concentrations at 0 (premeal), 1, and 2 hours after the start of midday meal. The other time points in morning and evening meals are collected in MMTT. The start time of midday meal should be 6 hours after planned study intervention administration time.
Glucose Management			
Training on SMPG, participant diary issued		X	Training may be completed at any time during the first inpatient visit up until discharge from the CRU.

Procedure	Screening ^{a, b}	Lead-in	Comments
Week	-6/-4 to -1	-1	
Day	-42/-28 to -2	-1	
IWRS Visit	1		
Investigative Tests			
Meal intake test		X	Meal intake test will be performed for each meal (morning, midday, and evening). Morning and evening meals are also used for MMTT.
Appetite VAS		X	To be performed 1 hour prior to the start of the meal (morning, midday, and evening).

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; HbA1c = glycated hemoglobin; HIV = human immunodeficiency virus; IP = investigational product; IWRS = interactive web response system; MMTT = mixed meal tolerance test; OAM = oral antidiabetic medication; SMPG = self-monitored plasma glucose; VAS = visual analog scale.

^a Screening may occur up to 28 days prior to enrollment for participants who do not require withdrawal from OAM. However, screening may occur up to 42 days prior to enrollment for participants who are required to withdraw from OAM in order to meet inclusion criterion #4 (that is, withdrawal of OAM for at least 28 days prior to dosing).

^b Participants who completed screening for Part A (Cohorts 1a and 1b) will not repeat screening prior to enrolling in Part B.

Note: If multiple procedures take place at the same time point, vital signs and ECG should be measured before collection of blood samples at nominal time points.

Study Schedule for Protocol J2A-JE-GZGB: Part B – All Cohorts: Treatment Period (Weeks 1 to 8)

Procedure	Treatment Period															
Week	1	1	1	2	2	3	3	4	4	4	5	5	6	6	7	8
Day	1	2	3	8	10	15	17	22	24	28	29	31	36	38	43	50
IWRS Visit	2			3		4		5			6		7		8	
Clinical Procedures																
Admission to CRU ^a										X Chrts 1b, 2a, 2b, 3a, 3b						
Discharge from CRU			X Chrts 1b, 2a, 2b, 3a, 3b								X Chrts 1b, 2a, 2b, 3a, 3b			X Chrt 1a		
Outpatient visit				X Chrts 1b, 2a, 2b, 3a, 3b		X Chrts 1b, 2a, 2b, 3a, 3b		X Chrts 1b, 2a, 2b, 3a, 3b					X Chrts 1b, 2a, 2b, 3a, 3b		X All Chrts	X Chrts 2a, 2b
IWRS ^b	X			X		X		X			X		X		X	
Weight ^c	P			P		P		P			P		P		P	P
Waist circumference	P			P		P		P			P		P		P	P
Medical assessment ^d	P		X	X	X	X	X	X	X		X	X	X	X	X	X
Vital signs (hr)	P, 8	24		P		P		P		P, 8	24		P		P	P
Triplicate ECG (hr) ^e	P, 0.5, 1, 2,4, 6, 8	24		P		P		P		P, 0.5, 1, 2, 4, 6, 8	24		P		P	P
Concomitant medications ^f	←															→
AEs ^f	←															→
Investigational Products																
Dispensing of IP ^g	X			X		X		X			X		X		X	

Procedure	Treatment Period															
Week	1	1	1	2	2	3	3	4	4	4	5	5	6	6	7	8
Day	1	2	3	8	10	15	17	22	24	28	29	31	36	38	43	50
IWRS Visit	2			3		4		5			6		7		8	
Glucose Management																
Review of participant diary				X Chrts 1b, 2a, 2b, 3a, 3b		X Chrts 1b, 2a, 2b, 3a, 3b		X Chrts 1b, 2a, 2b, 3a, 3b		X Chrts 1b, 2a, 2b, 3a, 3b			X Chrts 1b, 2a, 2b, 3a, 3b		X	X
Laboratory Tests																
Urine pregnancy test (local laboratory)	P															
Clinical laboratory tests ^{h, i} (central laboratory)	P		P	P	P	P	P	P	P		P	P	P	P	P	P
HbA1c ⁱ (central laboratory)	P										P					
MMTT (glucose, insulin, C-peptide, and glucagon) ^j										X						
Daily glucose profiles ^k (central laboratory)										X						
Fasting plasma glucose (central laboratory)	P			P		P		P			P		P		P	P
PD biomarkers ^l (hr)	P					P					P					
Lipid panel ^m	P					P					P					
PGx sample ⁿ	P															

Procedure	Treatment Period															
Week	1	1	1	2	2	3	3	4	4	4	5	5	6	6	7	8
Day	1	2	3	8	10	15	17	22	24	28	29	31	36	38	43	50
IWRS Visit	2			3		4		5			6		7		8	
Non-PGx sample ^o (hr)	P					P					P					
PK sampling (hr)	P, 0.5, 1, 2, 4, 6, 8, 12	24								P, 0.5, 1, 2, 4, 6, 8, 12	24					
Investigative tests																
Meal intake test ^p										X						
Appetite VAS ^q										X						

Abbreviations: AE = adverse event; chrt = cohort; CRU = clinical research unit; ECG = electrocardiogram; HDL = high-density lipoprotein; IP = investigational product; IWRS = interactive web response system; LDL = low-density lipoprotein; non-PGx = nonpharmacogenetics; MMTT = mixed meal tolerance test; P = predose; PD = pharmacodynamics; PGx = pharmacogenetic; PK = pharmacokinetics; VAS = visual analog scale; VLDL = very low-density lipoprotein.

- a Participants will arrive at the CRU prior to dosing after an overnight fast of at least 8 hours. Participants may be admitted to the CRU 1 day prior to the scheduled CRU admission date at the discretion of the investigator. Once admitted, participants must observe an overnight fast (at least 8 hours) on the evenings of the day of admission to the CRU (1 day prior to the scheduled admission) and the scheduled admission day.
- b All participants (excluding those previously randomized in Part A) will be randomized to treatment on Day 1 using the IWRS.
- c Weight will be measured twice for each participant in a consistent way using a calibrated scale (Section 8.5.1.3).
- d A medical assessment will be performed prior to discharge from the CRU and is to include medical review and targeted examination, as appropriate.
- e Predose ECGs are to be collected prior to blood sampling.
- f Adverse events and concomitant medication will be continuously monitored throughout the treatment period.
- g Before leaving the CRU at discharge or during outpatient visits, participants will be dispensed the appropriate amount of IP for daily self-administration at home until the next visit.
- h Clinical laboratory tests for safety include hematology, clinical chemistry, and urinalysis (see Appendix 2 [Section 10.2]). Blood samples will be taken predose on all dosing days.
- i Participants will be required to fast for at least 8 hours before each blood sample is drawn.

- j MMTT (glucose, insulin, C-peptide, and glucagon) sampling schedule (time points are relative to the start of each mixed meal): 0 (premeal), and 0.5, 1, 1.5, and 2 hours. Participants will start to consume morning and evening mixed meals 2 and 10 hours after study intervention administration, respectively. Participants should not take snack or drink (except for water) on the day of MMTT.
- k Time points for daily glucose profile: 0 (premeal), 1, and 2 hours after the start of midday meal. Other samples for glucose in morning and evening meals are collected and measured in MMTT. The start time of midday meal should be 6 hours after study intervention administration.
- l Pharmacodynamic biomarkers are insulin, C-peptide, and glucagon (Section 8.5.2). Participants will be fasted for at least 8 hours before each blood sample is drawn.
- m Lipid panel includes triglycerides, total cholesterol, LDL cholesterol, VLDL cholesterol, and HDL cholesterol. Participants will be fasted for at least 8 hours before each blood sample is drawn.
- n Pharmacogenetic samples will only be collected for participants that did not have a PGx sample taken in Part A.
- o Nonpharmacogenetic samples will be collected predose and while fasting for at least 8 hours before each blood sample is drawn.
- p Meal intake test will be performed for each meal (morning, midday, and evening) on the indicated days. Morning and evening meals are also used for MMTT.
- q To be performed 1 hour prior to the start of each meal (morning, midday, and evening) on the indicated days. Refer to Section 8.5.2.1.

Note: If multiple procedures take place at the same time point, vital signs and ECG should be measured before collection of blood samples at nominal time points.

Note: Days 10, 17, 24, 31, and 38 will be conducted only for Cohort 1a. Days 50, 64, and 78 will only be conducted for Cohorts 2a and 2b. Days 59 and 73 will be conducted only for Cohort 2a.

Note: For Days 57 and 71, Cohort 1 is permitted ± 1 day allowance. For Days 43, 57, and 71, Cohort 3 is permitted ± 1 day allowance.

Note: Participants in Cohort 1a may be discharged at the investigator's discretion 48 hours after the administration of a new dose level if no assessments are scheduled, participants will subsequently be required to return to the CRU prior to administration of the next scheduled dose level or assessment.

Study Schedule for Protocol J2A-JE-GZGB: Part B – All Cohorts: Treatment Period (Weeks 9 to 13)

[illegible]

Procedure	Treatment Period									
Week	9	9	10	11	11	12	12	13	13	13
Day	57	59	64	71	73	78	84	85	86	88
IWRS Visit	9			10						
Clinical laboratory tests ^{g, h} (central laboratory)	P	P	P	P	P	P		X		
HbA1c ^h (central laboratory)	P							X		
MMTT (glucose, insulin, C-peptide, and glucagon) ⁱ							X			
Daily glucose profiles ^j (central laboratory)							X			
Fasting plasma glucose (central laboratory)	P			P				X		
PD biomarkers ^k (hr)	P							X		
Lipid panel ^l	P							X		
Non-PGx sample ^m (hr)	P							X		
PK sampling (hr)	P			P			P, 0.5, 1, 2, 4, 6, 8, 12	24	48	96
Investigative tests										
Meal intake test ⁿ							X			
Appetite VAS ^o							X			

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; HDL = high-density lipoprotein; IP = investigational product; IWRS = interactive web response system; LDL = low-density lipoprotein; non-PGx = nonpharmacogenetics; MMTT = mixed meal tolerance test; P = predose; PD = pharmacodynamics; PK = pharmacokinetics; VAS = visual analog scale; VLDL = very low-density lipoprotein.

- a Participants will arrive at the CRU prior to dosing after an overnight fast of at least 8 hours. Participants may be admitted to the CRU 1 day prior to the scheduled CRU admission date at the discretion of the investigator. Once admitted, participants must observe an overnight fast (at least 8 hours) on the evenings of the day of admission to the CRU (1 day prior to the scheduled admission) and the scheduled admission day.
- b Weight will be measured twice for each participant in a consistent way using a calibrated scale (Section 8.5.1.3).
- c A medical assessment will be performed prior to discharge from the CRU and is to include medical review and targeted examination, as appropriate.
- d Predose ECGs are to be collected prior to blood sampling.

