Protocol Amendment J2A-JE-GZPE (b)

A Phase 3, Long-term Safety Study of LY3502970 in Adult Participants with Type 2 Diabetes and Inadequate Glycemic Control with Diet and Exercise Alone or in Combination with Oral Antihyperglycemic Medications (ACHIEVE-J)

NCT06010004

Approval Date: 11-Jul-2024

Title Page

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Protocol Title:

A Phase 3, Long-term Safety Study of LY3502970 in Adult Participants with Type 2 Diabetes and Inadequate Glycemic Control with Diet and Exercise Alone or in Combination with Oral Antihyperglycemic Medications (ACHIEVE-J)

Protocol Number: J2A-JE-GZPE

Amendment Number: b

Compound: LY3502970

Brief Title: A Long-term Safety Study of LY3502970 in Participants with Type 2 Diabetes

Study Phase: 3

Acronym: ACHIEVE-J

Sponsor Name: Eli Lilly Japan K.K.

Legal Registered Address: Kobe, Hyogo, Japan

Regulatory Agency Identifier Number(s): Not applicable

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

Document ID: VV-CLIN-077459

Medical Monitor Name and Contact Information will be provided separately.

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment a	8-Sep-2023
Original Protocol	27-May-2023

Amendment [b]

Overall Rationale for the Amendment:

The primary rationale for this amendment is to update certain appendices, analysis and laboratory measurements.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis (Objectives, Endpoints, and Estimands) and 3. Objectives, Endpoints, and Estimands	Added: Fatty liver index as an exploratory endpoint	To include this surrogate marker for fatty liver
5.1. Inclusion Criteria	Revised sex and contraceptive/barrier requirements	Revised text as per latest guidance
6.6.2. Concomitant Background Antihyperglycemic Medication	Revised text pertaining to the examples	Revised text to accommodate other examples
6.9.1. Prohibited or Restricted Use Medications	Deletion of text regarding moderate CYP3A inducers or inhibitor	Deletion in line with the updated list of prohibited medications
8.1.2. Hepatic Parameters	Added: Fatty liver index to the list of hepatic parameters	To include fatty liver index to the list of hepatic parameters
8.2.5 Pregnancy testing	Deleted the words, ‘female’ and ‘male’	To be consistent with the language used in Sections 8.3.1 and 8.3.2
8.2.6.2. Comprehensive Hepatic Evaluation	Deletion of text in table, on participants with ALT or AST ≥5x ULN for more than 2 weeks; ALT or AST ≥8x ULN; ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks and ALT or AST ≥4x baseline ≥400 U/L (whichever occurs first); frequency of clinical and laboratory monitoring updated to 1-3 times weekly;	Revised text as per latest guidance

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Section # and Name	Description of Change	Brief Rationale
	deletion of details regarding the follow-up required if hepatic event continues beyond the end date of the study	
8.2.6.3. Study Intervention Interruption or Discontinuation	Revised text in table to include international normalized ratio ≥1.5; updated frequency of clinical and laboratory monitoring to 1-3 times weekly	Revised text as per latest guidance
8.3.1. Timing and Mechanism for Collecting Events	Revised language on participants, related to pregnancy, in the table	Revised text as per latest guidance
8.3.2. Pregnancy	Revised language on the collection of pregnancy information; included the details on when not to collect pregnancy information	Revised text as per latest guidance
8.3.3.4. Hypoglycemia	Revised to clarify the medications to be stopped in participants who develop persistent or recurrent unexplained hypoglycemia	Revised text to indicate that study intervention will be adjusted/discontinued after reduction of concomitant antihyperglycemic agents
9.3.1. and 9.3.4. General Considerations and Secondary Endpoints and Estimands Analyses	Revised the general description of analyses	Revised text for consistency across studies
Appendix 1: 10.1.7. Data Quality Assurance	Included 'remote' access to source documents	Revised text as per latest guidance
Appendix 2: Clinical Laboratory Tests	Revised triglyceride limit to include 400 mg/dL	Error correction
Appendix 4: Contraceptive and Barrier Guidance	Updated definitions and contraceptive guidance	Updated text as per latest guidance
Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments	Revised link to the hepatic evaluation testing; updated HCV testing in the table	Corrected link to the hepatic evaluation testing;Instead of total antibody only IgG will be assessed.
Appendix 9: Prohibited Medications or Medications with Special Use Restrictions, Including Fixed-Dose Combination Drug	Revised the list of strong CYP3A4 inhibitors and inducers, strong OATP inhibitors, sensitive P-gp and BCRP substrates; deleted the list of moderate CYP3A inhibitors and inducers;	Updated text as per latest guidance

Section # and Name	Description of Change	Brief Rationale
	updated drugs affected by increase in gastric pH	
Appendix 12: Abbreviations and Definitions	Updated	To include terms used

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 3, Long-term Safety Study of LY3502970 in Adult Participants with Type 2 Diabetes and Inadequate Glycemic Control with Diet and Exercise Alone or in Combination with Oral Antihyperglycemic Medications (ACHIEVE-J)

Brief Title: A Long-term Safety Study of LY3502970 in Participants with Type 2 Diabetes (ACHIEVE-J)

Regulatory Agency Identifier Number(s): Not applicable

Rationale:

ACHIEVE-J (Study J2A-JE-GZPE) is designed to assess the safety and efficacy of LY3502970 (3, 12, or 36 mg) administered once daily (QD) for 52 weeks in Japanese participants with type 2 diabetes (T2D) and inadequate glycemic control that within 90 days prior to study entry have been treated with:

- diet and exercise alone
- therapeutic doses of sulfonylureas (SUs), biguanides, or sodium-glucose cotransporter type 2 inhibitors (SGLT-2i's) alone, or
- therapeutic doses of alpha-glucosidase inhibitors (a-GIs), thiazolidinedione (TZD), or glinides alone or in combination with metformin.

The primary endpoint will be to assess the safety and tolerability of LY3502970 during 52-week treatment as monotherapy or an add-on therapy to oral anti-hyperglycemic medication (OAM), based on the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1. 2010). Approximately 39 participants with diet and exercise alone will be enrolled to this study to complement the number of Japanese participants to be enrolled in the ACHIEVE-1 (Study J2A-MC-GZGT), to meet the guideline mentioned above.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To assess safety and tolerability of LY3502970 (3, 12, or 36 mg) administered QD during 52-week treatment as monotherapy or an add-on therapy to SUs, biguanides, SGLT-2i's, a-GIs, TZD, or glinides in the treatment of T2D.	• Incidence of TEAEs

Objectives	Endpoints
Secondary	
To assess safety and tolerability of LY3502970 (3, 12, or 36 mg) administered QD during 52-week treatment as monotherapy or an add-on therapy to SUs, biguanides, SGLT-2i's, a-GIs, TZD, or glinides in the treatment of T2D.	Summary of safety data, including number and incidence of: • SAEs • discontinuations from study intervention or study due to AEs • AEs of special interest
To assess efficacy of LY3502970 (3, 12, or 36 mg) administered QD during 52-week treatment as monotherapy or an add-on therapy to SUs, biguanides, SGLT-2i's, a-GIs, TZD, or glinides in the treatment of T2D.	From baseline to Week 52: • Change from baseline in HbA1c • Change from baseline in fasting serum glucose (central laboratory) • Change from baseline in body weight • Percentage change from baseline in body weight • Change from baseline in waist circumference • Change from baseline in BMI • Change from baseline in daily average 7-point SMBG At Week 52: • Proportion of participants who achieve HbA1c o <7.0% (<53 mmol/mol) o ≤6.5% (≤48 mmol/mol) o <5.7% (<39 mmol/mol) • Proportion of participants who achieve weight loss of ≥5%, ≥10%, and ≥15%
Exploratory	
To assess effects of LY3502970 (3, 12, or 36 mg) on lipid parameters.	• Percentage change from baseline in lipid parameters to Week 52: o Total cholesterol o HDL-cholesterol o LDL-cholesterol o VLDL-cholesterol o Non-HDL cholesterol o Triglycerides

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Objectives	Endpoints
To assess effects of LY3502970 (3, 12, or 36 mg) on hepatic parameters.	• Percentage change from baseline to Week 52: o ALT o AST • Change from baseline to Week 52: o Fibrosis-4 (Fib-4) index o FLI
To assess effects of LY3502970 (3, 12, or 36 mg) on blood pressure.	• Change from baseline in blood pressure to Week 52: o Systolic blood pressure o Diastolic blood pressure
To assess effects of LY3502970 (3, 12, or 36 mg) on markers of glucose metabolism and beta-cell function.	• Change from baseline to Week 52: o Fasting insulin o Fasting C-peptide o C-peptide index o Fasting glucagon o HOMA-IR o HOMA-B
To assess effects of LY3502970 (3, 12, or 36 mg) on patient-reported outcomes.	• Change from baseline to Week 52: o DTSQ o EQ-5D-5L health state utilities and VAS o Eating Behavior Questionnaire
To assess effect of LY3502970 (3, 12, or 36 mg) on body composition. (Measured by InBody770 at particular study sites)	• Change from baseline to Week 52: o Body weight o Body fat mass o Lean body mass

Abbreviations: a-GI = alpha-glucosidase inhibitor; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CV = cardiovascular; DTSQc = Diabetes Treatment Satisfaction Questionnaire-Change; DTSQs = Diabetes Treatment Satisfaction Questionnaire – Status; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level; FLI = fatty liver index; HbA1c= hemoglobin A1c; HDL = high density lipoprotein; HOMA-B = homeostasis model assessment of beta cell function；HOMA-IR = homeostatic model assessment for insulin resistance; LDL = low density lipoprotein; QD= once daily; SGLT-2i = sodium-glucose cotransporter type 2 inhibitor; SU = sulfonylurea; T2D = type 2 diabetes; TEAE = treatment-emergent adverse event; TZD = thiazolidinedione; VLDL = very-low-density lipoprotein.

Primary Estimand:

The primary clinical question of interest:

What is the safety and tolerability of LY3502970 during 52-week treatment as monotherapy or an add-on therapy to OAM in participants who meet the eligibility criteria irrespective of study treatment adherence or initiation of additional antihyperglycemic medications?

Rationale for the estimand - This estimand aims to assess safety and tolerability of LY3502970 regardless of study treatment adherence.

Overall Design:

ACHIEVE-J is a Phase 3, multicenter, randomized, open-label study to assess the safety and efficacy of LY3502970 (3, 12, or 36 mg) in Japanese participants with T2D who have inadequate glycemic control with either diet and exercise alone or who have been taking therapeutic doses of various OAMs; SUs, biguanides, or SGLT-2i's alone or a-GIs, TZD, or glinides alone or in combination with metformin.

Brief Summary:

The purpose of this study is to determine the long-term safety of the study intervention LY3502970 as monotherapy or in combination with OAM in participants with T2D.

This study includes 3 periods as follows:

- screening and lead-in period: up to 4 weeks
- treatment period: 52 weeks, including 20 weeks of dose escalation, and
- safety follow-up period: 2 weeks.

Study Population:

The study will include Japanese participants with T2D who have HbA1c between 7.0% and 10.5%, and inadequate glycemic control that within 90 days prior to study entry have been treated with:

- diet and exercise alone
- therapeutic doses of SUs, biguanides, or SGLT-2i's alone, or
- therapeutic doses of a-GIs, TZD, or glinides alone or in combination with metformin.

Number of Participants:

399 participants will be randomly assigned in a 1:1:1 ratio to LY3502970 3 mg QD, 12 mg QD, or 36 mg QD, respectively. 39 participants with inadequate glycemic control with diet and exercise alone and 360 participants who have been taking SUs, biguanides, SGLT-2i's, a-GIs, TZD, or glinides (60 participants each) with inadequate glycemic control will be enrolled in this study. This sample size was decided based on Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1. 2010).

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The randomization will be stratified by:

- background therapy (diet and exercise alone, SU, biguanide, SGLT-2i's, a-GI, TZD, or glinide)
- HbA1c (≤8.5%, >8.5% [≤69 mmol/mol, >69 mmol/mol]) at Visit 1, and
- metformin use (Yes or No). (will be adopted for a-GI, TZD, or glinide groups)

Intervention Groups and Duration:

The study interventions are LY3502970 at 3 mg, 12 mg, or 36 mg administered orally once daily. The treatment duration is 52 weeks.

Ethical Considerations of Benefit/Risk:

The safety and efficacy profile seen to date for LY3502970 supports the overall benefit/risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 receptor agonists (GLP-1 RAs), including gastrointestinal tolerability and increased heart rate. These risks are monitorable, usually mild to moderate in severity, reversible, and readily manageable. To date there are no recognized AEs from LY3502970 other than those related to GLP-1 receptor agonism.

The potential risks based on the knowledge for the GLP-1 RA class are considered being acceptable in the context of the potential benefits anticipated from treatment with LY3502970 in adult participants with T2D.

Data Monitoring Committee: No

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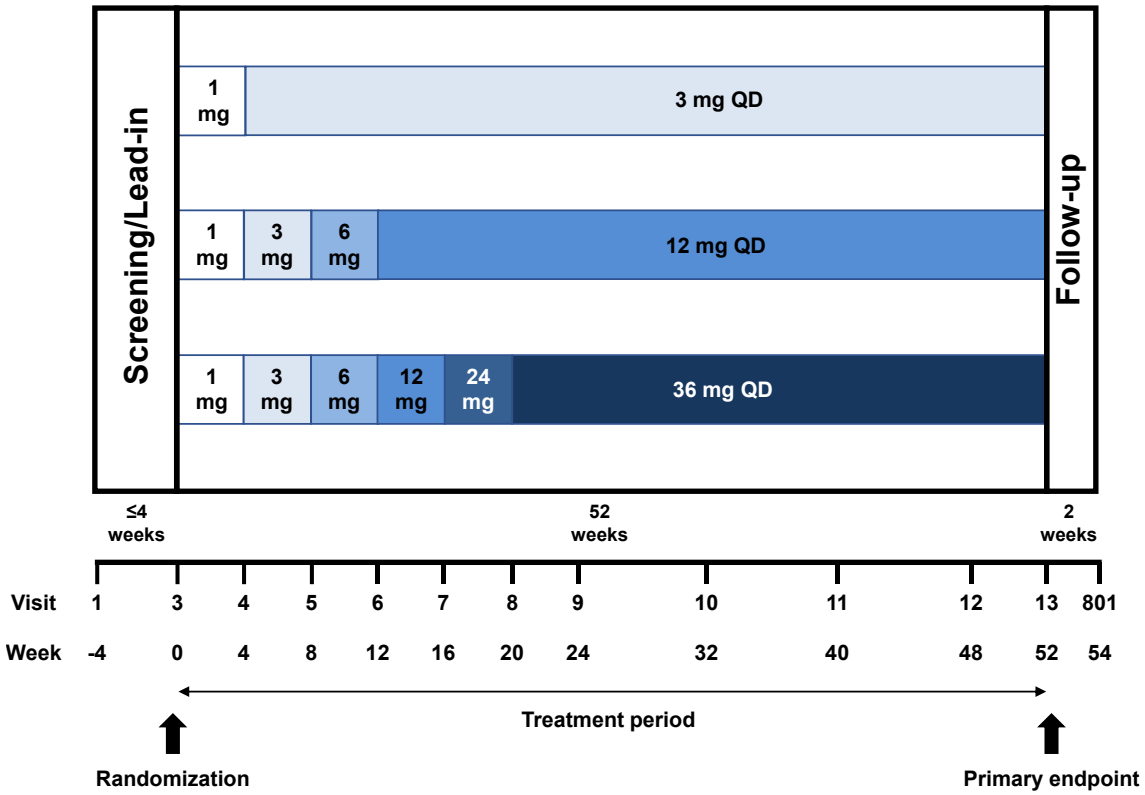
1.2. Schema



Abbreviation: QD = once daily.

1.3. Schedule of Activities (SoA)

The SoA described below should be followed for all participants enrolled in ACHIEVE-J (Study J2A-JE-GZPE). However, for those whose participation in this study is affected by exceptional circumstances, such as pandemics or natural disasters, please refer to Section 10.11 for additional guidance.

Fasting visits

The fasting state is defined as not having had anything to eat or drink but water for a minimum of 8 hours.