- e Adverse events and concomitant medication will be continuously monitored throughout the treatment period.
- f Before leaving the CRU at discharge or during outpatient visits, participants will be dispensed the appropriate amount of IP for daily self-administration at home until the next visit.
- g Clinical laboratory tests for safety include hematology, clinical chemistry, and urinalysis (see Appendix 2 [Section 10.2]). Blood samples will be taken predose on all dosing days.
- h Participants will be required to fast for at least 8 hours before each blood sample is drawn.
- i MMTT (glucose, insulin, C-peptide, and glucagon) sampling schedule (time points are relative to the start of each mixed meal): 0 (premeal), and 0.5, 1, 1.5, and 2 hours. Participants will start to consume morning and evening mixed meals 2 and 10 hours after study intervention administration, respectively. Participants should not take snack or drink (except for water) on the day of MMTT.
- j Time points for daily glucose profile: 0 (premeal), 1, and 2 hours after the start of midday meal. Other samples for glucose in morning and evening meals are collected and measured in MMTT. The start time of midday meal should be 6 hours after study intervention administration.
- k Pharmacodynamic biomarkers are insulin, C-peptide, and glucagon (Section 8.5.2). Participants will be fasted for at least 8 hours before each blood sample is drawn.
- l Lipid panel includes triglycerides, total cholesterol, LDL cholesterol, VLDL cholesterol, and HDL cholesterol. Participants will be fasted for at least 8 hours before each blood sample is drawn.
- m Nonpharmacogenetic samples will be collected predose and while fasting for at least 8 hours before each blood sample is drawn.
- n Meal intake test will be performed for each meal (morning, midday, and evening) on the indicated days. Morning and evening meals are also used for MMTT.
- o To be performed 1 hour prior to the start of each meal (morning, midday, and evening) on the indicated days. Refer to Section 8.5.2.1.

Note: If multiple procedures take place at the same time point, vital signs and ECG should be measured before collection of blood samples at nominal time points.

Note: Days 10, 17, 24, 31, and 38 will be conducted only for Cohort 1a. Days 50, 64, and 78 will be conducted only for Cohorts 2a and 2b. Days 59 and 73 will be conducted only for Cohort 2a.

Note: For Days 57 and 71, Cohort 1 is permitted ± 1 day allowance. For Days 43, 57, and 71, Cohort 3 is permitted ± 1 day allowance.

Study Schedule for Protocol J2A-JE-GZGB: Early Termination and Follow-Up for All Cohorts

Procedure (Early Termination, Follow-Up)	ET	Follow-up	Comments
Week	-	15^a	The final follow-up visit shall be approximately 2 weeks (± 3 days) after the last dose of study intervention.
Day	-	99 ± 3	
IWRS Visit		801	
Clinical Procedures			
IWRS	X	X	
Medical assessment	X	X	
Adverse events and concomitant medications	X	X	
Vital signs	X	X	Vital signs must be measured before any blood sample collection. Blood pressure and pulse rate should be measured in the sitting position (Section 8.2.2).
ECG (single)	X	X	Single ECGs will be collected locally and will not be transmitted/stored.
Weight and waist circumference	X	X	Weight will be measured twice for each participant in a consistent way using a calibrated scale (Section 8.5.1.3)
Laboratory Tests			
<u>Clinical laboratory tests:</u> • hematology • clinical chemistry • urinalysis	X	X	Samples are analyzed at the central laboratory. Samples are to be collected after a fast of at least 8 hours. See Appendix 2, Section 10.2.
HbA1c	X		Samples are analyzed at the central laboratory.
Urine pregnancy test	X	X	Performed at local laboratory. Females only.
Fasting plasma glucose (central laboratory)	X		Will not be conducted at ET for participants who discontinue prior to enrollment in Part B.
<u>PD biomarkers:</u> • insulin • C-peptide • glucagon	X		Participants will be fasted for at least 8 hours before the blood sample is drawn. Will not be conducted at ET for participants that discontinue prior to enrollment in Part B.
Lipid panel	X		Lipid panel includes triglycerides, total cholesterol, LDL cholesterol, VLDL cholesterol, and HDL cholesterol. Participants will be fasted for at least 8 hours before the blood sample is drawn. Will not be conducted at ET for participants that discontinue prior to enrollment in Part B.
Non-PGx sample	X		Samples are to be collected after a fast of at least 8 hours.
PK sampling	X	X	Upon early termination, a PK sample can be taken at any time during the visit.

Abbreviations: ECG = electrocardiogram; ET = early termination; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; IWRS = interactive web response system; LDL = low-density lipoprotein; non-PGx = non-pharmacogenetics; P = predose; PD = pharmacodynamics; PK = pharmacokinetics; VLDL = very low-density lipoprotein.

- ^a Participants who discontinue early will be encouraged to return for a follow-up visit at least 15 days (± 3 days) after the last dose of study intervention administration.

Note: If multiple procedures take place at the same time point, vital signs and ECG should be measured before collection of blood samples at nominal time points.

2. Introduction

LY3502970 is CCI

LY3502970 is being developed as CCI to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

2.1. Study Rationale

Study J2A-JE-GZGB (GZGB) is a Phase 1, single-ascending dose (SAD) and multiple-ascending dose (MAD) study designed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3502970 following oral administration of single dose or multiple once daily (QD) doses for 12 weeks in Japanese participants with T2DM.

Pharmacokinetic data from previous Phase 1 clinical studies supported QD administration of LY3502970 and found LY3502970 to be safe and well tolerated. The current study is intended to obtain sufficient safety, tolerability, PK, and PD data with preliminary efficacy measurements to support identification of an appropriate dose range for subsequent clinical studies of LY3502970 in Japanese patients with T2DM.

2.2. Background

CCI

LY3502970 is CCI

In the first-in-human SAD and MAD Study J2A-MC-GZGA (GZGA), a total of 108 healthy participants received LY3502970 up to 24 mg. In the ongoing 12-week multiple-dose Study J2A-MC-GZGC (GZGC), a total of 68 participants with T2DM have received either LY3502970 (up to 45 mg) or placebo. No deaths have been reported in these studies. CCI

All tested LY3502970 doses were tolerated in both healthy participants and patients with T2DM in these studies. CCI were the most frequently reported events. These AEs were mostly mild in severity and the majority resolved

without treatment. CCI

with LY3502970 compared to placebo in Study GZGC.

2.3. Benefit/Risk Assessment

No safety or tolerability concerns that preclude further investigation of LY3502970 have been identified in 108 healthy participants to date, up to the highest single dose given (6 mg) and multiple doses given (24 mg). Furthermore, no safety or tolerability concerns have been identified in the ongoing Phase 1 Study GZGA in participants with T2DM who have received treatment with up to 45 mg LY3502970.

To mitigate CCI, 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. It is anticipated that these dose-escalation steps will be CCI, and escalation will occur in the early part of the study until the target final dose is achieved. Participants will continue on that final target dose for the remainder of the treatment period.

CCI

These included:

CCI

These effects were reversible and monitorable. CCI

The no-observed-adverse-effect levels (NOAELs) for target organ toxicity have been identified in both rats and monkeys and are associated with the projected exposure multiples at the planned human doses (see [Table GZGB.1](#)). For monkeys, the NOAEL for target organ toxicity was characterized by effects that were consistent with exaggerated pharmacology or class effects, and that are considered monitorable and reversible in clinical trial participants. An adequate exposure multiple has been demonstrated for the rat and these data do not suggest any potential off-target toxicities. The observation of pharmacologically mediated effects in the monkey and the adequate margins observed in the rat for target organ toxicity are considered sufficient to enable further safe clinical investigation of LY3502970 in the proposed dose range. CCI

CCI

Table GZGB.1. Exposure Multiples for Oral Administration of LY3502970 Based on Predicted Human Exposures Relative to the NOAEL for Target Organ Toxicity in Chronic Toxicity Studies

Species Dose level	AUC (ng·hr/mL) ^d	AUC Exposure Multiple	C _{max} (ng/mL) ^d	C _{max} Exposure Multiple
CCI				

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum observed concentration;
NOAEL = no-observed-adverse-effect level; F = female; M = male.

^a Assume human body weight = 70 kg.

^b Highest dose administered in rat, 6-month toxicology Study CCI

^c Highest dose administered in monkey, 9-month toxicology Study CCI

^d Plasma pharmacokinetics shown were estimated from pharmacokinetic data for a CCI dose of LY3502970 in humans in Part B of Study J2A-MC-GZGA on Day 28.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3502970 may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To investigate the safety and tolerability of LY3502970 following single and multiple oral QD doses for 12 weeks in Japanese participants with T2DM.	- TEAEs - SAEs
Secondary	
- To characterize the PK profile of LY3502970 following single and multiple oral QD doses for 12 weeks in Japanese participants with T2DM. - To characterize the PD effects of LY3502970 following multiple oral QD doses for 12 weeks in Japanese participants with T2DM.	$C_{\max}$ and AUC - Changes from baseline in: - fasting glucose - HbA1c - body weight
Tertiary/Exploratory	
To characterize the PD effects of LY3502970 following multiple oral QD doses (parameters of glucose and lipid metabolism, endocrine pancreas function, insulin action, insulin secretion, energy balance) for 12 weeks in Japanese participants with T2DM.	- Changes from baseline in PD biomarkers: - insulin - C-peptide - glucagon - Changes from baseline in MMTT parameters: - glucose - insulin - C-peptide - glucagon - Changes from baseline in: - daily glucose profile - fasting lipids (triglycerides, total cholesterol, and LDL, HDL, and VLDL cholesterol) - appetite VAS - meal intake - waist circumference

Abbreviations: AUC = area under the concentration versus time curve; $C_{\max}$ = maximum observed drug concentration; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MMTT = mixed meal tolerance test PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; SAE = serious adverse event; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event; VAS = visual analog scale; VLDL = very low-density lipoprotein.

4. Study Design

4.1. Overall Design

Study GZGB is a Phase 1, multicenter, participant- and investigator-blinded, parallel, placebo-controlled, randomized, SAD (Part A), and a 12-week MAD (Part B) study in Japanese participants with T2DM to investigate the safety, tolerability, PK, and PD of LY3502970 administered as a single oral dose or multiple CCI [REDACTED], for 12 weeks. In Part A, single-ascending doses of LY3502970 will be administered in 2 subgroups (1a and 2a). After completing Part A, participants will subsequently be enrolled in Part B (12-week MAD; see Section 4.1.2). The safety data through Day 8 from each SAD cohort in Part A will be reviewed prior to initiation of the corresponding dose group in Part B (Section 6.5.1).