- Visit 1 (screening), Visit 2, and Visit 12: Fasting is not required.
- Visit 3 (randomization): Participant must attend Visit 3 in a fasting state. All procedures, including patient-reported outcomes, laboratory procedures and ECGs, should be completed prior to the participant taking study intervention at this visit.
- Visits 4 through 13 (except Visit 12): If a participant attends these visits in a non-fasting state, samples for laboratory testing should not be collected and the participant should be asked to return to the site in a fasting state as soon as possible within the visit window. All other procedures scheduled at the visit may be performed.

Early Discontinuation (ED)

Participants who are unable or unwilling to continue the study treatment period for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit.

Safety Follow-up

All participants are required to complete a safety follow-up visit (Visit 801), according to the SoA. Participants discontinuing the treatment period early and performing an ED visit will also be asked to perform the safety follow-up visit.

	Screening and Lead-in		Treatment												Safety follow-up	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**	V2 may occur as soon as criteria for V1 are confirmed; V3 to occur no sooner than 18 days after V1.
Weeks from Visit 3 (randomization)	**18 to 28 days**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**		**2 wk post end of TxP**	
Visit interval tolerance (days)	**-**	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±6**	**±6**	**±6**	**±3**		**±3**	
Fasting visit			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	
Consent and demographics																
Informed consent	X															The ICF must be signed before any protocol-specific tests or procedures are performed. See Section 10.1.3 for additional details.
Inclusion and exclusion criteria, confirmation of eligibility	X	X	X													Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention. See Sections 5.1 and 5.2.
Demographics	X															Includes year of birth, sex, and race.
Preexisting conditions and medical history, including relevant surgical history	X															Collect all ongoing conditions and relevant past surgical and medical history.
Prespecified medical history	X															
Prior treatments for indication	X															See Section 6.9.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 8.3.1 and Section 10.3. Additional data are collected for certain AEs. See Section 8.3.3.
Substance use (alcohol, caffeine, tobacco, nicotine replacement)			X													
Physical evaluation																
Height	X															See Section 10.10.
Weight	X		X	X	X	X	X	X	X	X	X		X	X	X	See Section 10.10.
Waist circumference			X		X		X		X	X	X		X	X		See Section 10.10.
Physical examination	X															Excludes pelvic, rectal and breast examinations unless clinically indicated. See Section 8.2.1.

	Screening and Lead-in		Treatment												Safety follow-up	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**	V2 may occur as soon as criteria for V1 are confirmed; V3 to occur no sooner than 18 days after V1.
Weeks from Visit 3 (randomization)	**18 to 28 days**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**		**2 wk post end of TxP**	
Visit interval tolerance (days)	**-**	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±6**	**±6**	**±6**	**±3**		**±3**	
Fasting visit			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	
Symptom-directed physical assessment			X													Symptom-directed physical assessment may be conducted at the discretion of the investigator.
Vital signs (triplicate)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes pulse rate and blood pressure. Measured in triplicate after participant has been sitting at least 5 minutes. Vital signs should be taken before ECG tracing. See Sections 8.2.2 and 10.10.
ECG 12-lead (triplicate; central)			X										X	X	X	Collect triplicate ECGs before blood samples for laboratory testing. ECG may be repeated at the investigator's discretion at any visit. See Section 8.2.3.
Fundus photography and further ophthalmological assessment		X							X				X	X		
	Eligibility (see exclusion criterion #13, Section 5.2) MUST be confirmed based on fundus photographs and any additional ophthalmological evaluation. Screening fundus photography should be performed only for participants eligible based on screening activities performed at Visit 1, including laboratory results. Follow-up fundus photography and any additional ophthalmological evaluation will be performed at Visit 9/Week 24 (±4 weeks) only if retinopathy or DME were present at baseline. At Visit 13/Week 52, the fundus photography and further assessment should be completed within 4 weeks prior to that visit. All fundus photographs and any additional ophthalmological evaluation for retinopathy or DME on photographs must be assessed by an ophthalmologist or other qualified healthcare professional. See Section 8.2.8.														
Body composition			X										X	X		Measured by InBody770 only at particular study sites. See Section 8.1.6.
Participant diary (electronic)																
Dispense eDiary		X														Includes hypoglycemia, daily dose of LY3502970, and 4-point and 7-point SMBG, as applicable. See Section 5.3.1.

	Screening and Lead-in		Treatment												Safety follow-up	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**	V2 may occur as soon as criteria for V1 are confirmed; V3 to occur no sooner than 18 days after V1.
Weeks from Visit 3 (randomization)	**18 to 28 days**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**		**2 wk post end of TxP**	
Visit interval tolerance (days)	**-**	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±6**	**±6**	**±6**	**±3**		**±3**	
Fasting visit			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	
eDiary review			X	X	X	X	X	X	X	X	X	X	X	X	X	eDiary review to include SMBG data, daily dosing, and hypoglycemia events.
Remind participants about 7-point SMBG		X										X				See Section 5.3.1. Site staff will remind participants of collection times at specified visits and approximately 1 week before subsequent visits.
Review 7-point SMBG			X										X			Participant will collect two 7-point SMBGs on non-consecutive days during the week preceding each visit specified.
eDiary return															X	
Participant education																
Diabetes education (includes BG meter and SMBG training)		X							X							See Section 5.3.1. All training should be repeated as needed to encourage participant compliance.
Dispense BG meter and supplies as needed		X	X													
Patient-reported outcomes (electronic)																
DTSQs			X													See Section 8.1.5.1.
DTSQc													X	X		See Section 8.1.5.1.
EQ-5D-5L			X										X	X		See Section 8.1.5.2.
Patient-reported outcomes (paper)																
Eating Behavior Questionnaire			X										X	X		See Section 8.1.5.3.
Laboratory tests and sample collections																
Hematology	X		X			X			X		X		X	X	X	See Section 10.2.
Clinical chemistry	X		X	X	X	X	X	X	X	X	X		X	X	X	See Section 10.2. If at V801, hepatic tests are elevated (participants with normal baseline: ALT or AST ≥3x ULN; participants with elevated baseline: ≥2x baseline), then repeat 2 weeks later.

	Screening and Lead-in		Treatment												Safety follow-up	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**	V2 may occur as soon as criteria for V1 are confirmed; V3 to occur no sooner than 18 days after V1.
Weeks from Visit 3 (randomization)	**18 to 28 days**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**		**2 wk post end of TxP**	
Visit interval tolerance (days)	**-**	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±6**	**±6**	**±6**	**±3**		**±3**	
Fasting visit			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	
Glucose (serum)			X	X	X	X	X	X	X	X	X		X	X	X	See "Fasting visits" in the SoA preamble.
HbA1c	X		X	X	X	X	X	X	X	X	X		X	X		See Section 10.2.
Lipids			X			X			X		X		X	X		See Section 10.2.
Lipase	X					X			X		X		X	X	X	See Section 10.2.
Pancreatic amylase	X					X			X		X		X	X	X	See Section 10.2.
Insulin			X			X			X		X		X	X		See Section 10.2.
Glucagon			X										X	X		See Section 10.2.
C-peptide			X			X			X		X		X	X		See Section 10.2.
Serum pregnancy	X															Collect for WOCBP. See Section 10.4.
Urine pregnancy (local)			X										X	X		The result must be available before the first dose of study intervention for WOCBP. Perform additional urine pregnancy tests if a menstrual period is missed or if there is clinical suspicion of pregnancy.
Follicle stimulating hormone	X															Perform as needed to confirm postmenopausal status. Definition in Section 10.4.
HCV screening tests	X															If HCV antibody test is positive, it must be followed by an HCV RNA test. Participants who are positive for HCV antibody and negative for HCV RNA may be enrolled. See exclusion criterion #17, Section 5.2.
HBV screening tests	X															For participants who are positive for HBcAb, testing for HBV DNA will be performed. See exclusion criterion #17, Section 5.2.
Calcitonin	X					X			X		X		X	X	X	See Section 10.2.
Cystatin-C	X		X			X			X		X		X	X		See Section 10.2.

	Screening and Lead-in		Treatment												Safety follow-up	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**	V2 may occur as soon as criteria for V1 are confirmed; V3 to occur no sooner than 18 days after V1.
Weeks from Visit 3 (randomization)	**18 to 28 days**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**		**2 wk post end of TxP**	
Visit interval tolerance (days)	**-**	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±6**	**±6**	**±6**	**±3**		**±3**	
Fasting visit			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	
eGFR	X		X			X			X		X		X	X		CKD-EPI cystatin-C (2012). See Section 10.2.
Urinary Albumin/Creatinine Ratio			X						X		X		X	X		See Section 10.2.
Stored samples																
Genetics sample			X													
Exploratory biomarker samples			X			X			X		X		X	X		
Randomization and dosing related activities																
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Randomization via IWRS			X													
Dispense study intervention via IWRS			X	X	X	X	X	X	X	X	X	X				
Dispense study intervention to participant (for at home dosing)			X	X	X	X	X	X	X	X	X	X				
Participant returns unused study intervention				X	X	X	X	X	X	X	X	X	X	X		
Assess study intervention compliance				X	X	X	X	X	X	X	X	X	X	X		

Abbreviations: AEs = adverse events; BG = blood glucose; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DME = diabetic macular edema; DNA = deoxyribonucleic acid; DTSQc = Diabetes Treatment Satisfaction Questionnaire-Change; DTSQs = Diabetes Treatment Satisfaction Questionnaire-Status; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level; FBG = fasting blood glucose; HbA1c = hemoglobin A1c; HBcAb= hepatitis B core antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = informed consent form; IWRS = interactive web response system; RNA = ribonucleic acid; SMBG = self-monitoring of blood glucose; SoA = Schedule of Activities; TxP = treatment period; V = Visit; WOCBP = women of childbearing potential.

2. Introduction

GLP-1 receptor agonism is an established therapeutic mechanism for glycemic control in T2D, as well as weight management in individuals with obesity or overweight. Unlike injectable or orally administered peptide GLP-1 RAs approved by regulatory authorities to date, LY3502970 is an oral, small molecule GLP-1 RA.

LY3502970 is being developed for the treatment of T2D and overweight or obesity.

2.1. Study Rationale

ACHIEVE-J (Study J2A-JE-GZPE [GZPE]) is designed to assess the safety and efficacy of LY3502970 (3, 12, or 36 mg) administered QD for 52 weeks in Japanese participants with T2D and inadequate glycemic control that within 90 days prior to study entry have been treated with:

- diet and exercise alone
- therapeutic doses of SUs, biguanides, or SGLT-2i's alone, or
- therapeutic doses of a-GIs, TZD, or glinides alone or in combination with metformin.

The primary endpoint will be to assess the safety and tolerability of LY3502970 during 52-week treatment as monotherapy or an add-on therapy to OAM, based on the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (PMDA 2010). Approximately 39 participants with diet and exercise alone will be enrolled to this study to complement the number of Japanese participants to be enrolled in the ACHIEVE-1 (Study J2A-MC-GZGT), to meet the guideline mentioned above.

The data from this trial, together with the data from other Phase 3 trials, are expected to provide robust benefit/risk profiles of individual doses of LY3502970, as required by regulatory agencies for regulatory submission and marketing approval for T2D in Japan.

2.2. Background

Type 2 diabetes

T2D is a metabolic condition characterized by impaired glycemic control caused by increased insulin resistance and progressive beta-cell failure and consequently inadequate insulin secretion. T2D is believed to be caused by environmental factors such as overeating (especially high fat foods), lack of exercise, and obesity, in addition to genetic factors such as a predisposition to decreasing insulin secretion or insulin resistance (JDS 2022).

In Japan, patients with T2D account for the majority of all patients with diabetes. Although growth of the total population of patients with diabetes, including patients with prediabetes, plateaued in 2007, there were still approximately 20,000,000 patients in 2016 including patients with prediabetes (MHLW 2017).

Treatment for T2D starts with appropriate diet therapy and exercise therapy (JDS 2022). If these non-drug treatments do not improve blood glucose control, drug treatment is added. Drug treatment for T2D starts with oral antidiabetics for patients with a low risk of hypoglycemia or

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GLP-1 RA based on the pathology and complications. If additional drug treatment is necessary, a combination of oral antidiabetics or combination with GLP-1 RA or insulin are considered.

Clinical Data for LY3502970

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

Phase 1

The clinical pharmacology, PK, and PD of LY3502970 were initially studied in 2 Phase 1 studies, J2A-MC-GZGA (GZGA) in healthy volunteers and J2A-MC-GZGC (GZGC) in participants with T2D. Results from these studies demonstrated a PK profile appropriate for once daily oral dosing that can be administered without limitations pertaining to food or water intake or time of day.

Japan Phase 1

In the completed single-dose and 12-week multiple-dose Study J2A-JE-GZGB (GZGB), a total of 62 Japanese participants with T2D received either LY3502970 (up to 45 mg) or placebo. No SAEs were reported. All tested LY3502970 doses were tolerated in this study. GI AEs (nausea, vomiting, and constipation) and decreased appetite were the most frequently reported events. These AEs were mostly mild in severity and the majority resolved without treatment. Also, most of the GI AEs occurred during the first week of dosing or early stage of dose escalation. There have been no reports of severe hypoglycemia in this study. There were statistically significant reductions in fasting glucose, HbA1c, and body weight with LY3502970 compared with placebo in Study GZGB.

Phase 2

Study J2A-MC-GZGE (GZGE) was a Phase 2, randomized, double-blind, parallel, placebo- and active comparator (1.5 mg dulaglutide once weekly)-controlled 26-week study. The objective of the study was to investigate antihyperglycemic and body weight-lowering efficacy, as well as tolerability and safety of LY3502970 (3 mg to 45 mg maintenance doses) in participants with T2D who failed to achieve adequate glycemic control on diet and exercise alone or when treated with metformin.

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Key efficacy and safety data at 26-weeks:

- Placebo-adjusted change from baseline in HbA1c ranged from -0.77% (3 mg LY3502970) to -1.67% at (45 mg LY3502970) compared with -0.67% for dulaglutide 1.5 mg, ($p<.001$ for all doses of LY3502970).
- HbA1c change from baseline at the 3-mg dose of LY3502970 was comparable to dulaglutide 1.5 mg (Estimated treatment difference -0.09%; $p=0.626$); while statistically significant difference observed at all other doses of LY3502970 (Estimated treatment difference range -0.69% to -1.00%; all $p<.001$).
- 65% to 96% of participants reached the target HbA1c <7% and 45% to 84% reached the target of HbA1c ≤6.5%.
- Placebo-adjusted change from baseline in fasting serum glucose ranged from -21.5 mg/dL (3 mg LY3502970) to -44.7 mg/dL at (45 mg LY3502970) compared with -22.1 mg/dL for dulaglutide 1.5 mg, ($p<.001$ for all doses of LY3502970).
- Placebo-adjusted change (% change) from baseline in body weight ranged from -1.6 kg (-1.5%) (3 mg LY3502970) to -7.9 kg (-7.4%) at (45 mg LY3502970) compared with -1.4 kg for dulaglutide 1.5 mg, ($p<.001$ for all doses of LY3502970).
- 33% to 81% of participants lost at least 5% of body weight and 8% to 48% lost at least 10% of body weight.
- The overall safety profile of LY3502970 was consistent with that established for the GLP-1 RA class, with most common TEAEs being GI related (nausea, vomiting, diarrhea, and constipation).
- The majority of the GI AEs were mild to moderate in severity and occurred mostly during dose-escalation period.

Data from these Phase 2 studies supported the further clinical development of LY3502970.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Study intervention

The potential risks associated with LY3502970 are similar to those of marketed GLP-1 RAs. The most commonly reported TEAEs observed in the LY3502970 clinical studies, in healthy participants or participants with T2D, are GI effects, including nausea, vomiting, diarrhea, and constipation. Most were mild to moderate in severity and tended to occur during the dose escalation period.

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Other potential risks associated with LY3502970 include:

- acute pancreatitis
- increases in heart rate
- hypoglycemia when used with insulin or insulin secretagogues
- hypersensitivity reactions, and
- thyroid C-cell effects (only observed in rodents).

Rapid improvements in glucose control have been associated with temporary worsening of diabetic retinopathy and is thus another potential risk associated with the study.

Sections 5.1, 5.2 and 8.2 address mitigation, management, and monitoring of the known potential risks associated with LY3502970.

Study procedures

Blood draws

Risks of blood draws for clinical laboratory assessments include the potential for some pain and a small risk of bruising or infection at the site.

ECG collection

Collection of ECGs may cause mild discomfort during placement and removal of leads from the skin. Some participants may experience local irritation or redness at the sites of lead attachment.

Retinal assessment

Dilating drops if used for pupil dilation for the eye examination may sting temporarily, and may cause temporary blurred vision, difficulty focusing, and light sensitivity. Pharmacologic dilatation may be contraindicated in some participants with eye conditions, for example, closed angle glaucoma.

2.3.2. Benefit Assessment

The known pharmacology of GLP-1 receptor agonism and the data from the Phase 2 studies of LY3502970 support an expectation of benefits on glycemic control and weight loss with LY3502970. Improvements in some cardiometabolic risk factors, including blood pressure and serum lipids, may also be expected. GLP-1 RAs have generally been associated with reduced risk of CV events in people with T2D (Giugliano et al. 2021).

Participants may also benefit from receiving personal health information, diabetes education, routine safety assessments, and frequent engagement with health care providers during the study, which provide opportunities for coaching and support.

2.3.3. Overall Benefit Risk Conclusion

The safety and efficacy profile seen to date for LY3502970 supports the overall benefit/risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 RAs, including GI tolerability and increased heart rate. These risks are monitorable, usually mild to moderate in severity, reversible, and readily manageable. To date

there are no recognized AEs from LY3502970 other than those related to GLP-1 receptor agonism.

The potential risks based on the knowledge for the GLP-1 RA class are considered being acceptable in the context of the potential benefits anticipated from treatment with LY3502970 in adult participants with T2D.

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3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To assess safety and tolerability of LY3502970 (3, 12, or 36 mg) administered QD during 52-week treatment as monotherapy or an add-on therapy to SUs, biguanides, SGLT-2i's, a-GIs, TZD, or glinides in the treatment of T2D.	• Incidence of TEAEs
Secondary	
To assess safety and tolerability of LY3502970 (3, 12, or 36 mg) administered QD during 52-week treatment as monotherapy or an add-on therapy to SUs, biguanides, SGLT-2i's, a-GIs, TZD, or glinides in the treatment of T2D.	Summary of safety data, including number and incidence of: • SAEs • discontinuations from study intervention or study due to AEs • AEs of special interest
To assess efficacy of LY3502970 (3, 12, or 36 mg) administered QD during 52-week treatment as monotherapy or an add-on therapy to SUs, biguanides, SGLT-2i's, a-GIs, TZD, or glinides in the treatment of T2D.	From baseline to Week 52: • Change from baseline in HbA1c • Change from baseline in fasting serum glucose (central laboratory) • Change from baseline in body weight • Percentage change from baseline in body weight • Change from baseline in waist circumference • Change from baseline in BMI • Change from baseline in daily average 7-point SMBG At Week 52: • Proportion of participants who achieve HbA1c o <7.0% (<53 mmol/mol) o ≤6.5% (≤48 mmol/mol) o <5.7% (<39 mmol/mol) • Proportion of participants who achieve weight loss of ≥5%, ≥10%, and ≥15%
Exploratory	
To assess effects of LY3502970 (3, 12, or 36 mg) on lipid parameters.	• Percentage change from baseline in lipid parameters to Week 52:

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Objectives	Endpoints
	○ Total cholesterol ○ HDL-cholesterol ○ LDL-cholesterol ○ VLDL-cholesterol ○ Non-HDL cholesterol ○ Triglycerides
To assess effects of LY3502970 (3, 12, or 36 mg) on hepatic parameters.	• Percentage change from baseline to Week 52: ○ ALT ○ AST • Change from baseline to Week 52: ○ Fibrosis-4 (Fib-4) index ○ FLI
To assess effects of LY3502970 (3, 12, or 36 mg) on blood pressure.	• Change from baseline in blood pressure to Week 52: ○ Systolic blood pressure ○ Diastolic blood pressure
To assess effects of LY3502970 (3, 12, or 36 mg) on markers of glucose metabolism and beta-cell function.	• Change from baseline to Week 52: ○ Fasting insulin ○ Fasting C-peptide ○ C-peptide index ○ Fasting glucagon ○ HOMA-IR ○ HOMA-B
To assess effects of LY3502970 (3, 12, or 36 mg) on patient-reported outcomes.	• Change from baseline to Week 52: ○ DTSQ ○ EQ-5D-5L health state utilities and VAS ○ Eating Behavior Questionnaire
To assess effect of LY3502970 (3, 12, or 36 mg) on body composition. (Measured by InBody770 at particular study sites)	• Change from baseline to Week 52: ○ Body weight ○ Body fat mass ○ Lean body mass

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Abbreviations: a-GI = alpha-glucosidase inhibitor; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CV = cardiovascular; DTSQ = Diabetes Treatment Satisfaction Questionnaire; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level; FLI = fatty liver index; HbA1c= hemoglobin A1c; HDL = high density lipoprotein; HOMA-B = homeostasis model assessment of beta cell function; HOMA-IR = homeostatic model assessment for insulin resistance; LDL = low density lipoprotein; QD= once daily; SGLT-2i = sodium-glucose cotransporter type 2 inhibitor; SU = sulfonylurea; T2D = type 2 diabetes; TEAE = treatment-emergent adverse event; TZD = thiazolidinedione; VLDL = very-low-density lipoprotein.

Primary estimand

The primary clinical question of interest is:

What is the safety and tolerability of LY3502970 during 52-week treatment as monotherapy or an add-on therapy to OAM, in participants who meet the eligibility criteria irrespective of study treatment adherence or initiation of additional antihyperglycemic medications?

The estimand for the primary endpoint is described by the following attributes:

- ***Population*** - Participants who meet the eligibility criteria. Further details can be found in Sections 5 and 9.
- ***Primary endpoint*** - Incidence of TEAEs.
- ***Treatment condition*** - The randomized treatment with allowance for potential dose interruptions and modifications, regardless of adherence to study intervention or initiation of additional antihyperglycemic medications.
- ***Intercurrent events*** - No ICEs are defined since treatment adherence and the initiation of additional antihyperglycemic medications are a part of the treatment condition.
- ***Population-level summary*** - Frequency counts and percentages of TEAEs during the treatment period plus the safety follow-up period.
- ***Rationale for the estimand*** - This estimand aims to assess the safety and tolerability of LY3502970 regardless of study treatment adherence.

4. Study Design

4.1. Overall Design

ACHIEVE-J (Study GZPE) is a Phase 3, multicenter, randomized, open-label study to assess the safety and efficacy of LY3502970 (3, 12, or 36 mg) in Japanese participants with T2D who have inadequate glycemic control with either diet and exercise alone or who have been taking therapeutic doses of various OAMs; SUs, biguanides, or SGLT-2i's alone or a-GIs, TZD, or glinides alone or in combination with metformin.

This study includes 3 periods as follows:

- screening and lead-in period: up to 4 weeks
- treatment period: 52 weeks, including 20 weeks of dose escalation, and
- safety follow-up period: 2 weeks.

Screening/Lead-in Period

Eligibility for this study will be determined at the initial screening visit (Visit 1). Screening procedures and participant training will be performed at Visits 1 and 2 (screening and lead-in periods). Participant training will include disease monitoring and management procedures, study eDiary, and study procedures.

Treatment Period

At Visit 3, participants will perform all required baseline study procedures (including the collection of all baseline laboratory measures) prior to randomization and prior to taking the first dose of study intervention. Following randomization, the participant will take the first dose of study intervention at the study site, according to the dose escalation regimen. The date and time of the first dose of study intervention should be recorded on the CRF.

Beginning at randomization, all participants will receive study intervention according to the randomized treatment arm for the duration of the 52-week treatment period.

Safety Follow-up Period

A safety follow-up visit will occur approximately 2 weeks following the last dose of the study intervention.

4.2. Scientific Rationale for Study Design

This study has been primarily designed to assess the safety of long-term treatment of once daily oral treatment with LY3502970 as:

- monotherapy in participants with T2D and inadequate glycemic control with diet and exercise alone within 90 days prior to study entry and
- an add-on therapy in participants with T2D and inadequate glycemic control with OAM within 90 days prior to study entry.

Study treatment will continue for up to 52 weeks to collect 1 year of safety data as monotherapy or in combination with OAM. SUs, biguanides, SGLT-2i's, a-GIs, TZD, or glinides have been chosen as combination therapy because they have a different mechanism of action from

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LY3502970 and are expected to be combined with LY3502970 in the clinical setting of T2D in Japan. The investigators will be instructed to maintain participants on stable doses of their OAMs during the study. However, OAM dose modifications may be required in the event of hypoglycemia (refer to Section 6.7).

4.3. Justification for Dose

The LY3502970 doses of 3 mg, 12 mg, and 36 mg QD administered orally will be evaluated as the target maintenance doses in this study. These doses were selected for the T2D program based on assessment of safety, efficacy (glycemic control and weight benefit), and GI tolerability data from Phase 2 studies. The Phase 2 data and exposure-response analysis have demonstrated a dose response in HbA1c lowering from baseline from 3 mg through 36-mg dose, with little additional effect of the 45-mg dose compared with 36 mg and no notable increase of GI events between the 12-mg and 36-mg doses.

The dose escalation method was selected to optimize GI tolerability based on assessment of different starting doses and escalation intervals used in the Phase 2 studies. The totality of these results and PK/PD modeling of GI tolerability suggested a starting dose of 1 mg for 4 weeks prior to escalating to 3 mg, followed by no more than a doubling of dose at 4-week intervals thereafter until the target maintenance dose is attained (Section 6.1). This dose regimen should permit adequate time for development of tolerance to GI events and is predicted to improve GI tolerability in the Phase 3 studies.

Based on the completed single-dose and 12-week multiple-dose study GZGB, there were no clinically meaningful differences in the PK, PD, and safety profile between Japanese participants and non-Japanese participants. Hence, the doses and associated escalation schemes chosen for this Phase 3 study GZPE are the same as that chosen for global studies.

The selected doses and dose escalation would enable further evaluation of the benefit/risk considerations for the 3 mg, 12 mg, and 36 mg doses of LY3502970.

4.4. End of Study Definition

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

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5. Study Population

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

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. Japanese participant must be at least 18 years of age at the time of signing the informed consent.

Type of participant and disease characteristics

2. Have a clinical diagnosis of T2D based on the World Health Organization classification.
3. Have HbA1c ≥7.0% (≥53 mmol/mol) to ≤10.5% (≤91 mmol/mol) as determined by the central laboratory at Visit 1 (screening).
4. Have not used any oral or injectable antihyperglycemic medications during the 90 days preceding Visit 1, or between Visit 1 and Visit 3 (randomization).

   OR

   Have been taking therapeutic doses of SUs (glibenclamide, gliclazide, or glimepiride), biguanides, or SGLT-2i's alone for at least 90 days preceding Visit 1, and have been maintained on the same dose for at least 8 weeks before Visit 1 (OAM minimum maintenance doses are provided in the table in Section 10.8).

   OR

   Have been taking therapeutic doses of a-GIs, TZD, or glinides alone or in combination with metformin for at least 90 days preceding Visit 1, and have been maintained on the same dose for at least 8 weeks before Visit 1 (OAM minimum maintenance doses are provided in the table in Section 10.8).

   Note: Participants who have been taking fixed-dose combination agents including metformin are also eligible.

5. Are motivated and willing to make themselves available for the duration of the study and are able to follow study procedures as required, including:
   - perform SMBG per protocol
   - maintain a study eDiary, and
   - complete participant questionnaires.

Weight

6. Are of stable weight (±5%) for at least 90 days prior to Visit 1 and agree to not initiate an intensive diet or exercise program during the study with the intent of reducing body weight other than the lifestyle and/or dietary measures for diabetes treatment.
7. Have a BMI ≥23.0 kg/m^2 at Visit 1.

Sex and contraceptive/barrier requirements

8. Individuals AMAB may participate in this trial. For individuals AMAB, no contraception is required except in compliance with specific local government study requirements. IOCBP and INOCBP may participate in this trial. See Appendix 10.4 for definitions and additional requirements related to contraception.

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

Informed consent

9. Are capable of giving signed informed consent as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical conditions

Diabetes related

10. Have T1D.
11. Have a history of ketoacidosis or hyperosmolar state or coma within the last 6 months prior to Visit 1, or between Visit 1 and Visit 3.
12. Have a history of severe hypoglycemia or hypoglycemia unawareness within the last 6 months prior to Visit 1, or between Visit 1 and Visit 3.
13. Are currently receiving or planning to receive treatment for diabetic retinopathy and/or macular edema (for example, laser photocoagulation or intravitreal injections of anti–VEGF inhibitors).

    Note: All participants will have a baseline fundus photography assessment. In the presence of any degree of diabetic retinopathy and/or macular edema, further ophthalmologic assessment will be performed to confirm eligibility.

Cardiovascular

14. Have New York Heart Association functional classification IV congestive heart failure.

15. Have had any of the following CV conditions within 60 days prior to Visit 1, or between Visit 1 and Visit 3
    - acute myocardial infarction
    - cerebrovascular accident (stroke), or
    - hospitalization for congestive heart failure.

Gastrointestinal

16. Have a known clinically significant gastric emptying abnormality, for example, severe diabetic gastroparesis or gastric outlet obstruction, have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery, for example, Lap-Band®, or chronically take drugs that directly affect GI motility.

Hepatic

17. Have acute or chronic hepatitis, including a history of autoimmune hepatitis, signs, or symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following as determined by the central laboratory during screening:
    - ALT or AST level >5.0x the ULN for the reference range
    - ALP level ≥1.5x the ULN for the reference range
    - TBL level ≥1.5x the ULN for the reference range, except for cases of known Gilbert's syndrome
    - Hepatitis B infection, defined as:
        - positive hepatitis B core antibody and positive for HBV DNA or
        - positive hepatitis B surface antigen
    - Positive hepatitis C antibody and positive for HCV RNA

    Note: Participants with nonalcoholic fatty liver disease are eligible to participate only if their ALT level is ≤5.0x the ULN for the reference range.

Renal

18. Have an eGFR <30 mL/min/1.73 m^2 as determined by the central laboratory at Visit 1 (calculated by CKD-EPI cystatin-c equation).

    Note: For participants taking biguanides and/or SGLT-2i, an eGFR <45 mL/min/1.73 m^2 calculated as described above is applied.

Hematologic

19. Have any hematological condition that may interfere with HbA1c measurement, for example, hemolytic anemias or sickle cell disease.

Malignancy

20. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy for less than 5 years.

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Exceptions: basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ or Grade 1 (for example, Gleason 6 or lower) prostate cancer.

Endocrine

21. Have family (first-degree relative) or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
22. Have a serum calcitonin level of ≥35 ng/L, as determined by the central laboratory at Visit 1.

General

23. Had chronic or acute pancreatitis any time.
24. Have had a transplanted organ or awaiting an organ transplant.

    Exception: corneal transplants (keratoplasty).

Prior/concomitant therapy

25. Within 90 days prior to Visit 1, or between Visit 1 and Visit 3
    - Are receiving or have received chronic (>14 days) systemic glucocorticoid therapy, excluding topical, intraocular, intranasal, interphalangeal, or inhaled preparations, or
    - have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that is likely to require, in the opinion of the investigator, such treatment during the study.
26. Have used any weight loss drugs or alternative remedies, including herbal or nutritional supplements, within 90 days prior to screening Visit 1, or between Visit 1 and Visit 3 (See Section 10.9 for examples).
27. Are receiving strong CYP3A inhibitors or CYP3A inducers, drugs that are P-gp or BCRP substrates with narrow therapeutic index, or strong OATP inhibitors. See Sections 6.9.1 and 10.9 for further details.

    Note: Participants using these medications may be eligible for the study if the excluded drug can be washed out and replaced with an alternative medication for at least 2 weeks prior to Visit 3.

Prior/concurrent clinical study experience

28. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
29. Have previously completed or withdrawn from this study or any other study investigating LY3502970 after receiving at least 1 dose of study intervention.

30. Have participated in a clinical study and received treatment, whether active or placebo, within the last 30 days or duration equal to 5 times the half-life of study intervention, whichever is longer.