The schema in Section 1.2 illustrates the study design.

4.1.1. Screening

Participants will be screened within 28 days prior to enrollment, unless they require withdrawal from monotherapy of oral antidiabetic medication (OAM). Participants on monotherapy of OAM, either metformin, dipeptidyl peptidase-4 (DPP-4) inhibitor, or sodium-glucose co-transporter-2 (SGLT2) inhibitor, will be required to withdraw from their treatment for at least 28 days washout prior to dosing study intervention. For these participants, the screening period may be increased by a maximum of 2 weeks, that is, participants may be screened within 42 days prior to enrollment.

4.1.2. Lead-In and Treatment Periods

Eligible participants who have satisfied the entry criteria and completed all screening assessments will return to the clinical research unit (CRU) on Day -1 for both Parts A (SAD) and B (MAD) for participation in the study. Participants may be admitted to the CRU on Day -2 at the discretion of the investigator.

Part A: Single-Ascending Dose

Participants randomized to Cohorts 1a and 2a will receive a single oral dose of LY3502970 or placebo on Day 1 after an overnight fast for at least 8 hours. Participants will remain resident in the CRU for PK sampling and safety monitoring until discharge on Day 5. Participants will then return to the CRU for 2 outpatient visits on Days 8 and 15 for additional safety assessments. Following completion of their participation in Part A, participants will be enrolled in Part B.

Safety assessments, including AEs, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and ECGs, and blood sampling for PK measurements, will be performed according to the Schedule of Assessments (SoA) for Part A (Section 1.3).

Part B: Multiple-Ascending Dose

Safety data through Day 8 from each SAD cohort in Part A will be reviewed prior to initiation of the corresponding dose group in Part B. For participants who participated in Part A, the lead-in period for Part B will occur after completion (Day 15) of Part A.

The study intervention will be administered orally QD for up to 12 weeks in all cohorts (1a, 1b, 2a, 2b, 3a, and 3b). Participants in Cohort 1a may remain resident in the CRU for safety monitoring for the first 6 weeks of the treatment period, however, participants may be discharged at the investigator's discretion 48 hours after the administration of a new dose level if no assessments are scheduled, subjects will subsequently be required to return to the CRU prior to administration of the next scheduled dose level or assessment. All participants in Cohort 1a will be discharged on Day 38 following the completion of all scheduled assessments. Participants in all other cohorts will remain in the CRU 2 days after dosing (discharge following 48-hour assessments on Day 3) for safety monitoring. Participants will be admitted to the CRU for a maximum of 5 planned inpatient stays for PK, PD, and safety assessments. Participants will also return to the CRU for regular outpatient visits throughout the treatment and follow-up periods (Figure GZGB.2). Apart from the planned inpatient stays, participants may remain resident in the CRU for safety monitoring following each visit, at the investigator's discretion.

Safety assessments, including AEs, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and ECGs, and blood sampling for PK and PD measurements will be performed according to the SoA (Section 1.3). The timing of the sampling may be adjusted in view of emerging safety, tolerability, PK, and/or PD data during the study. These changes must be appropriately documented and communicated by the sponsor to the investigator.

Progression of Cohorts through Study GZGB

Up to 3 cohorts are planned; each cohort is split into 2 subgroups (that is, 'a' and 'b') for a staggered dosing approach. Each cohort will comprise participants randomized to receive either LY3502970 or a corresponding placebo for 12 weeks as stated below:

- Part A
 - Cohort 1a; 8 LY:2 placebo; 2 mg
 - Cohort 2a; 9 LY:2 placebo; 3 mg
- Part B
 - Cohorts 1a and 1b; 8 LY:2 placebo; 2 mg (1 week) → 3 mg (1 week) → 6 mg (1 week) → 8 mg (1 week) → 12 mg (1 week) → 24 mg (7 weeks)
 - Cohort 2a; 9 LY:2 placebo; 3 mg (2 weeks) → 6 mg (2 weeks) → 12 mg (2 weeks) → 24 mg (2 weeks) → 36 mg (2 weeks) → 45 mg (2 weeks)
 - Cohort 2b; 9 LY:2 placebo; 2 mg (1 week) → 3 mg (1 week) → 6 mg (2 weeks) → 12 mg (2 weeks) → 24 mg (2 weeks) → 36 mg (2 weeks) → 45 mg (2 weeks)
 - Cohort 3a; 7 LY:2 placebo; 3 mg (2 weeks) → 6 mg (2 weeks) → 12 mg (8 weeks)
 - Cohort 3b; 7 LY:2 placebo; 2 mg (1 week) → 3 mg (1 week) → 6 mg (2 weeks) → 12 mg (8 weeks)

Safety data review will be required for progression within cohorts, that is, from cohort 'a' to cohort 'b', for progression to the next cohort, and for dose-escalation decisions of 1 dose level to the next higher dose level (see Section 6.5.1). The different safety data reviews are outlined in (Figure GZGB.1). Participants in Cohorts 1a and 2a are expected to proceed from Part A to

Part B; however, if a participant discontinues following Part A, they may be replaced for Part B (see Section 9.5).

The investigator and Lilly clinical pharmacologist (CP) will review all available safety data (AEs, vital signs, ECGs, concomitant medications, safety laboratory measurements, and medical assessments). Dosing following safety reviews will only occur after subsequent agreement between the investigator and the Lilly CP.

If the investigator decides not to up-titrate the dose level as planned for individual participants for any reason(s), participants may be discontinued for doses ≤ 12 mg or may remain dosing at the current dose level through to the last planned dose on Day 84 for doses ≥ 24 mg (see Section 6.5.1). See Section 6.5.2 for more information on dose-escalation stopping criteria.

4.1.3. Follow-Up

A follow-up visit approximately 2 weeks (Day 99 $\pm$ 3) after the last dose of study intervention will be performed according to the SoA (Section 1.3).

4.2. Scientific Rationale for Study Design

The SAD and MAD Study GZGA demonstrated that LY3502970 was well tolerated up to 6 mg SAD and 24 mg (4 week, weekly escalating doses; 2, 5, 12, and 24 mg) MAD in healthy participants. The most frequently reported AEs were CCI

The ongoing 12-week MAD Study GZGC has evaluated escalating doses of LY3502970 from starting dose of 3 mg to maintenance doses of either 9, 15, 27, or 45 mg in participants with T2DM, and there were significant reductions CCI compared to placebo through 45 mg.

This study will evaluate 5 escalating dosing regimens of LY3502970 in Japanese participants with T2DM. Participants with T2DM will be enrolled, rather than healthy participants, to evaluate the glucose-lowering effects of LY3502970 more accurately. Since this is the first study to administer LY3502970 to Japanese participants, the single dose safety (Part A) will be evaluated prior to 12-week MAD (Part B). The 12-week treatment duration will provide sufficient data to assess the safety, tolerability, PK, and PD of LY3502970. CCI

4.3. Justification for Dose

CCI

A large, bold, red watermark consisting of the letters 'CCI' is positioned on the left side of a solid black rectangular area that occupies the upper half of the page.

4.4. End of Study Definition

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

A participant is considered to have completed the study if the participant has completed all periods of the study, including the last scheduled procedure shown in the SoA (Section [1.3](#)).

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG.

The nature of any conditions present at the time of the physical examination and any pre-existing conditions will be documented.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only and at the discretion of the investigator through predose Day 1 for safety, not continuously throughout the trial.

Screening may occur up to 28 days prior to enrollment for participants who do not require withdrawal from OAM. However, screening may occur up to 42 days prior to enrollment for participants who are required to withdraw from OAM in order to meet inclusion criterion #4 (that is, withdrawal of OAM for at least 28 days prior to dosing). Participants who are not enrolled within 28 (no OAM withdrawal required) or 42 days (OAM withdrawal required) of screening may undergo an additional medical assessment (for example, medical history and physical examination) and clinical measurements to confirm their eligibility, at the discretion of the investigator.

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

5.1. Inclusion Criteria

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

Age

1. Participants must be 20 to 70 years of age, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are Japanese.
3. Have T2DM for at least 1 year before screening. Participants with comorbid conditions commonly associated with diabetes (for example, hypertension, hypercholesterolemia, hypothyroidism) may be eligible for inclusion if conditions are assessed by the investigator to be well controlled and stable for at least 30 days prior to screening.
4. Have T2DM controlled with diet and exercise alone or are stable on a single OAM; either metformin, DPP-4 inhibitor (other than omarigliptin or trelagliptin), or SGLT2 inhibitor only, for at least 3 months prior to screening. Participants must withdraw from their OAM treatment for at least 28 days prior to dosing.
5. Have a HbA1c value at screening of $\geq 7.0\%$ and $\leq 10.0\%$ for participants treated with diet and exercise alone, OR $\geq 6.5\%$ and $\leq 9.0\%$ for participants who have washed out antidiabetic medications.
6. Have had a stable body weight for the 3 months prior to randomization ($<5\%$ body weight change).

7. Have clinical laboratory test results within a normal range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator; abnormalities of blood glucose, serum lipids, urinary glucose, and urinary protein consistent with T2DM are acceptable. Laboratory tests may be repeated if there is a documented technical error, or once at the discretion of the investigator for any out-of-range results.

Weight

8. Body weight of at least 54.0 kg and body mass index within the range 20.0 to 35.0 kg/m² (inclusive).

Sex and Contraceptive/Barrier Requirements

9. Male or female

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

- a. Male participants:
 - Males may participate in this trial.
- b. Female participants:
 - Women not of childbearing potential may participate in this trial.

Please refer to Appendix 4 (Section 10.4) for definitions and additional guidance related to contraception.

Informed Consent

10. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
11. Are reliable and willing to make themselves available for the duration of the study and who will comply with the required study and dosing visits and abide by the investigative site policy and procedure and study restrictions.
12. Are willing to withdraw from their OAM treatment (metformin, DPP-4 inhibitor, or SGLT2 inhibitor) for at least 28 days prior to dosing, if taking stable doses of these medications at screening.

5.2. Exclusion Criteria

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

Medical Conditions

1. Have type 1 diabetes mellitus or latent autoimmune diabetes in adults.
2. Have uncontrolled diabetes defined as an episode of ketoacidosis or hyperosmolar state requiring hospitalization in the 6 months prior to screening.