Other exclusion criteria

31. Have any condition, unwillingness, or inability not covered by any of the other exclusion criteria, that, in the opinion of the investigator, might
    - jeopardize the safety of the participant; for example, hypersensitivity to trial product(s) or excipient or contraindication
    - compromise compliance with the protocol; for example, recreational drug use or alcohol abuse, or
    - confound data interpretation.
32. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
33. Are Eli Lilly and Company employees or are employees of any third party involved in the study who requires exclusion of their employees.
34. Are pregnant or intend to become pregnant or to breastfeed during the study.

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), participants will have access to qualified medical staff who will provide diabetes management counseling, which will include instructions on diet and exercise and education about the signs, symptoms, and treatment of hypoglycemia.

5.3.1. Diabetes Education

Diabetes education will be performed by personnel who are qualified to educate participants on symptoms and management of hyperglycemia and hypoglycemia and diabetes management. All trainings should be repeated as needed to ensure participant compliance.

Self-Monitored Blood Glucose (SMBG)

Participants will receive a study-approved glucometer and related testing supplies for use during the study.

Site personnel will train the participant on correct use of the glucometer for self-monitoring blood glucose and reporting of hypoglycemia.

Four-point SMBG

Participants will be instructed to perform 4-point SMBG measurements once weekly during the treatment period and to record all results in the eDiary according to instructions; these results will be used for assessment of severe persistent hyperglycemia (Section 6.9.3). Four-point SMBG profiles will consist of measurements obtained on a single day:

- before 3 main meals, and

- at bedtime.

During the weeks when the 7-point SMBG profiles are to be collected, participants will not be required to collect 4-point SMBG profiles, and the 4-point BG values included in the 7-point profiles may be used for assessment of severe persistent hyperglycemia.

Seven-point SMBG

Participants will also be instructed to collect two 7-point SMBG profiles on non-consecutive days during the week and record all results in the eDiary according to instructions preceding prespecified visits as shown in the SoA (Section 1.3); these results will be used for the efficacy analysis. Seven-point SMBG profiles will consist of measurements obtained on a single day:

- before 3 main meals,
- approximately 2 hours after 3 main meals, and
- at bedtime.

5.3.2. Meals and Dietary Restrictions

Participants should continue their usual exercise habits and generally follow a healthy meal plan, with consistent meal size and time of day, throughout the course of the study.

Dietary counseling may be reviewed throughout the study, as needed. Per inclusion criterion #6 (Section 5.1), participants should not initiate during the study an organized diet or exercise weight reduction program other than the lifestyle and/or dietary measures for diabetes treatment.

For certain assessments, the participants will be required to come to the site in a fasting state, except for water, of at least 8 hours as specified in the SoA (Section 1.3).

LY3502970 is a CYP3A4 substrate. Participants should refrain from consuming grapefruit and grapefruit juice while participating in the study due to the effect on CYP3A4.

5.3.3. Blood Donation

Study participants should be instructed not to donate blood or blood products during the study, starting at Visit 1, and up to Visit 801 following the study.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure), based upon the screening laboratory measurements, will have 1 rescreen opportunity with repeat screening laboratory tests.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

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

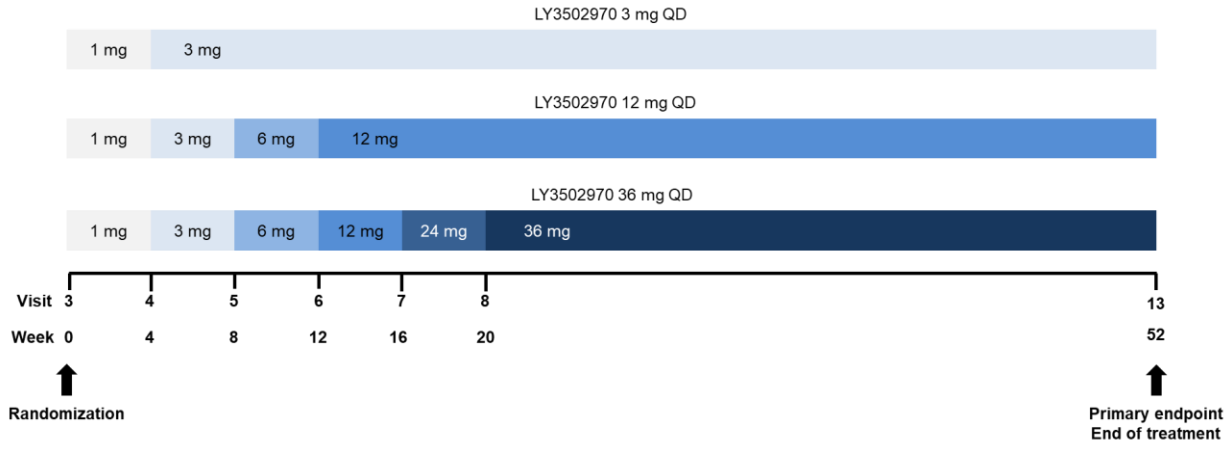
6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

Intervention Name	LY3502970
Dosage Level(s)	1 mg, 3 mg, 6 mg, 12 mg, 24 mg, and 36 mg capsules
Route of Administration	Oral QD

Dose escalation schema

All participants will initiate treatment with a 1 mg QD dose of LY3502970 and increase dose every 4 weeks until the randomized maintenance dose (3 mg, 12 mg, or 36 mg) is reached, as outlined in this figure.



The maintenance dose of LY3502970 (3 mg, 12 mg, 36 mg) will be continued for the remainder of the treatment period, unless temporary interruption of the study intervention is necessary. For management of participants with intolerable GI symptoms, see Section 6.6.1.1.

LY3502970 is administered orally once daily. In general, there are no restrictions on the time of day each dose is taken, but it is recommended to take the dose at approximately the same time each day. Medications that may be affected by an increase in gastric pH should be separated from study intervention administration by at least 2 to 4 hours (Section 6.9).

Participants should administer their first dose of LY3502970 at the end of Visit 3 prior to leaving the study site, after other study procedures and randomization are completed. The date and time of the first dose of study intervention should be recorded on the CRF. Participants will record the actual date and time of all dose administrations in their eDiary.

Background antihyperglycemic medications

Eligible participants, except for those who have not been treated with any OAMs for at least 90 days before Visit 1, should be taking therapeutic doses of any of the following OAMs during the 90 days before Visit 1 and have been maintained on the same dose for at least 8 weeks before Visit 1 (OAM minimum maintenance doses are provided in the table in Section 10.8):

- SUs
- biguanides
- SGLT-2i's
- a-GIs
- TZD
- Glinides

***Note:** SUs, biguanides, and SGLT-2i's must have been used alone. a-GI, TZD, and glinides can be taken alone or in combination with metformin, with the upper limit of metformin combination participants being 50% for each OAM class.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

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 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. For at-home administration, sponsor will provide storage instructions.

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 IP Instructions for Handling.

6.3. Assignment to Study Intervention

Method of treatment assignment

This is an open-label study. Participants who meet all criteria for enrollment will be randomly assigned to study intervention using an IWRS.

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

Randomization ratios and stratification factors

Participants will be randomized in a 1:1:1 ratio to receive a daily dose of LY3502970 3 mg, 12 mg, or 36 mg.

Participants will be stratified based on:

- background therapy (diet and exercise alone, SU, biguanide, SGLT-2i's, a-GI, TZD, or glinide)
- HbA1c (≤8.5%, >8.5% [≤69 mmol/mol, >69 mmol/mol]) at Visit 1, and
- metformin use (Yes or No). (will be adopted for a-GI, TZD, or glinide groups)

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned capsules, and reviewing the eDiary, and will be documented in the source documents and CRF.

Participants will be instructed to return any unused LY3502970 capsules at the times specified in the SoA (Section 1.3).

Treatment compliance for each visit interval is defined as taking at least 75% of the required doses of study intervention. Similarly, a participant will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of study intervention (more than 125%).

In addition to the assessment of a participant's compliance with study intervention administration, other aspects of compliance with the study will be assessed at each visit based on the participant's adherence to the visit schedule, compliance with the concomitant antihyperglycemic medication regimen, completion of study eDiaries, the results of home BG monitoring, and any other parameters the investigator considers necessary.

Participants considered to be poorly compliant with their study intervention and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol.

A record of the number of LY3502970 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 study intervention interruption or dose reductions will also be recorded in the CRF.

6.6. Dose Modification

6.6.1. LY3502970

The dose escalation period of the study occurs over the first 20 weeks to allow escalation to the maximum dose of 36 mg for those randomized to this treatment arm. All participants will undergo each dose escalation step regardless of randomized treatment assignment. During the dose escalation period, the investigator should make every effort to proceed through each dose escalation step per the study schedule in order for participants to achieve their randomized dose. Participants should continue on this dose for the duration of the treatment period.

Study intervention dose reduction during the entire course of the study is only permitted for management of intolerable GI symptoms (see Section 6.6.1.1).

6.6.1.1. Management of Gastrointestinal Symptoms

For participants who report intolerable GI symptoms during the treatment period, the investigator should implement the following steps:

1. Advise participants to eat smaller meals, for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full.
2. Continue Step #1, and prescribe symptomatic medication, for example, antiemetic or antidiarrheal medication, per individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the CRF.
3. Continue Steps #1 and #2 and consider temporarily interrupting LY3502970: omit 1 dose or a maximum of 2 consecutive doses. Refer to Section 7.1.3 for information on temporary study intervention interruption.
   After the interruption, the investigator should advise the participant to resume LY3502970 at the same dose, with the participant taking medication to alleviate their GI symptoms.

If GI symptoms become tolerable or resolve with the above measures, the participant should continue study intervention at the same dose level until the next scheduled dose escalation step (if during the dose escalation) or continue for the duration of the treatment period, if the participant has completed the final dose escalation step.

Dose de-escalation

If intolerable GI symptoms persist despite Steps #1 through #3, then the following guidance should be followed:

If a participant is currently taking…	then…
1 mg or 3 mg	permanently stop study intervention and have the participant remain in the study.
6 mg or 12 mg	reduce the dose to 3 mg.
24 mg or 36 mg	reduce the dose to 12 mg.

If de-escalation of the LY3502970 dose is necessary, the investigator will use the IWRS to receive the appropriate LY3502970 dispensing information. If de-escalation is needed between scheduled visits, the IWRS will have unscheduled visits (eg, Visit 5a) dedicated to providing dispensing information for participants whose dose has been de-escalated. Those participants who have their doses de-escalated, should continue study intervention at the same dose level for the duration of the treatment period, and the dose should not be escalated again. The dose can be de-escalated only once. After that, participants will have to discontinue LY3502970 if intolerable GI AEs persist.

All participants who discontinue study intervention should continue to attend scheduled study visits. Initiation of another antihyperglycemic medication should be considered (see Section 7.1.1).

6.6.1.2. Temporary Dose Interruptions Unrelated to GI Tolerability

All efforts should be made to keep participants on study intervention at the assigned dose throughout the study. However, the investigator may need to temporarily interrupt study intervention during the treatment period; for example, due to an AE unrelated to GI tolerability, a clinically significant laboratory value, or due to participant's personal circumstances (travel, hospitalizations, or planned or unplanned procedures).

Every effort should be made by the investigator to restart study intervention after any temporary interruption as soon as it is safe to do so. Guidance on continuing or resuming the study intervention after temporary interruption is provided in the table below. Distribution of study intervention at the correct dose will be per IWRS instructions.

If participant misses…	…when...	then…
Any number of doses	up to first 7 weeks of study treatment	continue assigned study intervention per protocol
<3 consecutive doses	any time during the treatment period	continue assigned study intervention per protocol
3 to 6 consecutive doses	after first 7 weeks of study treatment and prior to 24 weeks of study treatment	continue assigned study intervention per protocol OR at investigator's discretion (based on tolerability of prior doses, GI AEs, etc.), restart study intervention at 3 mg and re-escalate to the assigned maintenance dose
3 to 6 consecutive doses	after 24 weeks of study treatment	continue assigned study intervention per protocol
≥7 consecutive doses	after first 7 weeks of study treatment	restart study intervention at 3 mg and re-escalate to the assigned maintenance dose

If the interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 8.3.

6.6.2. Concomitant Background Antihyperglycemic Medication

Throughout the study, the investigator should maintain participants on stable doses of their OAMs. However, only if a participant requires an adjustment of the dosage of their OAM due to safety concerns (for example, occurrence of hypoglycemia, decreased eGFR and so on) the dose of OAMs may be adjusted by the investigator's decision.

In this case, the reason and details of the dose adjustment will be recorded on source documents and the details will be captured on the concomitant medication CRF.

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

LY3502970 will not be made available to participants after conclusion of the study.

6.8. Treatment of Overdose

Any dose of LY3502970 greater than 100 mg within a 24-hour time period will be considered a potential overdose and should be reported per criteria described in Section 10.3.1.

In the event of an overdose, the investigator should:

- Initiate supportive treatment according to the participant's clinical signs and symptoms.
- Contact the medical monitor immediately.

- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate until, for example, LY3502970 no longer has a clinical effect or can no longer be detected systemically based on estimated half-life (at least 7 days).

6.9. Prior and Concomitant Therapy

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

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

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

Drugs that may be affected by an increase in gastric pH should be separated from study intervention administration by at least 2 to 4 hours. Examples (not exhaustive) relevant to the study population include:

- simvastatin, levothyroxine, ferrous sulfate, bisphosphonates;
- other narrow therapeutic index substrates with potential pH-dependent solubility or stability (further examples provided in Section 10.9.2.1).

6.9.1. Prohibited or Restricted Use Medications

The following medications are prohibited throughout the study:

- Antihyperglycemic medications other than the study intervention and concomitant background OAM, except for those participants who require
  - permanent discontinuation of the study intervention (Section 7.1.1)
  - rescue therapy after randomization due to severe persistent hyperglycemia (Section 6.9.3), or
  - additional glycemic control during the safety follow-up period.

  Notes:

  - The following medications must not be included as a rescue intervention or otherwise used during the study: any other GLP-1 RA or other incretin-based therapies (for example, tirzepatide), pramlintide (amylin analogs), or DPP-4 inhibitors (Section 10.9.1.1).
  - Short-term insulin use for up to 14 days is allowed for certain clinical situations (for example, elective surgery, during hospitalization, hyperosmolar states) and

must be differentiated from insulin use as rescue therapy when reported in the CRF.

- Medications intended to promote weight loss, including prescribed, over-the-counter, or alternative remedies. Examples are provided in Section 10.9.1.2.
- Strong CYP3A inducers or inhibitors, drugs that are P-gp or BCRP substrates with a narrow therapeutic index, or strong inhibitors of OATPs. Participants using these medications may be eligible for the study if the excluded drug can be washed out and replaced with an alternative medication for at least 2 weeks prior to Visit 3. Examples of these classifications of medications are provided in Section 10.9.1.3.

Participants who have to initiate certain prohibited concomitant medications during this study will be discontinued from the study intervention (Section 7.1.1).

6.9.2. Prohibited Surgical Treatments or Procedures for Weight Management

Surgical treatments, endoscopic therapy, and/or device-based therapy for weight management are not permitted during the study.

6.9.3. Rescue Therapy for Severe, Persistent Hyperglycemia

Criteria for severe, persistent hyperglycemia

Investigators will be trained on how to apply decision criteria for the timing and method of intervention in participants who do not reach glycemic targets during the treatment period. Participants should continue administering assigned dose of study intervention. An additional therapeutic intervention should be considered in participants who are fully compliant with the assigned therapeutic regimen in the absence of any acute condition that raises BG, **AND** who meet any of the following criteria:

- Average BG from the once-weekly 4-point SMBG profile is
  - >270 mg/dL (15.0 mmol/L) over at least a consecutive 2-week period any time during the first 6 weeks post randomization

    OR
  - >240 mg/dL (13.3 mmol/L) over at least a consecutive 2-week period from 7 to 12 weeks post randomization

    OR
  - >200 mg/dL (11.1 mmol/L) over at least a consecutive 2-week period at any time beyond the first 12 weeks post randomization

    OR
- HbA1c ≥8.5% (69 mmol/mol) at or after Week 24

During the weeks when 7-point SMBG profiles are collected, the once-weekly 4-point SMBG values are included in the 7-point profiles.

Rescue medication

For participants who meet criteria for severe persistent hyperglycemia, the investigator will decide on an appropriate antihyperglycemic intervention (rescue therapy) that is not a prohibited medication listed in Sections 6.9.1 and 10.9. Investigators should follow Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020).