3. Have a history of proliferative diabetic retinopathy, diabetic maculopathy, or severe nonproliferative diabetic retinopathy that requires acute treatment.
4. Present comorbid conditions commonly associated with diabetes (for example, hypertension, hypercholesterolemia, hypothyroidism) which are not well controlled with stable medication doses for at least 30 days prior to screening.
5. Have had an episode of severe hypoglycemia, as defined by the occurrence of neuroglycopenic symptoms requiring the assistance of another person for recovery, within 6 months prior to screening visit, or have a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms. Any participant that the investigator feels will not be able to communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia should also be excluded.
6. Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction), have undergone gastric bypass (bariatric) surgery, sleeve gastrectomy, or restrictive bariatric surgery (for example, Lap-Band®), or chronically take medications that directly affect GI motility.
7. Have known definitive diagnosis of autonomic neuropathy as evidenced by urinary retention, resting tachycardia, orthostatic hypotension, or diabetic diarrhea.
8. Have obesity induced by other endocrine disorders (such as Cushing's syndrome or Prader-Willi syndrome).
9. Have had any of the following within the past 6 months prior to screening: myocardial infarction, unstable angina, coronary artery bypass graft, percutaneous coronary intervention (diagnostic angiograms are permitted), transient ischemic attack, cerebrovascular accident or decompensated congestive heart failure, or currently have New York Heart Association Class III or IV heart failure.
10. Have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study or may confound ECG (QT) data analysis, such as a QT interval corrected using Fridericia's formula (QTcF) >450 msec for males and >470 msec for women, short PR interval, or PR interval >220 msec, second or third degree atrioventricular block, intraventricular conduction delay with QRS >120 msec, right bundle branch block, left bundle branch block, or Wolff-Parkinson-White syndrome.
11. Have a pulse rate (PR) of <50 or >100 beats per minute.
12. Have a mean sitting systolic BP >160 mmHg and a mean sitting diastolic BP >95 mmHg (excluding white-coat hypertension; therefore, if a repeated measurement shows values within the range, the participant can be included in the trial).
13. Have an estimated glomerular filtration rate <45 mL/min/1.73 m², as determined by the local laboratory.

14. Have a history of severe atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis).
15. Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for <5 years prior to screening.
16. Have a known self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma.
17. Have a calcitonin ≥ 20 pg/mL.
18. Any history or presence of clinically relevant conditions constituting a risk while taking the study medication; or of interfering with the interpretation of data.
19. Have a history of acute or chronic pancreatitis or fasting serum triglyceride level of >500 mg/dL.
20. 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 $3 \times$ upper limit of normal (ULN).
21. Show evidence of hepatitis B, positive hepatitis B core antibody, and/or positive hepatitis B surface antigen.
22. Show evidence of hepatitis C and/or positive hepatitis C antibody.
23. Have a history of Gilbert's syndrome or have total bilirubin level (TBL) above $1.5 \times$ ULN.
24. Have evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
25. Show evidence of syphilis or have a positive syphilis test.
26. Have known or ongoing psychiatric disorders considered clinically significant in the opinion of the investigator.
27. Regularly use known drugs of abuse and/or suspected drug abuse by positive findings on drug screening.
28. Have an average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females) or are unwilling to stop alcohol consumption from 24 hours prior to CRU admission days, until the participant has been discharged 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).

29. Smoke more than 10 cigarettes, or cigarette equivalent (as determined by investigator), per day or are unable to abide by CRU tobacco and nicotine-containing product restrictions.
30. Have donated:
- a. any blood (including apheresis) within the last 4 weeks; or
 - b. at least 400 mL of blood within the last 16 weeks (females) or 12 weeks (males); or
 - c. at least 800 mL of blood (females) or 1200 mL of blood (males) within 12 months.
31. Have known hemoglobinopathy, hemolytic anemia, sickle cell anemia, or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with HbA1c methodology.
32. Have evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone that, in the opinion of the investigator, would pose a risk to participant safety. Participants on a stable dose of thyroid replacement therapy for at least the prior 3 months who are clinically euthyroid and who are anticipated to remain on this dose throughout the trial period may be eligible if they meet the other criteria.

Prior/Concomitant Therapy

33. Any glucose-lowering medications other than metformin, DPP-4 inhibitors, or SGLT2 inhibitors within 3 months prior to screening.
34. CCI [REDACTED]
35. Have been treated or plan to be treated with prescription medications such as Sanorex® (mazindol), or other non-approved imported drugs intended to promote weight loss, within 3 months prior to screening.
36. Have received chronic (lasting >2 weeks) systemic glucocorticoid therapy (excluding topical, intra-articular, and inhaled preparations) in the past year or have received any glucocorticoid therapy within 4 weeks before screening.
37. Are currently taking a central nervous system stimulant (for example, Ritalin-SR®) with the exception of caffeinated beverages.

Prior/Concurrent Clinical Study Experience

38. Have known allergies to CCI [REDACTED], LY3502970.
39. Are currently enrolled in a clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study.

40. Have participated, within the last 4 months, in a clinical study involving an IP. If the previous IP has a long half-life, 5 half-lives or 4 months (whichever is longer) should have passed.
41. Have previously completed or withdrawn from this study or any other study investigating LY3502970 and have previously received the IP.

Other Exclusions

42. Are women who are lactating.
43. Are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
44. Are employees of Eli Lilly and Company (Lilly) or the investigative site.
45. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

Study participants should be instructed not to donate blood or blood products during the study or for 90 days following the study.

5.3.1. Meals and Dietary Restrictions

During the study, participants should follow their usual dietary regimen that is a part of their diabetes management, as agreed with the investigator or his/her designee.

Participants will be required to attend the CRU in a fasting state, after an overnight fast (except for water) of at least 8 hours, for outpatient visits when clinical laboratory assessments, PD biomarker, lipid panel, and/or weight measures are performed as specified in the SoA (Section 1.3). Participants must be fasted for at least 10 hours prior to scheduled mixed meal tolerance test (MMTT) in the morning as specified in the SoA (Section 1.3).

While in the CRU, participants will be required to fast overnight for at least 8 hours before taking an oral dose of study intervention and for each study day when clinical safety laboratory, PK, and PD samples are taken. Postdose ECG measurements at 0.5- and 1-hour timepoints (see SoA in Section 1.3) should be taken prior to any food intake.

While self-administering IP at home, participants will take their dose before breakfast in the morning, but if they forget, it can be taken later that day.

On inpatient study days when there are no scheduled MMTTs or 0.5 and 1 hour postdose ECGs, a standard breakfast may be served approximately 15 minutes after dosing. Other than the standardized test meals for MMTT and meal intake assessment specified in the SoA (Section 1.3) and Section 8.5.2.1, standard meals will be provided during each participants' stay in the CRU. Participants will not be allowed to consume snacks or drinks (except for water) during MMTT assessment days. Water may be consumed at any time during the study.

When not resident at the CRU, participants will be encouraged to maintain their usual dietary habits during the study.

5.3.2. Caffeine, Alcohol, and Tobacco

Caffeine: Participants will be allowed to maintain their regular caffeine consumption throughout the study period, unless CRU confinement period restrictions require otherwise.

Alcohol: Alcohol will not be permitted 24 hours prior to CRU admission days until the participant has been discharged from the CRU.

A maximum of 21 units per week (males) or 14 units per week (females) will be permitted between each discharge from the CRU until the final follow-up visit.

Tobacco: Participants who smoke in excess of 10 cigarettes, or cigarette equivalent (as determined by investigator), per day are excluded from the study. Participants will be questioned about their smoking habits and use of other tobacco- or nicotine-containing products at screening. Smoking, and use of other tobacco- or nicotine-containing products, will be limited during the study confinement according to the CRU guidelines. Smoking, and use of other tobacco- or nicotine-containing products, will also not be permitted for 1 hour before assessments of vital signs and ECG.

5.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity/exercise during the study; strenuous exercise within 24 hours prior to admission to CRU should be avoided. When certain study procedures are in progress at the site, participants may be required to remain supine or seated.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Individuals may be rescreened up to 1 time. The interval between rescreenings should be at least 1 week. If rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

5.5. Criteria for Temporarily Delaying Enrollment or Randomization of a Participant

Not applicable.

6. Study Interventions and Concomitant Therapy

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

6.1. Study Interventions Administered

This study involves a comparison of LY3502970 administered as a single oral dose or daily oral dosing with placebo. [Table GZGB.2](#) shows the treatment regimens.

Table GZGB.2. Study Interventions Administered

Study Intervention	LY3502970	Placebo
Dosage Formulation	Capsule	Capsule
Unit dose strength(s)/Dosage Level(s)	2 mg capsule LY 3 mg capsule LY 6 mg capsule LY 8 mg capsule LY 12 mg capsule LY 24 mg capsule LY 36 mg capsule LY 45 mg capsule LY	Capsule of LY-placebo to match
Route of Administration	Oral	Oral

Abbreviation: LY = LY3502970.

6.1.1. Administration Details

While inpatient in the clinic, 1 capsule of the correct dosage of LY3502970 or a placebo capsule will be administered orally with approximately 200 mL of room temperature water in the morning of each dosing day, following an overnight fast of at least 8 hours. A standard breakfast may be served approximately 15 minutes after dosing, except when MMTTs or 0.5 and 1 hour postdose ECGs are scheduled. Participants will not be allowed to lie supine for 2 hours after dosing on days when PK and PD blood sampling is scheduled (see SoA in [Section 1.3](#)), unless clinically indicated or for study procedures.

When participants self-administer IP at home, they will be advised to take 1 capsule of the correct dosage of LY3502970 or a placebo capsule orally with approximately 200 mL of room temperature water before breakfast in the morning, but if they forget, it can be taken later that day.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a participant- and investigator-blinded study. To preserve the blinding of the study for LY3502970 and placebo, all study site personnel will be blinded to treatment allocation.

Using an interactive web response system (IWRS), all participants will be centrally assigned a participant number at screening and then randomized to study intervention predose on Day 1. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits summarized in SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician (CRP) for the participant to continue in the study.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the case report form (CRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by review of the participants' diaries by CRU staff during the site visits; this will be documented in the source documents and CRF. It is preferred that participants take their dose before breakfast in the morning, but if they forget, it can be taken later that day.

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 CRF.

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 study intervention administered at home by the participant via the participant's diary
- Information about the participant's adherence to the SoA
- Information about any other parameters the investigator considers necessary.

6.5. Dose Modification

6.5.1. Dose Escalation

Dose escalation is planned in both Parts A and B of the study. The dose escalation plan is illustrated in [Figure GZGB.1](#).