Initiation of insulin as the first rescue intervention for hyperglycemia should be reserved for

- participants with severe, persistent hyperglycemia with an average BG from the once-weekly 4-point SMBG profile ≥300 mg/dL (≥16.7 mmol/L) or
- participants with symptoms of hyperglycemia, if there is evidence of ongoing catabolism or in other clinical situations where the investigator believes more rapid glycemic control is warranted (ADA 2023).

Participants who receive rescue medicine for hyperglycemia management should also continue administering study intervention for the remaining period in the trial. Record the use of rescue medication as concomitant medication in the CRF.

If any new antihyperglycemic medication is initiated during the safety follow-up period, it will not be classified as rescue therapy.

6.9.4. Symptomatic Medication for Gastrointestinal Symptoms

The investigator may prescribe symptomatic medication for management of GI symptoms as needed during the study; for example, antiemetic or antidiarrheal medication (see Section 6.6.1.1). Record the use of symptomatic medication as concomitant medication in the CRF.

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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 Section 10.1.

7.1. Discontinuation of Study Intervention

7.1.1. Permanent Discontinuation from Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention and will remain in the study and follow procedures for all remaining study visits, as shown in the SoA (Section 1.3).

A participant must be permanently discontinued from study intervention if:

- the participant is diagnosed with acute or chronic pancreatitis, confirmed by adjudication. See Section 8.3.3.8.
- the participant is diagnosed with MTC and MEN2 syndrome
- the participant develops significant elevation of serum calcitonin. See Section 8.3.3.9.
- the participant is diagnosed with an active malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer [for example, Gleason 6 or lower])
- the participant is diagnosed with T1D
- in the opinion of the investigator, for safety reasons
- the participant has intolerable GI symptoms despite management as described in Section 6.6.1.1
- the participant initiates any other GLP-1 RA or other incretin-based therapies (for example, tirzepatide), pramlintide (amylin analogs), or DPP-4 inhibitors (see Section 10.9.1.1), if the participant will not or cannot discontinue the medication
- the participant develops any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken
- the participant interrupts concomitant OAM(s) for 14 or more consecutive days.

Study intervention may be discontinued if the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

Antihyperglycemic therapy after permanent discontinuation of study intervention

Following permanent discontinuation of study intervention for any reason, participants may require additional antihyperglycemic therapy to maintain glycemic control. Any approved antihyperglycemic therapy that is not a prohibited/restricted medication per Section 6.9.1 and is

not contraindicated for use in the participant may be prescribed in accordance with prescribing information.

The new antihyperglycemic intervention will be recorded on the concomitant medications CRF.

7.1.2. Hepatic Criteria for Study Intervention Interruption or Discontinuation

See Section 8.2.6.3 for hepatic criteria for study intervention interruption or discontinuation.

7.1.3. Temporary Interruption of Study Intervention

Refer to Sections 6.6.1.1, 6.6.1.2, 7.1.2, and 8.3.3.8 for information on temporary dose interruptions.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon. To minimize the amount of missing data and to enable assessment of study objectives as planned in the study protocol, every attempt will be made to keep participants in the study regardless of study intervention use.

Participants will be discontinued from the study if the participant becomes pregnant.

A participant may withdraw from the study

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee, for example, parents or legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or
- if enrolled in any other clinical study involving an investigational product or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an ED visit and safety follow-up, as shown in the SoA (Section 1.3). If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3).

Section 10.2 lists the laboratory tests that will be performed for this 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 (Section 1.3), 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.

See Section 3 for specific safety and efficacy endpoints.

8.1. Efficacy Assessments

The following efficacy measures will be collected at the times shown in the SoA (Section 1.3):

- HbA1c (measured through central laboratory; Section 10.2)
- FSG (measured through central laboratory; Section 10.2)
- Body weight (measuring method described in Section 10.10)
- BMI (derived using body weight in kilograms divided by the square of height in meters)
- Waist circumference (measuring method described in Section 10.10)
- 7-point SMBG (see Section 5.3.1)
- Lipid parameters (see Section 8.1.1)
- Hepatic parameters (see Section 8.1.2)
- Blood pressure (see Section 8.1.3) (measuring method described in Section 10.10)
- Markers of glucose metabolism and beta-cell function (see Section 8.1.4)
- Patient-reported outcomes (see Section 8.1.5)
- Body composition (measured by InBody770 at particular study sites; Section 8.1.6)

8.1.1. Lipid Parameters

Percent change from baseline in lipid parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, non-HDL cholesterol, and triglycerides) to Week 52 will be evaluated.

8.1.2. Hepatic Parameters

Percent change from baseline in ALT and AST to Week 52 and change from baseline in Fibroses-4 (Fib-4) index and fatty liver index (FLI) to Week 52 will be evaluated.

8.1.3. Blood pressure

Change from baseline in blood pressure (systolic and diastolic) to Week 52 will be evaluated.

8.1.4. Markers of glucose metabolism and beta-cell function

Change from baseline in markers of glucose metabolism and beta-cell function (fasting insulin, fasting C-peptide, C-peptide index, fasting glucagon, HOMA-IR, and HOMA-B) to Week 52 will be evaluated.

8.1.5. Patient-Reported Outcomes

The self-reported questionnaires will be translated into Japanese, linguistically validated, and administered according to the SoA (Section 1.3). At these visits, the questionnaires should be completed before the participant has discussed their medical condition or progress in the study with the investigator and/or site staff, if the participant is not adversely affected by their fasting condition.

8.1.5.1. Diabetes Treatment Satisfaction Questionnaire

The Diabetes Treatment Satisfaction Questionnaire will be assessed at baseline and Week 52. At baseline, the DTSQs will be used. At Week 52, the DTSQc will be used.

DTSQs

The DTSQs (Bradley and Lewis 1990; Bradley 1994) is an 8-item diabetes-specific patient-reported outcome instrument that assesses the overall treatment satisfaction and perceived frequency of hyperglycemia and hypoglycemia over the past few weeks, prior to the visit. It is appropriate for use in both T1D and T2D.

Each item is rated on a 7-point Likert scale. Items 1, 4 to 7, and 8 are rated from 0 to 6. These 6 items can be summed up to produce a treatment satisfaction score, with higher scores indicating greater satisfaction. Items 2 and 3 evaluate the perceived frequency of hyperglycemia and hypoglycemia and are rated from 0 (none of the time) to 6 (most of the time), with lower scores indicating better glycemic control.

DTSQc

The DTSQc (Bradley 1999) has the same 8 items as the status version but is reworded slightly to measure the change in treatment satisfaction rather than absolute treatment satisfaction.

Each item is scored on a 7-point scale ranging from -3 to +3. For most items (items 1, 4-7, and 8), higher scores indicate greater improvement in treatment satisfaction, lower scores indicate greater deterioration in treatment satisfaction, and a score of 0 represents no change. For item 2 (perceived frequency of hyperglycemia) and item 3 (perceived frequency of hypoglycemia), lower scores indicate better glycemic control.

8.1.5.2. EQ-5D-5L

The EQ-5D-5L (EuroQol Research Foundation 2019) is a standardized 5-item, self-administered instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L assesses 5 dimensions of health:

- mobility
- self-care
- usual activities
- pain/discomfort, and
- anxiety/depression.

Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled as "best imaginable health state" (100) and "worst imaginable health state" (0).

8.1.5.3. Eating Behavior Questionnaire

The Eating Behavior Questionnaire is 55-item patient-reported questionnaire that assesses eating behavior (JASSO 2022).

Each question within the questionnaire can be answered with one of the following four responses: 1. Not at all; 2. Sometimes yes; 3. Have a tendency; and 4. Absolutely yes.

8.1.6. Body Composition

Body composition will be measured at particular study sites.

Change from baseline in body composition (body weight, body fat mass, lean body mass) to Week 52 will be evaluated.

Total body water (L), protein (kg), minerals (kg), and body fat mass (kg) will be measured by InBody770 (Inbody Japan). The lean body mass (kg) will be calculated based on total body water, protein, and minerals. Body weight (kg) will be calculated based on total body water, protein, minerals, and body fat mass.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Complete physical examination

A complete physical examination will include, at a minimum, assessments of these systems:

- CV
- respiratory
- GI
- neurological

A complete physical examination excludes pelvic, rectal and breast examinations unless clinically indicated.

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

Additional assessments

Height, weight, waist circumference, and vital signs will also be measured and recorded. See Section 10.10 for further details on physical examinations.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted in triplicate according to the SoA (Section 1.3) and following the study-specific recommendations included in Section 10.10.

Any clinically significant findings from vital signs measurement that result in a diagnosis and occur during the study should be reported to the sponsor as an AE via CRF.

8.2.3. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the SoA (Section 1.3) using centrally provided ECG equipment. Participants should be supine for approximately 5 to 10 minutes before ECG collections and remain supine but awake during the ECG collection. The recording of each ECG should occur at approximately 1-minute intervals. The collection of all replicates at a time point should not exceed 5 minutes. Collect ECG before blood samples for laboratory testing.

ECGs 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 for immediate participant management, should any clinically relevant findings be identified. Any clinically relevant findings from ECGs that result in a diagnosis should be reported as an AE via CRF.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be overread by a cardiologist at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements. The machine-read ECG intervals and heart rate may be used for data analysis and report-writing purposes, unless a cardiologist overreading of the ECGs is conducted prior to completion of the final study report (in which case, the overread data would be used).

The investigator, or qualified designee, must document their review of the ECG printed at the time of evaluation and any alert reports.

8.2.4. Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

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

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

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA (Section 1.3), standard collection requirements, and laboratory manual.

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

8.2.5. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA (Section 1.3).

Participants who become pregnant during the study should be permanently discontinued from the study (Section 7.2). Participants who become pregnant will complete procedures for an ED visit and safety follow-up, as shown in the SoA (Section 1.3).

Details of all pregnancies in participants and, if indicated, partners of participants will be collected as outlined in Sections 8.3.1 and 8.3.2.

8.2.6. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Intervention Interruption or Discontinuation

The following 2 tables summarize actions to take based on abnormal hepatic laboratory or clinical changes.

Summary of actions to take with participants with normal or near-normal baseline liver enzymes (ALT, AST, or ALP<1.5x ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring (see Section 8.2.6.1)	Initiate comprehensive evaluation (see Section 8.2.6.2)	Interrupt or discontinue study intervention (see Section 8.2.6.3)
ALT or AST ≥3x ULN	X		
ALP ≥2x ULN	X		
TBL ≥2x ULN[a]	X		
ALT or AST ≥5x ULN	X	X	
ALP ≥2.5x ULN	X	X	
ALT or AST ≥3x ULN with hepatic signs or symptoms[b]	X	X	X
ALT or AST ≥5x ULN for more than 2 weeks	X	X	X
ALT or AST ≥8x ULN	X	X	X
ALT or AST ≥3x ULN and TBL ≥2x ULN[a] or INR≥ 1.5	X	X	X
ALP ≥3x ULN	X	X	X
ALP ≥2.5x ULN and TBL ≥2x ULN[a]	X	X	X
ALP ≥2.5x ULN with hepatic signs or symptoms[b]	X	X	X

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

[a] In participants with Gilbert's syndrome the threshold for TBL may be higher.

[b] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

Summary of actions to take with participants with elevated baseline liver enzymes (ALT, AST, or ALP≥ 1.5x ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring (see Section 8.2.6.1)	Initiate comprehensive evaluation (see Section 8.2.6.2)	Interrupt or discontinue study intervention (see Section 8.2.6.3)
ALT or AST ≥2x baseline	X		
ALP ≥2x baseline	X		
TBL ≥2x ULN[a]	X		
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first)	X	X	
ALP ≥2.5x baseline	X	X	
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[b]	X	X	X
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST ≥4x baseline or ≥400 U/L (whichever occurs first)	X	X	X
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[a] or INR ≥1.5	X	X	X
ALP ≥3x baseline	X	X	X
ALP ≥2.5x baseline and TBL ≥2x ULN[a]	X	X	X
ALP ≥2.5x baseline with hepatic signs or symptoms[b]	X	X	X

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

[a] In participants with Gilbert's syndrome the threshold for TBL may be higher.

[b] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

8.2.6.1. Close Hepatic Monitoring

If a participant develops any one of these changes, initiate close hepatic monitoring:

Participants with normal or near-normal baseline liver enzymes (ALT, AST, or ALP<1.5x ULN)	**Participants with elevated baseline liver enzymes (ALT, AST, or ALP≥ 1.5x ULN)**
ALT or AST ≥3x ULN **or**	ALT or AST ≥2x baseline **or**
ALP ≥2x ULN **or**	ALP ≥2x baseline **or**
TBL ≥2x ULN[a]	TBL ≥2x ULN[a]

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

[a] In participants with Gilbert's syndrome the threshold for TBL may be higher.

Close hepatic monitoring should include these actions:

- Laboratory tests (Section 10.6) including ALT, AST, ALP, TBL, D. Bil, GGT, CK, and CBC with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2-3 times weekly until levels normalize or return to approximate baseline values.
- In addition to lab tests, basic 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
    - current symptoms
    - recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures)
    - recent travel
    - concomitant medications (including over-the-counter), herbal and dietary supplements
    - history of alcohol drinking, and
    - other substance abuse.

8.2.6.2. Comprehensive Hepatic Evaluation

If a participant develops any one of the following laboratory or clinical changes, initiate a comprehensive hepatic evaluation:

Participants with normal or near-normal baseline liver enzymes (ALT, AST, or ALP<1.5x ULN)	**Participants with elevated baseline liver enzymes (ALT, AST, or ALP≥ 1.5x ULN)**
ALT or AST ≥5x ULN **or**	ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) **or**
ALP ≥2.5x ULN **or**	ALP ≥2.5x baseline **or**
ALT or AST ≥3x ULN with hepatic signs or symptoms[a] **or**	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR≥ 1.5	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[b] or INR≥ 1.5

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

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] In participants with Gilbert's syndrome the threshold for TBL may be higher.

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include
  - physical examination and a thorough medical history, as outlined in Sections 1.3 and 8.2.1
  - tests for
    - PT-INR
    - viral hepatitis A, B, C, and E, and
    - 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, and additional tests including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

- Clinical and laboratory monitoring should continue at a frequency of 1-3 times weekly until levels normalize or return to approximate baseline values.
- All the medical information and tests results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.6.3. Study Intervention Interruption or Discontinuation

If a participant develops any one of the following laboratory or clinical changes, interrupt the study-intervention and continue close monitoring and comprehensive hepatic evaluation as described in Sections 8.2.6.1 and 8.2.6.2.

Participants with normal or near-normal baseline liver enzymes (ALT, AST, or ALP<1.5x ULN)	**Participants with elevated baseline liver enzymes (ALT, AST, or ALP≥ 1.5x ULN)**
ALT or AST ≥3x ULN with hepatic signs or symptoms[a] **or**	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST ≥5x ULN for more than 2 weeks **or**	ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks **or**
ALT or AST ≥8x ULN **or**	ALT or AST ≥4x baseline or ≥400 U/L (whichever occurs first) **or**
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR≥ 1.5 **or**	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[b] or INR≥1.5 **or**
ALP ≥3x ULN **or**	ALP ≥3x baseline **or**
ALP ≥2.5x ULN and TBL ≥2x ULN[b] **or**	ALP ≥2.5x baseline and TBL ≥2x ULN[b] **or**
ALP ≥2.5x ULN with hepatic signs or symptoms[a]	ALP ≥2.5x baseline with hepatic signs or symptoms[a]

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

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] In participants with Gilbert's syndrome the threshold for TBL may be higher

Interruption or discontinuation of study intervention should include these actions:

- While the participant is not receiving the study intervention, clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until liver tests normalize or return to approximate baseline values.
- If the hepatic event continues past the anticipated end of the study (that is, data lock) the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study (that is, data lock date).
- All the medical information and tests results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

- Resumption of the study intervention after interruption for a hepatic reason can be considered only in consultation with the Lilly designated medical monitor and only if the liver test results returned to near baseline and if a self-limited non-study-drug etiology is identified. Otherwise, the study intervention should be permanently discontinued.

8.2.7. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2. Laboratory results are provided to the sponsor via the central laboratory.

8.2.8. Diabetic Retinopathy Screening and Evaluation

Baseline fundus photography should be performed on participants who remain eligible based on screening activities performed at Visit 1 (including laboratory results). The overall ophthalmological evaluation of the baseline fundus photographs must be completed prior to randomization to confirm eligibility. Participants with any degree of diabetic retinopathy or macular edema on the baseline assessment that warrants treatment based on the clinical judgement of the ophthalmologist will be excluded (see Exclusion Criterion #13).

All participants will have follow-up fundus photography performed according to the SoA (Section 1.3). Only participants with any degree of retinopathy or macular edema present at baseline will repeat the fundus photography at Week 24 (±4 weeks), and all participants will repeat the fundus photography at Week 52 (-4 weeks), that is, within the 4 weeks prior to Visit 13. Fundus photography may be performed more frequently if warranted based on the severity of retinopathy or macular edema at baseline or during the study consistent with screening guidelines for diabetic retinopathy (Solomon et al. 2017; Flaxel et al. 2020).

Fundus photography should be performed in both eyes (unless precluded due to severe cataract, prosthesis, or other conditions) using the broadest field of view available to the site or associated qualified eye care professional, including 7-standard views, 4-wide field views, or at a minimum 2-field views with at least 60-degree field of view. Photographs may be performed at the study site if equipment and staff trained in collecting the required views are available; otherwise, they should be referred to an ophthalmologist or other suitable qualified health care provider.

All fundus photographs will be evaluated by an ophthalmologist or other qualified health care provider experienced in the assessment of diabetic retinopathy and macular edema. The evaluation will include whether diabetic retinopathy and/or macular edema are present and whether treatment is recommended. Fundus photographs deemed unevaluable for any reason will be repeated as recommended by the ophthalmological evaluator. Whenever possible, the same qualified evaluator should review all photographs for an individual participant throughout the

study. Any evidence of diabetic retinopathy, macular edema, or other clinically significant findings on the fundus photographs will require additional ophthalmological follow-up per standards of care. The use of optical coherence tomography should be encouraged to confirm cases of macular edema.

Results from the overall ophthalmological evaluation, including final diagnoses of nonproliferative retinopathy, proliferative retinopathy, or diabetic macular edema, will be provided to the investigator, and recorded on a specific retinopathy CRF. Any interventions initiated for diabetic retinopathy or macular edema during the study will be captured on the concomitant medication CRF.

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

The definitions of the following events can be found in Section 10.3:

- AEs
- SAEs, and
- 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 intervention or study (see Section 6.9.1).

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 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 or causality. Further information on follow-up procedures is provided in 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					

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE[a] – 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 participants and partners of participants	After the start of study intervention	At least 30 days after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A

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	

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

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

8.3.2. Collection of Pregnancy Information

Participants with partners who become pregnant

When to collect pregnancy information

In most circumstances, the investigator will attempt to collect pregnancy information from a participant's partner who becomes pregnant while the participant is in this study.

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

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

The 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.

When not to collect pregnancy information

It is not necessary to collect information about a pregnancy in the partner of a study participant in these circumstances

- the partner of the study participant was not exposed to the study intervention, or
- the participant did not contribute the sperm or ova that resulted in the pregnancy.

Participants who become pregnant

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

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

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

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

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

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

8.3.3. Adverse Events of Special Interest

The following event categories are AEs of special interest for this program:

- major adverse cardiovascular events (see Section 8.3.3.1)
- arrhythmias and cardiac conduction disorders (see Section 8.3.3.2)
- hypotension, orthostatic hypotension, and syncope (see Section 8.3.3.3)
- hypoglycemia (see Section 8.3.3.4)
- severe persistent hyperglycemia (see Section 8.3.3.5)
- severe gastrointestinal adverse events (see Section 8.3.3.6)
- acute renal events (see Section 8.3.3.7)
- pancreatitis (see Section 8.3.3.8)
- thyroid malignancies and C-cell hyperplasia (see Section 8.3.3.9)
- diabetic retinopathy complications (see Section 8.3.3.10)
- malignancies (see Section 8.3.3.11)

- hepatic disorders (see Section 8.3.3.12)
- gallbladder and biliary tract disorders (see Section 8.3.3.13)
- hypersensitivity reactions (see Section 8.3.3.14)
- abuse potential (see Section 8.3.3.15)

8.3.3.1. Major Adverse Cardiovascular Events

Nonfatal CV AEs and all deaths will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment. The nonfatal CV AEs to be adjudicated include:

- myocardial infarction
- hospitalization for unstable angina
- hospitalization for heart failure
- coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention), and
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

The investigator must first report these events as an AE as described in Section 8.3.1 and then report them as an endpoint on the CRF with all required source documents provided for adjudication to the CEC (see Section 10.1.5).

8.3.3.2. Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac arrhythmias and conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG, which should be submitted to the central ECG laboratory. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 10.3.2 must be reported as SAEs.

8.3.3.3. Hypotension, Orthostatic Hypotension, and Syncope

All events of hypotension or orthostatic hypotension and syncope should be evaluated, and additional diagnostic tests performed as needed.

8.3.3.4. Hypoglycemia

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia, and instructed to record relevant information for each episode of hypoglycemia in the study eDiary.

Participants will record information on episodes of hypoglycemia starting from Visit 2 until the last study visit.

All hypoglycemic episodes will be recorded in the study eDiary. Because all hypoglycemic episodes will be recorded in the study eDiary, they should not be recorded on the AE CRF unless the event meets criteria of severe hypoglycemia which should then be recorded as serious on the AE CRF and reported to the sponsor as an SAE.

To avoid duplicate reporting, all consecutive BG values <70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

If a participant experiences hypoglycemia as described above, to confirm the increased risk, the study sites must ensure that the participant has been fully compliant with the assigned therapeutic regimen and that there is no evidence of other possible causes of hypoglycemia (for example, omission of meal, unexpected increase in exercise).

Participants who develop persistent or recurrent unexplained hypoglycemia during the treatment period will be asked to reduce the dose of any concomitant antihyperglycemic agents. Study intervention discontinuation for recurrent hypoglycemia should be considered only if concomitant antihyperglycemic agents is discontinued (see Section 7.1.1). Further details of modifications of concomitant antihyperglycemic medications for management of hypoglycemia is described in Section 6.6.2.

Hypoglycemia definitions and categories

Investigators should use the following classification of hypoglycemia. The plasma glucose values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips.

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

Level 1 hypoglycemia can alert the participant 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

Level 3 hypoglycemia is 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 the sponsor as an SAE.

Nocturnal hypoglycemia

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

8.3.3.5. Severe Persistent Hyperglycemia

Criteria for severe, persistent hyperglycemia are provided in Section 6.9.3.

Occurrences of severe, persistent hyperglycemia that meet these criteria for rescue therapy should be reported as an AE on the CRF.

8.3.3.6. Severe Gastrointestinal Adverse Events

LY3502970 may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs, as well as antiemetic or antidiarrheal use, will be collected in the AE and concomitant medications CRFs, respectively. For detailed information concerning the management of GI AEs, please refer to Sections 6.6.1.1 and 6.9.4.

8.3.3.7. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute renal failure or worsening of preexisting chronic renal failure. GI AEs have been reported with LY3502970 including nausea, diarrhea, and vomiting. This is consistent with other GLP-1 RA (Aroda and Ratner 2011). The events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Participants should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

8.3.3.8. Pancreatitis

Diagnosis of acute pancreatitis

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

- abdominal pain, characteristic of acute pancreatitis (that is, epigastric pain radiating to the back, often associated with nausea and vomiting)
- serum amylase and/or lipase ≥3x ULN
- characteristic findings of acute pancreatitis on CT scan or 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

  Note: Abdominal ultrasound may be used as an alternative method only if CT and MRI cannot be performed.

  and

- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone or gall bladder disease, hypertriglyceridemia, and concomitant medications.

Discontinuation for acute pancreatitis

If acute pancreatitis is suspected by the investigator, the participant must temporarily discontinue use of the study intervention (Section 7.1.3). In this case, the participant may receive an appropriate alternative antihyperglycemic regimen. Afterwards, if pancreatitis is confirmed by the adjudication committee, the study intervention must be permanently discontinued (Section 7.1.1), and the participant should be followed throughout the duration of the study. If the case is not confirmed, then the participant can restart the study intervention if the investigator deems as clinically appropriate as described in Section 6.6.1.2.

Case adjudication and data entry

An independent CEC will adjudicate all suspected cases of acute pancreatitis. The investigator must first report these events as an AE as described in Section 8.3.1 and then report them as an endpoint on the CRF with all required source documents provided for adjudication to the CEC (see Section 10.1.5). Clinical event reporting begins after randomization.

Asymptomatic elevation of serum amylase and/or lipase

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

Cases of pancreatic hyperenzymemia with symptoms or asymptomatic cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up will be submitted for adjudication.

8.3.3.9. Thyroid Malignancies and C-Cell Hyperplasia

Participants who are diagnosed with MTC and/or MEN2 during the study will have study intervention stopped (Section 7.1.1) and should continue follow-up with an endocrinologist.

The assessment of thyroid safety during the trial will include reporting of any case of thyroid neoplasms (including MTC, papillary carcinoma, and others) and measurements of calcitonin. The purpose of calcitonin measurements is to assess the potential of LY3502970 to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Calcitonin measurements

A significant increase in calcitonin for participants is defined as post-randomization calcitonin value of ≥35 ng/L that has increased at least 50% over baseline.

If this increased calcitonin value is observed in a participant who has been administered a medication that is known to increase serum calcitonin, then this medication should be stopped, and calcitonin levels should be measured after an appropriate washout period of that concomitant medication (that is, 5 times the half-life).

Study intervention should be discontinued if the increased concentration of calcitonin is confirmed. The participant must be recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist to exclude AEs on the thyroid gland.

For participants who require additional endocrine assessment because of increased calcitonin concentration as defined in this section, data from the follow-up assessment will be collected in the specific section of the CRF.

8.3.3.10. Diabetic Retinopathy Complications

Diabetic retinopathy and macular edema will be monitored using retinal fundus photography and additional ophthalmological follow-up as warranted throughout the study (Section 8.2.8). Diabetic retinopathy will be assessed as nonproliferative (mild, moderate, or severe), proliferative, and diabetic macular edema as present or absent. All TEAEs of new or worsening diabetic retinopathy, macular edema, and other related complications will also be assessed.

8.3.3.11. Malignancies

All events of malignancy or other suspected events related to malignancy should be evaluated and additional diagnostic tests performed as needed.

8.3.3.12. Hepatic Disorders

All events of hepatic disorders or other suspected events related to hepatic disorders should be evaluated and additional diagnostic tests performed as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.2.6.

8.3.3.13. Gallbladder and Biliary Tract Disorders

All events of treatment-emergent biliary colic, cholecystitis, cholelithiasis or other suspected events related to acute gallbladder disease should be evaluated and additional diagnostic tests performed, as needed.

8.3.3.14. Hypersensitivity Reactions

Refer to Section 8.2.7.

8.3.3.15. Abuse Potential

All events of abuse potential should be evaluated, and additional investigations performed as needed.

8.4. Pharmacokinetics

PK is not evaluated in this study.

8.5. Pharmacodynamics

Efficacy measures will be used as indicators of PD response.

8.6. Genetics

A whole blood sample will be collected from participants to enable DNA isolation for exploratory pharmacogenetics analysis as specified in the SoA (Section 1.3).

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future.

Samples may be used to investigate variable exposure or response to LY3502970 and to investigate genetic variants thought to play a role in obesity, diabetes mellitus, and related clinical traits or complications, including nonalcoholic steatohepatitis. Assessment of variable response may include evaluation of AEs or differences in PD, mechanistic, safety, or efficacy measures.

See Section 10.5 for information regarding genetic research and Section 10.1.12 for details about sample retention and custody.

8.7. Biomarkers

Plasma and serum samples will be collected to enable exploratory nonpharmacogenetic biomarker research.

Biomarker research is performed on stored samples to address questions of relevance to:

- drug disposition
- target engagement
- PD
- mechanism of action
- variability of participant response, including safety, and
- clinical outcomes.

Samples may be used for research on:

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

Samples will be collected according to the schedule described in the SoA (Section 1.3).

Sample retention is described in Section 10.1.12.

8.8. Immunogenicity Assessments

Immunogenicity parameters are not evaluated in this study.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

The first version of the SAP will be approved 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

No formal hypothesis testing is planned for this study.

9.1.1. Multiplicity Adjustment

No multiplicity adjustments will be made because no formal hypothesis testing is planned.

9.2. Analyses Sets

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

Participant Analysis Set	**Description**
Entered participants	All participants who sign informed consent.
Randomized participants	All participants who are randomly assigned a study intervention.
Safety participants	All participants who are randomly assigned a study intervention and who take at least 1 dose of study intervention.

The following data point sets are defined:

Data Points Sets	Description
Safety data points set	All data points obtained during the treatment period and the follow-up period defined as at or after baseline and up to the date of study withdrawal including the follow-up period, regardless of study intervention discontinuation or initiation of additional antihyperglycemic medications.[a]
Treatment regimen estimand data points set	All data points obtained during the treatment period defined as at or after baseline and up to the last visit within the treatment period, regardless of study intervention discontinuation or initiation of additional antihyperglycemic medications.[a]
Efficacy estimand data points set	All data points obtained during the treatment period defined as at or after baseline and up to the earliest date of discontinuation of study intervention or initiation of additional antihyperglycemic medications.[a]

[a] "Additional antihyperglycemic medications" refers to any antihyperglycemic therapy that is initiated after baseline and used for more than 2 weeks (14 days).

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis will be the responsibility of Lilly or its designee.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or the CSR. Additional exploratory analyses of data will be conducted, as deemed appropriate.

Baseline is defined as the last available non-missing measurement prior to the first dose of study intervention, unless otherwise specified.

General descriptions of analyses

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the CI will be calculated at 95%, 2-sided. In statistical summaries and analyses, participants will be analyzed as randomized.

The safety assessments will be guided by an estimand comparing safety of LY3502970 arms, irrespective of adherence to study intervention or initiation of additional antihyperglycemic medications. Thus, safety analyses will be conducted using the safety participants and the safety data point set. A selected safety analyses (e.g., hypoglycemia) will be conducted after excluding data while on additional therapy or data after starting another permitted glycemic medication following permanent discontinuation of study intervention.

The efficacy assessment, guided by the "treatment regimen" estimand will be evaluated using the randomized participants and the treatment regimen estimand data points set. The efficacy

assessment, guided by the "efficacy" estimand will be evaluated using the randomized participants and the efficacy estimand data points set.

Summary statistics will be presented by LY3502970 arms in overall population and each background therapy. Summary statistics for continuous and discrete count measures will include sample size, mean, SD, median, minimum, and maximum. The Kaplan-Meier method will be used for estimation of cumulative event-free survival rates over time for each treatment. Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Fisher's exact test or Chi-Squared test will be used to examine the treatment difference in categorical outcomes. Dose response relationship will be assessed if appropriate.

The analysis model for continuous measures assessed over time will be a MMRM, with fixed effects of visit, and treatment, stratification factors, and baseline measurement all nested within visits. An unstructured covariance structure will model the relationship of within-patient errors. The analysis model for single time point measures will be a ANCOVA model with adjustment for baseline and stratification factors.

For efficacy and safety analyses, the overall population and each background therapy analysis will be conducted separately, using the same statistical model. When MMRM/ANCOVA is used for each background therapy, background therapy will be excluded from the model.

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

Other statistical methods may be used, as appropriate, and details will be described in the SAP.

9.3.2. Treatment Group Comparability

9.3.2.1. Participant Disposition

A detailed description of participant disposition will be provided.

Frequency counts and percentages of all randomized participants will be presented by treatment groups. A listing of randomized participants not receiving study intervention will be provided. All participants who discontinue the study will be identified and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized by treatment groups. Kaplan-Meier analyses of time from baseline to premature discontinuation from study and premature discontinuation from study intervention by treatment group will be provided.

9.3.2.2. Participant Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for all randomized participants.

9.3.2.3. Concomitant Therapy

Concomitant medications, including previous therapy, will be summarized by treatment group for the randomized participants during treatment period.