All available safety and tolerability data will be reviewed in order to make dose-escalation decisions. Safety data will be the primary criteria for the dose escalation. Safety parameters to be assessed will include all available data from AEs, ECGs, vital signs (BP and PR), body weight, hypoglycemic events, and laboratory tests. In addition, if available at the time of the dose escalation decision, PK and/or PD data may be used as supporting data for dose escalation, but such data are not required.

Part A

Following administration of single doses of LY3502970 to Cohorts 1a and 2a in Part A, the following reviews will be conducted:

- to review the safety data through Day 8 from Cohort 1a (single dose 2 mg LY3502970) prior to commencing dosing Cohort 2a (single dose 3 mg LY3502970)
- to review the safety data through Day 8 from Cohorts 1a and 2a prior to commencing administration of multiple daily doses of the corresponding dose level in Part B.

Decisions to escalate the dose in Part A and to commence multiple daily doses in Part B will not occur without prior discussion and agreement between the investigator and the Lilly CP.

Part B

In Part B, doses are planned to be escalated from a 2 mg starting dose through 3, 6, 8, 12, and 24 mg LY3502970 in Cohort 1, from a 2 or 3 mg starting dose through 6, 12, 24, 36, and 45 mg LY3502970 in Cohort 2, and from a 2 or 3 mg starting dose through 6 and 12 mg LY3502970 in Cohort 3.

In Cohorts 1a and 2a, dose escalation decisions throughout the 12-week treatment period will be made for individual participants based on all of that participant's available data, up to and including the day of the dose escalation (that is, predose assessments on the day of escalation may be considered) and will be at the discretion of the investigator. If, when a participant is at

the 24 or 36 mg dose level, the investigator decides not to escalate that participant to the planned next dose level, for any reason(s), then the participant may continue at their current dose level through to the last planned dose on Day 84. Participants who are at a dose level of ≤ 12 mg and are not recommended to escalate to the next dose level will be discontinued.

The decision to commence daily dosing in the following cohorts will be made after the review of the following safety data:

- the decision to commence with multiple daily dosing with 2 mg in Cohort 1a will be made based on all available safety data from the single dose of 2 mg LY3502970 administered in Cohort 1a in Part A.
- the decision to commence dosing with 2 mg in Cohorts 1b, 2b, and 3b will be made based on review of all available safety data at 2 mg through Day 8 in Cohort 1a.
- the decision to commence with multiple daily dosing with 3 mg in Cohort 2a will be made based on all available safety data from the single dose of 3 mg LY3502970 administered in Cohort 2a in Part A.
- the decision to commence with 3 mg in Cohort 3a will be made based on review of all available safety data at 3 mg through Day 8 in Cohort 2a.

The decision to escalate dose levels in Cohorts 1b and 2b will be made after the review of safety data of the following corresponding dose levels in the preceding staggered group in the cohort (Figure GZGB.1).

- the decision to escalate to the 3-, 6-, 8-, 12-, and 24-mg dose levels in Cohort 1b will be made based on review of all available safety data, through 7 days postdose, for the corresponding dose level in Cohort 1a.
- the decision to escalate to the 36- and 45-mg dose levels in Cohort 2b will be made based on review of all available safety data, through 7 days postdose, for the corresponding dose level in Cohort 2a.

Decisions to commence dosing to Cohorts 1b, 2b, and 3b, and to escalate corresponding doses in Cohorts 1b and 2b, will not occur without prior discussion and agreement between the investigator and the Lilly CP.

6.5.2. Dose Stopping Criteria

If any of the following scenarios occur, the study treatment may be discontinued or the dose level decreased if participants are at the 36- or 45-mg dose level, in which case participants may continue with a daily dose of ≥ 24 mg. If in the group safety reviews for Cohort 1a or 2a, the following scenarios occur, then escalation to the corresponding dose level in Cohorts 1b, 2b, and/or 3 will be stopped.

- One treatment-emergent SAE considered related to LY3502970 treatment (unless due to anticipated pharmacology of LY3502970, for example, hypoglycemia).
- Two or more clinically significant events (CSEs; see Section 10.8) considered related to LY3502970 treatment, defined as moderate-to-severe symptoms, clinical signs, and/or clinical laboratory findings that could cause harm to health and would preclude further dosing of a participant who experiences this effect. Clinically significant events will be

determined by the investigator or suitable designee and may include findings that do not fulfill the criteria for SAEs.

- $\geq 40\%$ of participants in a dose level experience a symptomatic hypoglycemic episode with plasma glucose values < 3.0 mmol/L (54 mg/dL) and these events are deemed to be related to LY3502970 administration.
- Two or more participants develop persistent (> 1 week) symptoms suggestive of acute pancreatitis. Refer to algorithm for the monitoring of asymptomatic hyperenzymemia in Section 8.2.7.2.

Participants experiencing CSEs thought to be related to the study intervention will be encouraged to complete a 15-day follow-up period before study discharge.

6.5.3. Dose Reductions

No dose reductions are permitted for doses up to and including 24 mg LY3502970 QD.

A decrease in dose to 24 or 36 mg is permitted at any time if an individual participant is unable to tolerate the 36- or 45-mg dose levels. If a dose is reduced, the participant will continue the decreased dose level through to the last planned dosing on Day 84. Participants who are unable to tolerate study intervention after a decrease in dose level may discontinue study intervention at the discretion of the investigator (Section 7.1). In order to maintain blinding to study intervention, the site should contact the IWRS help desk for next steps.

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

Not applicable.

6.7. Treatment of Overdose

For this study, any dose of LY3502970 greater than the dose assigned through randomization within a 24-hour time period will be considered an overdose.

The treatment for overdose is supportive care; refer to the Investigator's Brochure.

In the event of an overdose, the investigator should:

- Contact the CP/CRP immediately.
- Evaluate the participant to determine, in consultation with the CP/CRP, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.8. Concomitant Therapy

Any medication or vaccine (including 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

In addition, any OAM discontinued within 3 months prior to signing the ICF must be recorded as prior therapy.

The CP/CRP should be contacted if there are any questions regarding concomitant or prior therapy.

Participants treated with stable (at least 3 months prior to screening) monotherapies of OAMs must discontinue this treatment for at least 28 days prior to dosing.

Participants who enter the study on diet and exercise alone will not be allowed to initiate antihyperglycemic therapy after study entry unless criteria for rescue therapy are met.

Doses of antihypertensive and lipid-lowering therapies must be stable for 30 days prior to screening. Doses of antihypertensive and lipid-lowering agents should not be changed during this study unless necessary to protect participant's safety on an emergency basis (for example, hypertensive crisis).

Doses of other prescription medications for treatment of concurrent medical conditions should remain constant during the study whenever possible. The sponsor should be contacted to clarify if an individual medication is allowed in the study. If the need for additional concomitant medication arises, the participant may be continued in the study on study medication if, in the investigator's opinion, the addition of the new medication does not pose a safety risk. If an additional concomitant medication is started, the sponsor should be informed as soon as possible.

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 (at doses of up to 3 grams/day), cough suppressants, antihistamines, vitamin/mineral supplements, antibiotics, and topical ointments may be used on an as-needed basis without notifying the sponsor and are not restricted by the stable dosing requirements listed earlier.

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

Specifically excluded concomitant medications include the following:

- chronic use of medications that directly reduce GI motility including, but not limited to, anticholinergics, antiemetics, and opiates (for example, metoclopramide, promethazine, dicyclomine, and morphine)
- chronic use of medications that directly promote GI motility (for example, bethanechol and cisapride)
- prescription or over-the-counter medications to promote weight loss
- chronic (lasting >2 weeks) systemic glucocorticoid therapy (excluding topical, intra-articular, and inhaled preparations) in the past year, or have received any glucocorticoid therapy within 4 weeks before screening
- central nervous system stimulants (for example, Ritalin-SR)
- hormone therapy (for example, estrogen and progesterone)

- CCI
- glucose-lowering medications other than metformin, DPP-4 inhibitors, or SGLT2 inhibitors within 3 months prior to screening
- any drug, other than those provided in this study, that has not received regulatory approval.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

Participants discontinuing from study intervention prematurely for any reason should complete AE and other follow-up procedures per the SoA (Section 1.3).

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study. See the SoA 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.

Discontinuation of IP 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
- if a clinically significant finding is identified in ECG parameters (including, but not limited to, QTc >500 msec or an increase from baseline of ≥ 60 msec, from at least 2 consecutive readings), the participant will be discontinued. For other clinically significant findings, 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 AE.

7.1.1. Liver Chemistry Stopping Criteria

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

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

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

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in 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.

7.1.3. Intolerable Gastrointestinal Events

In the presence of persistent GI events, participants who are unable to tolerate study intervention, even after a decrease in dose level (Section 6.5.3) for ≥ 2 weeks (have persistent vomiting or moderate-to-severe nausea), may be discontinued from using the study intervention at the discretion of the investigator.

7.1.4. Persistent Hyperglycemia/Hypoglycemia

Discontinuation of the study intervention should be considered by the investigator for participants with any persistent severe hyperglycemia, defined as a persistent fasting plasma glucose level above 240 mg/dL, without an identified cause (for example, intercurrent illness).

Discontinuation of the IP should be considered by the investigator for participants with severe hypoglycemia (Level 3 according to Section 8.2.7.4) 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 enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

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 from both the study intervention and the study at that time.

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

7.3. Lost to Follow-Up

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

8. Study Assessments and Procedures

Study procedures and their timing (including tolerance limits for timing) are summarized in the SoA (Section 1.3).

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF. Failure or being late (that is, outside stipulated time allowances) to perform procedures or obtain samples due to legitimate clinical issues (for example, equipment technical problems, venous access difficulty, or participant defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations, but the CRU will still be required to notify the sponsor in writing via a file note.

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.

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.

8.1. Efficacy Assessments

The exploratory efficacy measure is the absolute change in HbA1c from baseline to Week 12.

The planned time points for HbA1c assessments are provided in the SoA (Section 1.3).

8.2. Safety Assessments

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

8.2.1. Physical Examinations/Medical Assessments

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded.

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

8.2.2. Vital Signs

For each participant, vital sign measurements should be done before collection of blood samples according to the SoA (Section 1.3).

Blood pressure and PR should be measured twice after at least 5 minutes in the sitting position.

If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 2 minutes.

Additional vital signs may be measured during each study period if warranted.

Body temperature will be measured according to the SoA (Section 1.3).

8.2.3. Electrocardiograms

Electrocardiograms must be recorded before collecting any blood for safety or pharmacokinetic/pharmacodynamic (PK/PD) tests. Participants must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times when deemed clinically necessary.

Electrocardiograms will be interpreted by 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. This interpretation is to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.