9.3.2.4. Treatment Compliance

Treatment compliance is defined as taking at least 75% and no more than 125% of required study intervention during the treatment period. Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment group using the safety participants during the treatment period.

9.3.3. Primary Endpoint and Estimand Analysis

The primary endpoint is incidence of TEAEs and will be evaluated using the safety participants and the safety data points set (Section 9.2). The safety analysis detail can be found in Section 9.3.6. Additional details will be provided in the SAP.

9.3.4. Secondary Endpoints and Estimands Analyses

The secondary safety endpoints will be evaluated using the safety participants and the safety data points set (Section 9.2). The secondary efficacy endpoints will be evaluated using the randomized participants and the treatment regimen estimand data points set, and/or the randomized participants and the efficacy estimand data points set (Section 9.2). Continuous variables will be analyzed by MMRM/ANCOVA models as described in Section 9.3.1. Details for secondary endpoints analyses will be provided in the SAP.

9.3.5. Exploratory Endpoints and Estimands Analyses

Details for exploratory endpoints analyses will be provided in the SAP.

9.3.6. Safety Analyses

Safety analyses will be conducted using the safety participants and the safety data points set, unless otherwise specified.

AEs will be coded from the actual term using the Medical Dictionary for Regulatory Activities and reported by preferred terms within system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized Medical Dictionary for Regulatory Activities Queries. Summary statistics will be provided for incidence of TEAEs, SAEs, study discontinuation due to AEs, study intervention discontinuation due to AEs, deaths, and other CV endpoints. Counts and percentages of participants experiencing AEs will be reported for each treatment group.

9.3.6.1. Adverse Events of Special Interest and Other Safety Topics

The analysis details for the AEs of special interest and other safety topics (as defined in Section 8.3.3) will be provided in the SAP.

9.3.6.2. Gastrointestinal Events

Summaries and analyses for incidence and severity of nausea, vomiting, constipation, and diarrhea will be provided by treatment.

9.3.6.3. Central Laboratory Measures, Vital Signs, and Electrocardiograms

Actual and change from baseline to postbaseline values of central laboratory measures, vital signs, and selected ECG parameters will be summarized at each scheduled visit. Continuous variables will be analyzed by MMRM models as described in Section 9.3.1. The percentages of participants with treatment-emergent abnormal, high, or low measures (including laboratory, vital, and ECG parameters) will be summarized.

9.3.7. Other Analyses

Subgroup analyses

Subgroup analyses will be made to assess consistency of the intervention effect of LY3502970 across the following subgroups:

- Age group (<65, ≥65 years)
- Sex (female, male)
- Baseline HbA1c (≤8.5%, >8.5%)
- Baseline BMI (<25 or ≥25 kg/m^2)
- Duration of T2D (≤median, >median)
- Beta-cell function such as c-peptide and CPI etc. (≤median, >median)
- Age and baseline BMI
  - <65 years and <25 kg/m^2
  - <65 years and ≥25 kg/m^2
  - ≥65 years and <25 kg/m^2
  - ≥65 years and ≥25 kg/m2

Additional subgroup analyses may also be performed.

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

Since the primary objective is to assess the safety of long-term treatment of LY3502970 and no formal hypothesis testing on the efficacy measures are planned, statistically derived power calculations were not considered for the determination of sample size. This sample size was decided based on the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1. 2010). By taking account for the overall drop-out rate of approximately 10%, 39 participants with diet and exercise alone and 60 participants for combination with each OAM (SUs, biguanides, SGLT-2i's, a-GIs, TZD, or glinides) are planned to be randomized; therefore, a total of 399 participants are planned to be randomized. Up to 50% of participants who are taking metformin in combination with a-GI, TZD, or glinides will be enrolled. The sponsor or designee will inform the study sites when the upper limit is approaching.

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 CIOMS International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

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

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

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

The investigator will be responsible for the following:

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

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

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

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

Potential participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.

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

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and ERB consenting guidance.

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

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

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

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

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

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the GDPR.

10.1.5. Committees Structure

10.1.5.1. Clinical Endpoint Committee

An independent CEC with membership external to the sponsor will be responsible for event adjudication in a blinded fashion.

10.1.6. Dissemination of Clinical Study Data

Reports

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

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

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data.

Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement.

Data and documents, including the study protocol, SAP, CSR, and blank or annotated CRFs, will be provided in a secure data-sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.7. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on printed or 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. This includes laboratory tests, medical records, and clinical notes.

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

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

Data monitoring and management

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 CSR.

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

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

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

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

Records retention and audits

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 CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, 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.

Electronic data capture system

An EDC system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided 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.

Clinical outcome assessments

The eCOA data (participant-focused outcome instrument) will be directly recorded by the participant, into an instrument (for example, handheld smart phone or tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data.

Data storage and access

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

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source data can be found in the site confirmation of source data.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

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

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

10.1.10. 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.

10.1.11. Investigator Information

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

10.1.12. Sample Retention

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

This table lists the maximum retention period for sample types. The retention period begins after the last participant’s last visit in this study.

Sample Type	Custodian	Maximum Retention Period After the Last Participant Visit[a]
Exploratory biomarkers	Sponsor or designee	Up to 15 years
PK samples	Sponsor or designee	1 year
Genetics/PD	Sponsor or designee	Up to 15 years

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

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

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

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

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

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

Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs)	
Absolutes count of	
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Clinical chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Lipid panel	
High density lipoprotein cholesterol (HDL-C)	Assayed by Lilly-designated laboratory.
Total cholesterol	Assayed by Lilly-designated laboratory.
Triglycerides	Assayed by Lilly-designated laboratory.

Clinical Laboratory Tests	Comments
Low-density lipoprotein cholesterol (LDL-C)	Calculated by Lilly-designated laboratory. If triglycerides are ≥400 mg/dL, the direct LDL-C will be assayed.
Very Low-density lipoprotein cholesterol (VLDL-C)	Calculated by Lilly-designated laboratory.
Non-High density lipoprotein cholesterol (non-HDL)	Calculated by Lilly-designated laboratory.
Hepatitis serology	Assayed by Lilly-designated laboratory.
Hepatitis C Virus (HCV) testing:	
HCV antibody	
HCV RNA	Performed only for participants who test positive for anti-HCV
Hepatitis B Virus (HBV) testing:	
HBV DNA	Performed only for participants who test positive for anti-HBc.
HBV core antibody (HBc-Ab)	
HBV surface antigen (HBsAg)	
HBV surface antibody (anti-HBs)	
Hormones (female)	Assayed by Lilly-designated laboratory unless stated otherwise.
Serum pregnancy	
Urine pregnancy	Evaluated locally
Follicle-stimulating hormone (FSH)	
Urine chemistry	Assayed by Lilly-designated laboratory.
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI)	CKD-EPI Cystatin-C equation (2012) Results will be used for eligibility criteria.
Urinary albumin/creatinine ratio (UACR)	
Other testing	Assayed by Lilly-designated laboratory.
HbA1c	
Calcitonin	
Pancreatic amylase	
Lipase	
Glucose	Serum
Glucagon	Results will not be provided to investigative sites.
Insulin	Results will not be provided to investigative sites.
C-peptide	Results will not be provided to investigative sites.

Clinical Laboratory Tests	Comments
Cystatin-C	Results will not be provided to investigative sites.
Genetics sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Whole blood (EDTA)	
Exploratory biomarker storage samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
Plasma (EDTA)	

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RBC = red blood cells; VLDL-C = very low-density lipoprotein cholesterol; WBC = white blood cells.

10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up pre-dose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess post-event return-to-baseline values.

Timing	Laboratory Test[a]
Collect from 30 minutes to 4 hours after the start of the event. Note: The optimal collection time is from 1 to 2 hours after the start of event.	Total tryptase

[a] All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

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

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital signs measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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 or disorder being studied or expected progression, signs, or symptoms of the disease or 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:

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

hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:

- deficiencies in labeling information, and
- use errors for device or drug-device combination products due to ergonomic design elements of the product.

PCs related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.

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

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

AE, SAE, and PC recording

When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.

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

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant

number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

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

Assessment of intensity

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

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

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

Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB in their assessment.

The investigator **must** review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.5. Reporting of SAEs

SAE reporting via an electronic data collection tool

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a SAE paper form (see next section) or to the sponsor by telephone.

Contacts for SAE reporting can be found on the SAE form.

SAE Reporting via Paper Form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found on the SAE form.

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 toward 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 evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Individuals assigned female at birth (AFAB)	Individuals assigned the female sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are potentially capable of gestating a fetus, and thus are capable of exposing an egg, embryo, or fetus to study drug or drug effects.
Individuals assigned male at birth (AMAB)	Individuals assigned the male sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are not capable of gestating a fetus, but are capable of exposing a fetus to study drug or drug effects via their semen. Individuals AMAB are considered to be not of reproductive potential if they have had orchiectomy (orchidectomy) with or without penectomy, confirmed by operative note.
Individuals of childbearing potential (IOCBP) [a]	Adult individuals AFAB are considered IOCBP unless they are INOCBP. Note: Adolescent or adult individuals AFAB who are receiving hormone therapy as part of gender transition are considered IOCBP unless they meet the conditions outlined below for INOCBP.
Individuals not of childbearing potential (INOCBP) [b]	Individuals AFAB are considered INOCBP if they are not capable of producing ova or embryo, and/or are not capable of potentially gestating a fetus. Such individuals include those who • have a congenital anomaly such as Müllerian agenesis, resulting in confirmed infertility • are infertile due to surgical sterilization, or • are menopausal. Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Menopausal state [c]	The menopausal state is defined as an individual: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[c], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, and with a follicle-stimulating hormone ≥40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy.

a IOCBP is inclusive of the concept of women of childbearing potential (WOCBP or WCBP), a term often used in literature and regulatory guidance documents.
b INOCBP is inclusive of the concept of women not of childbearing potential (WNOBCP).
c The individual **should not** be taking medications during amenorrhea such as oral contraceptives, hormone replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea. Individuals on HRT and those whose menopausal status cannot be confirmed will be required to comply with the protocol contraception requirements if they wish to continue HRT during the study. Otherwise they must discontinue HRT to allow confirmation of menopausal status before study enrollment.

10.4.2. Contraception Guidance

Individuals AFAB

IOCBP who are completely abstinent as their preferred and usual lifestyle, or exclusively engage in sexual relations with other individual(s) who are AFAB as their preferred and usual lifestyle must follow the rules in this table.

Must…	**Must not…**

agree to either remain abstinent or exclusively engage in sexual relations with other individual(s) who are AFAB, and not plan a pregnancy during the study	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

IOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or who do NOT exclusively engage in sexual relations with other individual(s) who are AFAB as their preferred and usual lifestyle must follow the rules in this table.

Must…
agree to use 2 methods of effective contraception, where at least 1 method must be highly effective. These methods of contraception must be used during the study and for at least 30 days after the last dose of the study intervention.

Examples of different methods of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the INOCBP definition above. • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injected contraceptives • contraceptive patch (only individuals <198 pounds or 90 kg) • total abstinence • sexual relationships exclusively between individuals who are assigned the same sex at birth • vasectomy – for individuals AMAB in clinical trials and for the partner of an individual AFAB (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • vaginal ring containing combination hormone medication, or • intrauterine devices
Effective contraception	• penile condom with spermicide • vaginal condom with spermicide • diaphragm with spermicide • cervical sponge with spermicide, or • cervical cap with spermicide Note: Penile and vaginal condoms should not be used in combination.
Ineffective methods of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

Individuals AMAB

Individuals AMAB may participate in this trial. For individuals AMAB, no contraception is required except in compliance with specific local government study requirements.

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10.5. Appendix 5: Genetics

Use/analysis of DNA

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

DNA samples will be used for research related to LY3502970 or diabetes, obesity, and related traits or complications, including nonalcoholic steatohepatitis and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3502970, study interventions related to this drug class, or diabetes, obesity, and related traits or complications, including nonalcoholic steatohepatitis and related diseases. Genetic research may consist of the analysis of one 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 related to this class to understand study disease or related conditions.

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

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

The samples will be retained while research on LY3502970 or diabetes, obesity, and related traits or complications, including nonalcoholic steatohepatitis and related diseases, continues but no longer than the sample retention limits described in Section 10.1.12, or other period as per local requirements.

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

Hepatic evaluation testing

See Section 8.2.6 for guidance on appropriate test selection.

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

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

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

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

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts[c]	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA[b]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (ethanol, EtOH)	HSV (Type 1 and 2) DNA[b]
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology Culture:**
Ethyl glucuronide (EtG)	Blood
Epstein-Barr virus (EBV) testing:	Urine
EBV antibody	
EBV DNA[b]	

[a] If lab does not offer total antibody testing, IgG and IgM are acceptable substitutes.

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

[c] Availability of acetaminophen protein adducts testing is limited, so testing may be performed at central labs, if needed.

10.7. Appendix 7: World Health Organization Classification of Diabetes and Diagnostic Criteria

Type 1 diabetes

T1D is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary not only to control hyperglycemia but also to prevent spontaneous ketosis and death.

Type 2 diabetes

T2D, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in T2D but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) due to an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with T2D later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998).

10.8. Appendix 8: Oral Antihyperglycemic Medication (OAM) Minimum Maintenance Dose

Eligible participants must have been taking SUs (glibenclamide, gliclazide, glimepiride), biguanides, or SGLT-2i's alone or a-GIs, TZD, or glinides alone or in combination with metformin for at least 90 days before Visit 1 and must have been maintained on the same dose for at least 8 weeks before Visit 1 and have an inadequate glycemic control. This minimum maintenance dose will also be applied to metformin which is taken as a combination therapy with a-GIs, TZD, or glinides.

This table lists the minimum maintenance dose of each OAM.

OAM	Generic Name	Minimum Maintenance Dose (mg/day)
SUs	glibenclamide	1.25
	gliclazide	40
	glimepiride	0.5
Biguanides	buformin	100
	metformin	750
SGLT-2i's	ipragliflozin	50
	dapagliflozin	5
	luseogliflozin	2.5
	tofogliflozin	20
	canagliflozin	100
	empagliflozin	10
a-GIs	acarbose	300
	voglibose	0.6
	miglitol	150
TZD	pioglitazone	15
Glinides	nateglinide	270
	mitiglinide	30
	repaglinide	0.75

Abbreviations; a-GIs = alpha-glucosidase inhibitors; SGLT-2i's = sodium glucose transporter 2 inhibitors; SUs = sulfonylureas; TZD = thiazolidinedione.

10.9. Appendix 9: Prohibited Medications or Medications with Special Use Restrictions, Including Fixed-Dose Combination Drug

10.9.1. Excluded/prohibited medications

Medications within the following categories are strictly prohibited during the study (Section 6.9.1). The lists below provide examples of each category of medication, but the examples are not exhaustive. As stated in Section 6.9.1, participants who have to initiate certain prohibited concomitant medications during this study will be discontinued from the study (Section 7.1.1).

10.9.1.1. Antihyperglycemic Medications

The following antihyperglycemic medications are prohibited within 90 days of Visit 1, or between Visit 1 and Visit 3, as we all as at any time during the study.

- DPP-4 inhibitors
- GLP-1 RAs
- tirzepatide

10.9.1.2. Weight Loss Medications

Weight loss medications are prohibited within 90 days of Visit 1, or between Visit 1 and Visit 3, as well as at any time during the study.

- Bofutsushosan (Chinese herbal medicine)
- Boiogito (Chinese herbal medicine)
- Daisaikoto (Chinese herbal medicine)
- mazindol
- orlistat
- semaglutide 2.4 mg (Wegovy®)

10.9.1.3. Strong CYP3A Inhibitors or Inducers, P-gp or BCRP Substrates with a Narrow Therapeutic Index, and Strong OATP Inhibitors

10.9.1.3.1. Strong CYP3A4 Inhibitors and Strong CYP3A inducers

- aminoglutethimide
- apalutamide
- atazanavir and cobicistat
- boceprevir
- carbamazepine (if daily dose exceeding 600 mg)
- ceritinib
- clarithromycin
- cobicistat
- conivaptan

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- danoprevir and ritonavir
- elvitegravir and ritonavir
- enzalutamide
- forsamprenavir and ritonavir
- grapefruit juice
- idelalisib
- indinavir and ritonavir
- itraconazol
- ivosidenib
- josamycin
- ketoconazole
- lonafarnib
- lopinavir and ritonavir
- lumacaftor
- mitotane
- nefazodone
- nelfinavir
- nirmatrelvir and ritonavir
- paritaprevir and ritonavir and ombitasvir and/or dasabuvir
- phenobarbital
- phenytoin and fosphenytoin
- posaconazole
- ribociclib
- rifabutin
- rifampin
- rifapentine
- ritonavir
- saquinavir and ritonavir
- St. John’s wort
- telithromycin
- tipranavir and ritonavir
- tucatinib, and
- voriconazole.