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

Single ECGs

For each participant, a single 12-lead ECG will be collected locally at screening, during the treatment period, and at the follow-up (or ET) visits as shown in the SoA (Section 1.3). All single ECGs recorded must be reviewed by the investigator or qualified designee and should be stored at the investigational site. Single ECGs will not be analyzed.

Triplicate ECGs

At scheduled times in the study (Section 1.3), consecutive replicate ECGs will be obtained in triplicate at approximately 1-minute intervals. Collection of more ECG replicates than expected at a particular time point will be permitted to ensure high-quality records.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the participant for symptoms (for example, 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.

All triplicate digital ECGs (scheduled and unscheduled) will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details), then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

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

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and 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 2 weeks 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, and standard collection requirements.

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

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

8.2.5. Pregnancy Testing

Pregnancy testing will be conducted for female participants at scheduled times shown in the SoA (Section 1.3). See Appendix 2 (Section 10.2) for details.

8.2.6. Self-Monitored Glucose

Participants will receive training on self-monitored plasma glucose (SMPG) and paper diary completion required during the study. When outpatient, participants should self-monitor and record glucose concentrations if they experience any symptoms of hypoglycemia. The SMPG device used in this study tests blood but displays the equivalent plasma glucose value.

8.2.7. Safety Monitoring

8.2.7.1. Nausea, Vomiting, and Diarrhea

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 times), and investigator's opinion of relatedness to study treatment and protocol procedure will be captured.

8.2.7.2. Pancreatic Safety (Elevated Lipase or Amylase Levels)

Glucagon-like peptide 1 agonists have been associated with a possible risk of acute pancreatitis. Acute pancreatitis is an AE of interest in this study of LY3502970.

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). Further diagnostic assessments (as per the algorithm for the monitoring of pancreatic events in Appendix 6 [Section 10.6]) will be recommended whenever lipase and/or amylase are confirmed to be $\geq 3 \times$ ULN at any visit posttreatment, even if the participant is asymptomatic, and if pancreatitis is suspected, the case will be further defined during detailed review.

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

Diagnosis of acute pancreatitis

The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 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 $\geq 3 \times$ 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 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 IP.

Asymptomatic elevation of serum amylase and/or lipase

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).

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

8.2.7.3. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 7, Section 10.7), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

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

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and 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 <1.5× ULN	ALT or AST ≥3× ULN with hepatic signs/symptoms*, or ALT or AST ≥5× ULN
ALP <1.5× ULN	ALP ≥3× ULN
TBL <1.5× ULN	TBL ≥2× ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5× ULN	ALT or AST ≥2× baseline with hepatic signs/symptoms*, or ALT or AST ≥3× baseline
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL ≥1.5× ULN	TBL ≥2× baseline (except for participants with Gilbert's syndrome)

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

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

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

1. Elevation of serum ALT to ≥5× ULN on 2 or more consecutive blood tests (if baseline ALT <1.5× ULN)
 - In participants with baseline ALT ≥1.5× ULN, the threshold is ALT ≥3× baseline on 2 or more consecutive tests
2. Elevated TBL to ≥2× ULN (if baseline TBL <1.5× ULN) (except for cases of known Gilbert's syndrome)
 - In participants with baseline TBL ≥1.5× ULN, the threshold should be TBL ≥2× baseline

3. Elevation of serum ALP to $\geq 2 \times$ ULN on 2 or more consecutive blood tests (if baseline ALP $< 1.5 \times$ ULN)
 - In participants with baseline ALP $\geq 1.5 \times$ ULN, the threshold is ALP $\geq 2 \times$ baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study intervention due to a hepatic event.

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

8.2.7.4. Hypoglycemia Reporting

Participants or site personnel will collect information on episodes of hypoglycemia at each study visit according to the SoA (Section 1.3).

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

Investigators should use the following classification of hypoglycemia (plasma glucose equivalent values):

Level 1 hypoglycemia:

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

Level 2 hypoglycemia:

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

Level 3 hypoglycemia:

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

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.

- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

Nocturnal hypoglycemia:

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

8.2.7.5. Persistent Hyperglycemia

Add-on glycemic rescue therapy will be allowed for participants who experience persistent hyperglycemia as defined fasting glucose values >270 mg/dL (>15 mmol/L) by clinical laboratory test over at least a consecutive 2-week period anytime during the treatment period.

Investigators should first confirm that the participant is fully compliant with the planned dosing regimen and that the participant does not have an acute condition to increase fasting glucose.

Investigator should follow the guidance for treatment of diabetes (Araki et al. 2020).

Antihyperglycemic medications, including insulin, will be allowed as the rescue intervention. In this case, GLP-1 receptor agonists and DPP-4 inhibitors are not allowed as rescue therapies.

Participants may continue study treatment after starting rescue therapy at a discretion of investigator.

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

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

- AEs
- SAEs
- Product complaints (PCs)

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

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

Care will be taken not to introduce bias when detecting events. Open-ended and 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 8.3.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the 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	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Signing of the ICF	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – after participant’s study participation has ended and the investigator becomes aware	After participant’s study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female partners of male participants	After the start of study intervention	35 days after the last dose.	Within 24 hours (see Section 8.3.2)	SAE paper form	SAE paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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	

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LY3502970.

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 gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

8.3.3. Adverse Events of Special Interest

Adverse events of special interest for this program include:

- cardiovascular events
- GI events
- hypoglycemia

If any AE of special interest is reported, sites will be prompted to collect additional details/data.

8.4. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of LY3502970. Up to 2 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded, as well as the date and time of each LY3502970 dose.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.4.1. Bioanalysis

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

Concentrations of LY3502970 will be assayed using a validated liquid chromatography mass spectrometry method. Analyses of samples collected from participants who received placebo are not planned.

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

8.5. Pharmacodynamics

8.5.1. Pharmacodynamic Markers

Blood samples will be collected to determine changes from baseline in HbA1c and fasting glucose. In addition, changes from baseline in body weight will be evaluated as a secondary PD parameter.

The samples will be identified by the participant number (coded) and stored for up to a maximum of 1 year after the last participant visit for the study at a facility selected by the sponsor.

8.5.1.1. Daily Glucose Profiles

Blood samples for the daily glucose profiles will be drawn for assessment of plasma glucose at times indicated in the SoA (Section 1.3). Blood samples in the morning and evening meals will be collected in MMTT (Section 8.5.2.2). Other blood samples in midday meal will be collected at 0 (premeal), 1, and 2 hours after the start of meal, as specified in the SoA (Section 1.3).

8.5.1.2. Fasting Glucose and HbA1c

Blood samples will be collected as indicated in the SoA (Section 1.3) for the evaluation of fasting plasma glucose and HbA1c. Participants must be fasted for at least 8 hours prior to collection of these samples.

8.5.1.3. Body Weight

Body weight will be measured as indicated in the SoA (Section 1.3). Wherever possible, the same scale will be used for all weight measurements throughout the study and the scale will not be moved or re-calibrated.

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 screening, lead-in, and treatment period, weight will be measured twice on each scheduled occasion, with the participant stepping off the scale between measurements. The average of the 2 weight measurements will be recorded in the source document and the eCRF.

8.5.2. Exploratory Assessments

Exploratory PD may include, but are not limited to, fasting and postprandial:

- insulin
- C-peptide
- glucagon
- lipid panel (triglycerides, total cholesterol, and LDL, VLDL, and HDL cholesterol)

Plasma concentrations of glucagon, insulin, and C-peptide will be assayed using validated analytical methods. Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor. The samples will be identified by the participant number (coded) and stored for up to a maximum of 1 year after the last participant visit for the study at a facility selected by the sponsor.

For more details on timing of assessments, see the SoA (Section 1.3).

8.5.2.1. Meal Intake and Appetite Analysis

To explore the effects of LY3502970 on food intake and appetite sensation, participants will be provided standardized mixed meals for morning, midday, and evening at 2, 6, and 10 hours after study intervention administration, according to the SoA (Section 1.3).

The meal and individual nutrition intake will be recorded in the source document and eCRF. After completion of each meal, the individual nutrient (protein, fat, and carbohydrate) and total caloric intake will be evaluated by the site personnel by weighing the leftover meal or visual inspection and will be recorded in the source document and the eCRF.

The standardized mixed meals shall be defined by:

- total energy of approximately 600 kcal
- macronutrient contents:
 1. approximately 20% protein,
 2. approximately 25% fat,
 3. approximately 55% carbohydrate.

Participants will be asked to rate their subjective appetite sensations using a 100-mm visual analog scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption in the fasted state while inpatient (Section 1.3). A paper-based tool will be used to obtain the VAS ratings.

The VAS is a validated tool to assess appetite sensation parameters (Flint et al. 2000). The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually “extremely” and “not at all.” Participants are required to rate their subjective sensations on four 100-mm scales combined with questions similar to the following:

4. “How hungry do you feel right now?”
5. “How satisfied do you feel right now?”
6. “How full do you feel right now?”
7. “How much food do you think you could eat right now?”

Overall appetite score is calculated as the average of the 4 individual scores: (satiety + fullness + [100-prospective food consumption] + [100-hunger])/4 (van Can et al. 2014). The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

8.5.2.2. Mixed Meal Tolerance Test

In Part B, all participants are required to consume a mixed meal in the morning and evening on the days specified in the SoA (Section 1.3). Participants shall maintain their regular carbohydrate intake 3 days before the scheduled MMTT, and on the evening before the MMTT. Participants should be fasted (except for water) for at least 10 hours before start of morning MMTT. The participants should start to consume the morning mixed meal 2 hours after the study intervention administration (for Day -1 this will be based on the planned study intervention administration time) and complete the meal within approximately 15 minutes. The midday meal will be provided approximately 6 hours after study intervention administration (for Day -1 this will be based on the planned study intervention administration time). Participants should start to consume evening mixed meal 10 hours after the study intervention (for Day -1 this will be based on the planned study intervention administration time) administration and complete the meal within approximately 15 minutes. Participants will not be allowed to consume any snacks or drinks (except for water) on MMTT assessment days. If a participant develops symptoms of hypoglycemia, the bedside blood glucose concentration may be measured and the participant will be treated per investigator discretion.

The standardized test meal is described in the Meal Intake and Appetite Analysis section (Section 8.5.2.1).

Fasting and post-meal glucose, insulin, C-peptide, and glucagon will be measured to assess effects of LY3502970 on glycemic control, insulin secretion, and insulin sensitivity. Blood samples will be drawn for assessment of glucose, insulin, C-peptide, and glucagon at times indicated in the SoA (Section 1.3). Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

8.5.2.3. Waist Circumference

Waist circumference should be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest. The participant should stand with feet close together, arms at the side and body weight evenly distributed, and should wear little clothing. The participant should be relaxed, and the measurements should be taken at the end of a normal expiration. During the screening, treatment, and follow-up periods, waist circumference will be measured twice on each scheduled occasion. The average of the 2 measurements will be recorded in the source document and the eCRF.

8.6. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3), where local regulations allow.

See Appendix 5 (Section 10.5) for information regarding genetic research.

8.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Serum and plasma samples for nonpharmacogenetic biomarker research will be collected at the times specified in the SoA (Section 1.3), where local regulations allow.

Samples may be used for research on the drug target, disease process, variable response to LY3502970, pathways associated with diabetes mellitus, and related clinical traits or complications, including nonalcoholic steatohepatitis or obesity, mechanism of action of LY3502970, and/or research method, or for validating diagnostic tools or assay(s) related to diabetes mellitus.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and/or Ethical Review Boards (ERBs)/Institutional Review Boards (IRBs) impose shorter time limits, at a facility selected by Lilly or its designee. This retention period 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 is commercially available.

8.8. Health Economics

Health economics are not evaluated in this study.

9. Statistical Considerations

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

9.1. Statistical Hypotheses

The primary objective is to investigate the safety and tolerability of LY3502970 versus placebo. There are no formal statistical hypotheses confirmed for this study.

9.2. Analyses Sets

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF.
Enrolled	All participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis	All enrolled participants who received at least 1 dose of LY3502970 and have evaluable PK data.
Pharmacodynamic Analysis	All enrolled participants who received at least 1 dose of study intervention and have evaluable PD data.

Participants may be excluded from the PK and PD summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

9.3. Statistical Analyses

9.3.1. General Considerations

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

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

9.3.2. Primary Endpoint: Safety

9.3.2.1. Clinical Evaluation of Safety

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

The incidence of AEs for each treatment in each part will be presented by severity and by association with IP as perceived by the investigator. Adverse events reported to occur prior to enrollment 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 IP-related SAEs will be reported.

9.3.2.2. Statistical Evaluation of Safety

In addition to AEs, safety parameters that will be assessed include laboratory tests, vital signs, body weight, hypoglycemic events, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analyses may be performed if warranted based upon review of the data.

Clinical laboratory measurements will be summarized regarding 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 regarding observed values and change from baseline (Day 1, predose) values by treatment at each time point using descriptive statistics. For change from baseline values, a mixed-model repeated-measure model with treatment, time point (of measurement), and treatment-by-time point interaction as fixed effects, participant as random effect, and baseline as covariate will be used to determine the effects of LY3502970. Least squares means as well as 90% confidence intervals (CIs) will be reported.

Electrocardiogram parameters will be summarized, including the PR, QT, RR, and QTcF intervals, QRS duration, and HR. A plasma LY3502970 concentration-ECG parameter analysis will be performed according to International Council for Harmonisation (ICH)-E14 (the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs) guidelines. Additional analysis may be performed if warranted upon review of the data.

9.3.3. Secondary Endpoint: Pharmacokinetic

9.3.3.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3502970 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max} , area under the concentration versus time curve (AUC), and t_{max} of LY3502970. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported. If deemed necessary, additional model-based analysis may be performed. Full details of the PK parameters to be calculated will be provided in the SAP.

9.3.3.2. Pharmacokinetic Statistical Inference

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

Pharmacokinetic dose proportionality will be evaluated. Log-transformed $C_{\max}$ and AUC of LY3502970 will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% CIs. The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. A subinterval within the highest and lowest doses may also be considered for assessment of dose proportionality using the same approach. Additional details will be provided in the SAP.

The parameter $t_{\max}$ of LY3502970 will be analyzed using a nonparametric method.

9.3.4. Pharmacodynamic Analysis

9.3.4.1. Pharmacodynamic Parameter Estimation

Inferences will be sought regarding the effect of LY3502970 on the PD endpoints. Such effects will be explored over different doses of LY3502970 and at applicable time points as per the SoA (Section 1.3).

9.3.4.2. Pharmacodynamic Statistical Inference

Pharmacodynamic parameters may be transformed before statistical analyses, if deemed necessary. Actual values, as well as change from baseline, in each parameter will be analyzed using mixed effects models to evaluate treatment effects, as well as treatment comparisons. The model will include treatment, time point, and treatment-by-time point interaction as fixed effects and participant as a random effect. Baseline values, as well as other influencing variables, may be used as covariates. Differences between each LY3502970-treated group and placebo group will be estimated. Participants who received placebo will be pooled across all cohorts. Least squares means and 90% CIs will be reported.

All PD parameters, including the baseline-corrected parameters (actual parameter value minus baseline value), will be summarized and tabulated by treatment group and time point. Summary statistics will be provided.

The individual observed and mean time profile of the postdose PD parameters will be plotted by treatment group.

9.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/PD modeling may be evaluated to characterize the exposure-response relationships between LY3502970 concentrations and various PD endpoints, provided data are sufficient.

The relationship between LY3502970 doses and/or concentrations and efficacy (fasting glucose, HbA1c, weight) measures and tolerability (such as nausea, vomiting) may be assessed via PK/PD analyses or graphical explorations. Endpoints may include, but are not necessarily limited to, those listed earlier.

9.3.6. Other Analyses

9.3.6.1. Appetite Analysis

The study assessment will be the overall appetite score as measured according to the 0- to 100-mm VAS. Descriptive statistics will be used to summarize the baseline, postdose time points, and absolute change from baseline in overall appetite score by treatment group. Details will be provided in the SAP.

9.4. Interim Analysis

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

9.5. Sample Size Determination

Up to 65 participants may be enrolled to study intervention to ensure approximately 15 evaluable participants in each cohort (1, 2, and 3; Groups a and b combined) complete Part B of the study. Assuming that the dropout rate is higher at higher dose cohorts due to CCI [REDACTED], approximately 18, 20, and 22 participants will be randomized.

CCI [REDACTED]

Participants who are randomized but not administered treatment may be replaced to ensure that enough participants may complete the study. Participants in Cohorts 1a and 2a who discontinue prior to start of dosing in Part B may be replaced after consultation with the investigator and sponsor. This replacement participant may not repeat Part A and will go through the same treatment assignment from Part B as the discontinued participant. Participants who discontinue early during Part B will not be replaced.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

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

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local

regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

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

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

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

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

10.1.3. Data Protection

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

The participant must be informed that 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.

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

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

Reports

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

Data

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

10.1.5. Data Quality Assurance

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

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

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

Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.

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

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

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

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

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

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

Data Capture System

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

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

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

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

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

10.1.6. Source Documents

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

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

Definition of what constitutes source data can be found in Section [10.1.5](#).

10.1.7. Study and Site Start and Closure**First Act of Recruitment**

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

Study or Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.8. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the local laboratory at screening and central laboratory at all other time points, unless indicated otherwise.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

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

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

Investigators must document their review of the laboratory safety results.

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

Clinical Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Magnesium
Mean cell volume	Bicarbonate ^c
Mean cell hemoglobin	Chloride
Mean cell hemoglobin concentration	Calcium
Leukocytes (WBC)	Phosphorus
Differential WBC [Absolute counts and/or %] of:	Glucose (fasting)
Neutrophils	Blood urea nitrogen
Lymphocytes	Total protein
Monocytes	Albumin
Eosinophils	Total bilirubin (total, direct, and indirect)
Basophils	Alkaline phosphatase
Platelets	Alanine aminotransferase
	Aspartate aminotransferase
	Gamma-glutamyl transferase
	Creatinine
	Lipase (fasting)
	Amylase
	Triglyceride
	Total cholesterol
Urinalysis	Other
Specific gravity	HbA1c ^d
pH	Calcitonin ^{e,f}
Protein	Syphilis test ^{e,f}
Glucose	Serum ^{e,f} /urine pregnancy test ^e
Ketones	Follicle-stimulating hormone ^{e,f}
Bilirubin	Thyroid-stimulating hormone ^{e,f}
Urobilinogen	Ethanol test and urine drug screen ^e
Blood	
Leukocytes ^a	
Microscopy ^b	
Serology^{e,f}	
Hepatitis B surface antigen	
Hepatitis B core antibody	
Hepatitis C antibody	
HIV	

Abbreviations: HbA1c = glycated hemoglobin; HIV = human immunodeficiency virus; RBC = red blood cell; WBC = white blood cell.

^a Qualitative test (+/-) will be performed at screening.

^b If clinically indicated, per the investigator's discretion.

^c Not performed at screening.

^d Analyzed by the central laboratory.

^e Analyzed by the local laboratory.

^f Performed at screening only.

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

Please refer to SoA (Section [1.3](#)) for full list of analytes and assessment time points during the treatment period, early termination, and follow-up.

10.2.1. Blood Sampling Summary

This table summarizes the maximum number of venipunctures and blood volumes for all blood sampling during the study (Parts A and B inclusive).

Protocol J2A-JE-GZGB Sampling Summary

Purpose	Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Total Volume (mL)
Screening tests ^a			
• Clinical chemistry, hematology	16	1	16
• Calcitonin, thyroid-stimulating hormone	6	1	6
• Serology/syphilis	8.5	1	8.5
• Serum pregnancy test, follicle-stimulating hormone (female)	3	1	3
• HbA1c	2	1	2
Clinical laboratory tests ^a			
▪ Baseline (central laboratory)	10.5	2	21
▪ Study period and follow-up	10.5	19	199.5
Pharmacokinetics			
▪ Scheduled samples (Section 1.3)	2	44	88
▪ Two additional samples (Section 8.4)	2	2	4
Fasting plasma glucose	2	11	22
Daily glucose profile			
▪ Baseline	2	1 profile x 3 samples = 3	6
▪ Study period	2	2 profiles x 3 samples = 6	12
HbA1c	2	4	8
MMTT (plasma glucose, insulin, C-peptide, and glucagon)			
▪ Baseline	5	1 test x 10 samples = 10	50
▪ Study period	5	2 tests x 10 samples = 20	100
PD biomarkers (insulin, C-peptide, and glucagon)	4.5	5	22.5
Lipid panel ^b	2.5	5	12.5
Pharmacogenetics (stored)	10	1	10
Nonpharmacogenetic sampling (storage)	6.5	5	32.5
Total			623.5

Abbreviations: HbA1c = glycated hemoglobin; MMTT = mixed meal tolerance test; PD = pharmacodynamics.

^a Additional samples may be drawn if needed for safety purposes. Because the screening tests, including clinical laboratory tests (chemistry and hematology) at screening, will be performed at the local laboratories of each site, the volumes are an estimate and will vary depending on the local laboratory's testing requirements.

^b Lipid panel includes triglycerides, total cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

Note: If a participant is withdrawn from the study and has blood draws performed at an early termination visit, it is possible that they will have more blood drawn than shown in this table, depending on the timing of withdrawal.

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

10.3.1. Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. - The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. - Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

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

10.3.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical

events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 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 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 Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

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

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

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 the SAE Report.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

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

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman of Childbearing Potential

Females are considered a woman of childbearing potential if:

- they have had at least 1 cycle of menses, or
- they have Tanner 4 breast development.

Any amount of spotting should be considered menarche.

Woman not of Childbearing Potential

Females are considered women not of childbearing potential if:

- they have a congenital anomaly such as Mullerian agenesis,
- they are infertile due to surgical sterilization, or
- they are post-menopausal.

Examples of surgical sterilization include: hysterectomy, bilateral oophorectomy, tubal ligation.

The post-menopausal state is defined as:

1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or
2. A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND
With a follicle-stimulating hormone >40 mIU/mL; or
3. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or
4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

* Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance*Females*

All females must have a negative serum pregnancy test result at screening followed by a negative urine result within 24 hours prior to treatment exposure.

Women not of childbearing potential are not required to use contraception.

Males

The table below describes contraception guidance for men.

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for 3 months after the last dose of IP
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study, and for 3 months after the last dose of IP
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

Examples of unacceptable methods of contraception can be found below.

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

DNA samples may be used for research related to LY3502970 or T2DM, diabetic complications, and related diseases, including obesity, and nonalcoholic fatty liver disease. 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 or analysis of the entire 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 or related classes of medications to understand study disease or related conditions.

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

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

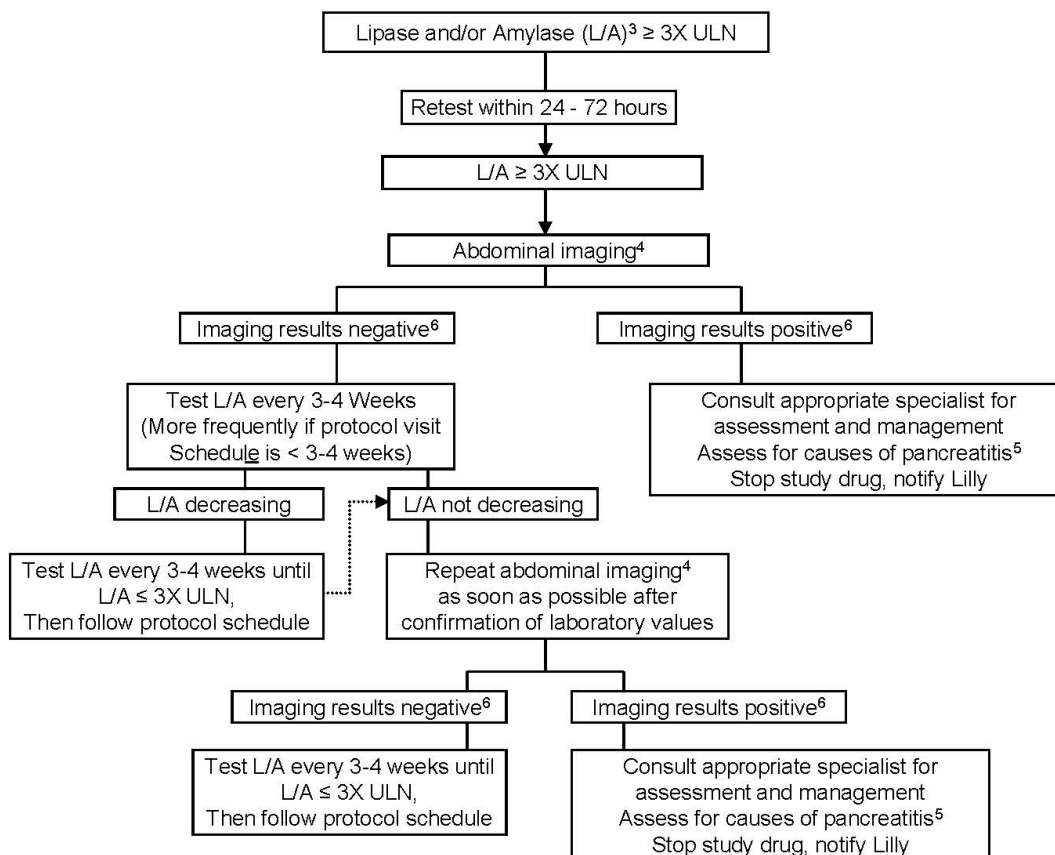
The samples will be retained while research on LY3502970 or T2DM continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Pancreatic Monitoring

See Section 8.2.7.2 for guidance.

Pancreatic Enzymes: Safety Monitoring Algorithm for Subjects/Patients without Symptoms of Pancreatitis^{1,2}

Follow this algorithm when the value(s) for serum lipase and/or amylase are $\geq 3X$ ULN.



1. Symptomatic – related primarily to abdominal pain consistent with pancreatitis; however, severe nausea, vomiting and other symptoms may be considered by the investigator as symptomatic as well.

2. If, at any time, in the opinion of the investigator, patient/subject has symptoms of acute pancreatitis irrespective of L/A results:

- (a) Consult appropriate specialist for assessment and management
- (b) Assess for causes of pancreatitis
- (c) Stop study drug
- (d) Notify Lilly

3. L/A = Lipase and/or amylase. Either or both enzymes can be measured and either or both can be used to meet the algorithm criteria.

4. Abdominal imaging is most valuable when performed at the time of elevated enzyme values. If in the opinion of the radiologist or investigator, it is safe for the patient/subject to receive contrast, an enhanced abdominal CT is preferred. MRI is also an acceptable imaging modality.

5. As minimum, test hepatic analytes, triglycerides, and calcium, and record all concomitant medications

6. Imaging results positive or negative for signs of acute pancreatitis

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

10.7. Appendix 7: Liver Safety: Suggested Actions and Follow-Up Assessments

Hepatic Evaluation Testing

See Section 8.2.7.3 for guidance on appropriate test selection.

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

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

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

Hematology	Clinical Chemistry
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	Other Chemistry
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	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)
Hepatitis 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
Hepatitis 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.

10.8. Appendix 8: Clinically Significant Adverse Events

The table below summarizes the type and severity of symptoms, clinical signs, and clinical laboratory findings that may qualify as a clinically significant event. These are intended as a guideline to the investigator(s), not as a set of absolute criteria. The underlying principle is to define a level of moderate-to-severe abnormality in safety findings that could cause harm to health and would preclude further dosing of a participant who experiences this effect. Safety parameters not included in this table may be interpreted in a similar fashion according to investigator judgment.

Parameter	CSE level
Symptoms	
Severe hypoglycemia	One episode of severe hypoglycemia defined as low blood glucose with mental status impairment severe enough to require third-party assistance
Dizziness/hypotension	Orthostatic CNS symptoms (dizziness, confusion) that are not vasovagal responses to provocative stimuli (for example, phlebotomy, nausea, bowel or bladder function), and are associated with orthostatic SBP decrease >20 mm Hg or DBP decrease >10 mm Hg or heart rate >105 bpm, for >3 hours
Sensorium	Disorientation to time, place, or identity. Any abnormal ideation
Mood	Feelings of grief or loss that interfere with study procedures or activities of daily living. Any suicidal ideation
Headache/pain	Any focal or generalized head pain that disrupts normal activities and is not responsive to medical therapies
Pruritus	Generalized itching over >24 hours unresponsive to oral antihistamine
Hypersensitivity	Clinically significant systemic-hypersensitivity reaction occurs following administration of the IMP (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) that requires parenteral medication, does not respond to symptomatic medication, or results in clinical sequelae or an anaphylactic reaction
Signs	
Systolic blood pressure	>30 mm Hg increase from baseline values and an absolute level >190 mm Hg
Diastolic blood pressure	>20 mm Hg increase from baseline values and an absolute level >115 mm Hg
Heart rate	Resting (sitting or recumbent) HR >120 bpm
Cardiac rhythm	Any rhythm other than sinus rhythm, mild sinus bradycardia, or mild sinus tachycardia
QTc	>500 msec or >60 msec increase from baseline value
QRS morphology	Significant prolongation of QRS interval or new onset of bundle branch block
Tremor	Readily visible tremor during normal movement deemed unrelated to hypoglycemia
Reflexes	New onset of clonic reflexes
Clinical Laboratory	(confirmed by repeat measurements within 48 hours)
Hemoglobin	Absolute value <10 g/dL and >2 g/dL reduction from baseline
Neutropenia	Absolute neutrophils <1,500/ μ L and >1,000 μ L decrease from baseline
Lymphopenia	Absolute lymphocyte count <800/ μ L and >500/ μ L decrease from baseline
Platelet count	<75,000/ μ L and >50,000/ μ L decrease from baseline
Creatinine	>2 mg/dL and >0.5 mg/dL increase from baseline value
Urea	>8 mmol/L and >3 mmol/L increase from baseline values
Alanine aminotransferase	>5-fold above laboratory reference upper limit value
Aspartate aminotransferase	>5-fold above laboratory reference upper limit value
Bilirubin (total)	>1.5-fold above laboratory reference upper limit value
Potassium	<2.5 or >5.5 mEq/L and >0.5 mEq/L change from baseline value
Sodium	<130 or >150 mEq/L and >10 mEq/L change from baseline value

Abbreviations: bpm = beats per minute; CNS = central nervous system; CSE = clinically significant effect; DBP = diastolic blood pressure; HR = heart rate; IMP = investigative medicinal product; QRS = 3 graphical deflections on a typical electrocardiogram; corresponds to the depolarization of the right and left ventricles of the human heart; QTc = corrected QT interval; SBP = systolic blood pressure.

10.9. Appendix 9: Abbreviations

Term	Definition
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CCI	
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.
BP	blood pressure
C _{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CP	clinical pharmacologist
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CSE	clinically significant event
CT	computed tomography
CCI	
DPP-4	dipeptidyl peptidase-4
ECG	Electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.

enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board
ET	early termination
GCP	good clinical practice
GI	gastrointestinal



HbA1c	glycated hemoglobin
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IP	investigational product
IRB	Institutional Review Board
IWRS	interactive web response system
MAD	multiple-ascending dose
MMTT	mixed meal tolerance test
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse-effect level
OAM	oral antidiabetic medication
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
PC	product complaint

CCI

PK/PD	pharmacokinetics/pharmacodynamics
PR	pulse rate
PT-INR	prothrombin time-International Normalized Ratio
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SGLT2	sodium-glucose co-transporter-2
SMPG	self-monitored plasma glucose
SoA	Schedule of Activities
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VAS	visual analog scale

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