Note: To be eligible for screening into this study, participants taking ketoconazole, itraconazole, voriconazole, or posaconazole should discontinue taking these medications for at least 2 weeks prior to screening. However, if the participant is unable to wash out these drugs, then if appropriate, the participant could switch to:

- miconazole
- clotrimazole, or
- fluconazole.

For participants taking clarithromycin or telithromycin, azithromycin may be substituted 2 weeks prior to beginning screening. Participants who chronically use these drugs should be excluded.

10.9.1.3.2. Strong OATP inhibitors

- rifampin
- cyclosporine
- faldaprevir
- tipranavir/ritonavir
- glecaprevir/pibrentasvir
- telaprevir
- sofosbuvir/velpatasvir/voxilaprevir
- lopinavir/ritonavir
- darunavir/ritonavir, and
- elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

10.9.1.3.3. Sensitive P-gp substrates where small increases in exposure may result in serious toxicity

- colchicine
- cyclosporine
- dabigatran etexilate
- digoxin
- everolimus
- pimozide
- quinidine
- quinine
- sirolimus, and
- tacrolimus.

10.9.1.3.4. Sensitive BCRP substrates where small increases in exposure may result in serious toxicity

- prazosin.

10.9.2. Medications with Special Use Restrictions

10.9.2.1. Drugs Affected by Increase in Gastric pH

Drugs that may be affected by an increase in gastric pH should be separated from study drug administration by at least 2 to 4 hours. Examples include:

- simvastatin
- levothyroxine
- ferrous sulfate
- bisphosphonates
- other narrow therapeutic index substrates with potential pH-dependent solubility or stability, and
- tyrosine kinase inhibitors
  - erlotinib
  - dasatinib
  - nilotinib
  - acalabrutinib
  - bosutinib
  - gefitinib
  - lapatinib, and
  - pazopanib
- antiretrovirals
  - rilpivirine
  - atazanavir
  - nelfinavir
  - ledipasvir/sofosbuvir
  - fosamprenavir
  - delavirdine mesylate
  - Emtricitabine+rilpivirine+tenofovir+ disoproxil fumarate (Complera®)
  - Ledipasvir+sofosbuvir (Harvoni®), and
  - raltegravir, sofosbuvir+velpatasvir (Epclusa®).

10.10. Appendix 10: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs

The following information has been adapted from standardized physical measurement protocols for the WHO's STEPS (WHO 2017).

Measuring height

Step 1. Ask the participant to remove their footwear and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the participant at every clinic visit when their height is measured).

Step 2. Ask the participant to stand on the calibrated height measuring board (stadiometer) or against a wall with their feet together and their knees straight with their heels against the backboard, the stadiometer, or the wall.

Step 3. Ask the participant to look straight ahead without tilting their head up.

Step 4. Ask the participant to breathe in and stand tall. Measure and record the participant's height in centimeters to 1 decimal place.

Measuring weight

- Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms to 1 decimal place.
- All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.

Step 1. Ask the participant to empty their pockets, remove their footwear, outerwear (coat, jacket, etc.), and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the participant at every clinic visit when weight is measured).

Step 2. Make sure the scale is placed on a firm, flat, even surface (not on carpet, on a sloping surface, or a rough, uneven surface).

Step 3. Ask the participant to step onto the scale with 1 foot on each side of the scale.

Step 4. Ask the participant to stand still with arms by sides and then record weight in kilograms to the nearest one-tenth kilogram.

Measuring waist circumference

- Waist circumference should be measured in the horizontal plane and at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.
- Measurements should be taken at the end of a normal expiration using a non-stretchable measuring tape. The tape should lie flat against the skin without compressing the soft tissue.

- The waist circumference should be measured twice, rounded to the nearest 0.5 cm. The measuring tape should be removed between the 2 measurements. Both measurements will be recorded in the CRF. If the difference between the 2 measurements exceeds 1 cm, this set of measurements should be discarded and the 2 measurements repeated.

Step 1: Ask the participant to wear little clothing (if available, garments could also be used).

Step 2: Ask the participant to stand with their feet close together, arms at their side, body weight evenly distributed.

Step 3: Ask the participant to relax and measure the participant's waist circumference.

Vital sign measurements

- Vital sign measurements (BP and HR, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing.
- The participant should sit quietly for 5 minutes before vital signs measurements are taken.
- For each parameter, 3 measurements will be taken using the same arm, preferably the nondominant arm.
- The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and BP needs to be recorded in the CRF.
- BP must be taken with an automated BP instrument.
- If BP and pulse measurements are taken separately, pulse should be taken prior to BP.

Note: In the event pulse measurement cannot be taken via an automated BP instrument, the preferred location for measurement of pulse is the radial artery.

10.11. Appendix 11: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Informed consent

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

- participation in remote visits, as defined in Section "Remote Visits,"
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

Telemedicine:

Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, collection of AEs, review SMBG values and concomitant medications.

Mobile healthcare or other alternative locations:

Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to, concomitant medications, vital signs (BP and PR), body weight, collection of blood samples, physical assessments, and collection of health information.

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: Visit 1, Visit 3, Visit 9, Visit 13, ED, and Visit 801. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

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

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies.

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These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit are valid for a maximum of 30 days.

The following rules will be applied for active, nonrandomized participants whose participation in the study must be interrupted due to exceptional circumstances:

- If screening is interrupted for less than 30 days from Visit 1 to randomization visit: the participant will proceed to the next study visit per the usual SoA (Section 1.3), provided that randomization visit must be conducted within 30 days from Visit 1.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - The site should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is interrupted for more than 30 days from screening visits to randomization visit: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA (Section 1.3) should be followed, starting at screening visit to ensure participant eligibility by randomization visit.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA (Section 1.3). To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 1 through 3	≤30 days from Visit 1 to Visit 3
Visit 4 through 9	within 6 days before or after the intended date per the SoA
Visit 10 through 13	within 12 days before or after the intended date per the SoA
Visit 801	up to 28 days after the intended date

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.12. Appendix 12: Abbreviations and Definitions

Term	Definition
AEs	Adverse events
a-GIs	Alpha glucosidase inhibitors
Abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
CBC	Complete blood count
CEC	Clinical endpoint committee
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CFR	Code of Federal Regulations
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.
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CSR	Clinical study report

Term	Definition
CT	Computerized tomography
CTA	Clinical Trial Agreement
CV	Cardiovascular
CYP3A	Cytochrome P4503A
D. Bil	Direct bilirubin
DF	Disoproxil fumarate
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl peptidase-4
DTSQc	Diabetes Treatment Satisfaction Questionnaire-Change Version
DTSQs	Diabetes Treatment Satisfaction Questionnaire-Status Version
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
ED	Early discontinuation
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
Enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethics Review Board
EU	European Union
FSG	Fasting serum glucose
GDPR	General Data Protection Regulation
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1

Term	Definition
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycated hemoglobin
HBV	Hepatitis B virus
HDL	High density lipoprotein
HOMAR-B	Homeostasis model assessment of beta cell function
HOMAR-IR	Homeostasis model assessment of insulin resistance
HR	Heart rate
IB	Investigator's Brochure
ICEs	Intercurrent events
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
Informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INOCBP	individuals not of childbearing potential
Interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IOCBP	individuals of childbearing potential
IRB	Institutional Review Board
IWRS	Interactive web-response system
MEN2	Multiple endocrine neoplasia type 2

Term	Definition
Medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
Misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer
OAMs	Oral anti-hyperglycemic medications
OATP	Organic anion transporting polypeptide
P-gp	P-glycoprotein
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
PK/PD	Pharmacokinetics/pharmacodynamics
PR	Pulse rate
PT-INR	Prothrombin-international normalized ratio
QD	Once daily
QTLs	Quality tolerance limits
RNA	Ribonucleic acid
SAE	Serious adverse event

Term	Definition
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.
SD	Standard deviation
SMBG	Self-monitored blood glucose
SoA	Schedule of activities
SGLT-2i's	Sodium glucose co-transporter 2 inhibitors
STEPS	STEPwise approach to surveillance
SUs	Sulfonylureas
SUSARs	Suspected unexpected serious adverse reactions
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TZD	Thiazolidinediones
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
VLDL	Very low density lipoprotein
WHO	World Health Organization
WOCBP	Women of child-bearing potential
WNOCBP	Women not of child-bearing potential

10.13. Appendix 13: Protocol Amendment History

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

Amendment [a]: (8-Sep-2023)

Overall Rationale for the Amendment:

The primary rationale for this amendment is to

- remove "full participants" and replaced with "randomized participants" in statistical considerations as part of analysis sets
- increase monitoring frequency for clinical chemistry assessment, and
- update exclusion criteria and prohibited medication for potential drug-drug interactions.

Minor editorial and formatting changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis (Objectives, Endpoints, and Estimands)	Table: added "Objectives" to the column title	Correction
1.1. Synopsis (Objectives, Endpoints, and Estimands) 3. Objectives, Endpoints, and Estimands	Secondary Efficacy Endpoints: moved "Proportion of participants who achieve HbA1c" and "Proportion of participants who achieve weight loss" under "At Week 52"	Correction
1.1. Synopsis (Overall Design) 4.1. Overall Design	First paragraph: revised to read "… who have inadequate glycemic control with <u>either</u> diet and exercise alone or who have been taking therapeutic doses of various OAMs; …"	Clarification
1.1. Synopsis (Number of Participants)	Second sentence: revised to read "… (60 participants each) <u>with inadequate glycemic control</u> will be enrolled in this study."	Correction
1.3. Schedule of Activities (SoA)	"Fasting visits" subsection: • "Visit 1 (screening)" revised to "Visit 1 (screening)<u>, Visit 2, and Visit 12</u>" • "Visits 4 through 13" revised to "Visits 4 through 13 <u>(except Visit 12)</u>"	Alignment with SoA

Section # and Name	Description of Change	Brief Rationale
	"Early discontinuation (ED)" subsection, first sentence: revised to read "Participants who are unable or unwilling to continue the study <u>treatment period</u> for any reason will perform an ED ~~of treatment~~ visit."	Clarification
	"Fundus photography and further ophthalmological assessment" row and footnotes "a" and "b": • Consolidated footnotes "a" and "b" with the SoA comment • Placed the revised comment horizontally	For ease of navigation
	"Diabetes education (includes BG meter and SMBG training)" row, at V9, replaced "F" with "X"	Correction
	"Clinical chemistry" row: • Added X's for Weeks 4, 8, 16, 20, and 32 • Added a comment regarding V801	To increase monitoring of clinical chemistry assessment
4.3. Justification for Dose	First paragraph: • deleted the mention of Phase 1 studies • added the rationale for selection of 36 mg QD as the highest dose in this study	Clarification
5.1. Inclusion Criteria (inclusion criterion #1)	Removed ", whichever is older"	Correction
5.2. Exclusion Criteria (exclusion criterion #18)	Note was revised to read "<u>For</u> ~~P~~<u>p</u>articipants taking biguanides and/or SGLT-2i, ~~may not have~~ an eGFR <45 mL/min/1.73 m^2 calculated as described above <u>is applied</u>."	Correction
5.2. Exclusion Criteria (exclusion criterion #27) 6.9.1. Prohibited or Restricted Use Medications	• Added "or BCRP"	To minimize potential drug-drug interaction risk to study participants

Section # and Name	Description of Change	Brief Rationale
10.9.1.3 Strong CYP3A Inhibitors or Inducers, P-gp or BCRP Substrates with a Narrow Therapeutic Index, and Strong OATP Inhibitors	• In Section 10.9.1.3, added examples of BCRP substrates with narrow therapeutic index	
5.3.2. Meals and Dietary Restrictions	Third sentence: modified to read "… in a fasting state, ~~after an overnight fast,~~ except for water, of at least 8 hours as specified in the SoA (Section 1.3)."	Flexibility and consistency
5.3.2. Meals and Dietary Restrictions 10.9.1.3 Strong CYP3A Inhibitors or Inducers, P-gp or BCRP Substrates with a Narrow Therapeutic Index, and Strong OATP Inhibitors	Added grapefruit, besides grapefruit juice, for patients to refrain from	Clarification
6.6.1.1 Management of Gastrointestinal Symptoms	Added "Step(s)" for #2 and #3 criteria	Clarification
6.6.1.2. Temporary Dose Interruptions Unrelated to GI Tolerability	Table, rows that mention 7 weeks of study treatment: added "first": ("up to <u>first</u> 7 weeks of study treatment" or "after <u>first</u> 7 weeks of study treatment")	Clarification
6.9.1. Prohibited or Restricted Use Medications	First bullet, revised to read "Antihyperglycemic medications other than the study intervention <u>and concomitant background OAM</u>, except for those participants who require"	Clarification
6.9.3. Rescue Therapy for Severe, Persistent Hyperglycemia (Rescue medication)	Second paragraph (initiation of insulin as the first rescue intervention for hyperglycemia): • re-structured as a bulleted list, and • in the second bullet, added "participants with symptoms of hyperglycemia, if there is evidence of ongoing catabolism or" and reference to ADA 2023	Clarification

Section # and Name	Description of Change	Brief Rationale
7.1.1. Permanent Discontinuation from Study Intervention	Last bullet, added "the participant interrupts concomitant OAM(s) for 14 or more consecutive days."	Clarification of the condition of OAM interruption
7.2. Participant Discontinuation/Withdrawal from the Study	• In the first paragraph, added an instruction sentence for minimizing the missing data • Discontinuation from the study for the participant who becomes pregnant was revised to mandatory	Clarification and correction
8.2.6.2. Comprehensive Hepatic Evaluation 8.2.6.3. Study Intervention Interruption or Discontinuation	Added minor revisions in these sections	Updated based on latest guidance
8.2.8. Diabetic Retinopathy Screening and Evaluation	Second paragraph, second sentence: revised to read "Only participants with any degree of retinopathy or macular edema present at baseline will repeat the fundus photography at Week 24 (±4 weeks), and …"	Correction
8.3.3.4. Hypoglycemia	Sixth paragraph: revised to read "… will be asked to reduce the dose ~~or discontinue~~ of any concomitant antihyperglycemic agents other than study intervention, if applicable. Study intervention discontinuation for recurrent hypoglycemia should be considered only if these events continue despite ~~complete discontinuation~~ the dose reduction of concomitant medications (see Section 7.1.1)."	Corrected for consistency with Section 6.6.2
9.2. Analyses Sets	First table: deleted "Full participants"	To protect the integrity of randomization
	Second table:	Clarification

Section # and Name	Description of Change	Brief Rationale
	• first row: revised to read "All data points obtained during the treatment period and the follow-up period defined as at or after baseline …" • second row: revised to read "All data points obtained during the treatment period defined as at or after baseline …" • last row: revised to read "All data points obtained during the treatment period defined as at or after baseline …" • added footnote "a", ""Additional antihyperglycemic medications" refers to any antihyperglycemic therapy that is initiated after baseline and used for more than 2 weeks (14 days)."	
9.2. Analyses Sets (second table) 9.3.1. General Considerations (General descriptions of analyses)	Replaced "rescue antihyperglycemic medications" or "rescue therapy" with "additional antihyperglycemic medications" or "additional therapy" respectively	Correction
9.3.1. General Considerations (General descriptions of analyses) 9.3.4. Secondary Endpoints and Estimands Analyses	Replaced "full participants" with "randomized participants"	Per correction in Section 9.2
9.3.2.1. Participant Disposition 9.3.2.3. Concomitant Therapy	Replaced "safety participants" with "randomized participants"	Correction
10.4. Contraceptive and Barrier Guidance	Updated the definitions and female contraception criteria	Per current Lilly guidance, for clarity
10.6. Liver Safety: Suggested Actions and Follow-up Assessments	Updated the tables and footnotes	Per current Lilly guidance

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Section # and Name	Description of Change	Brief Rationale
10.9.1.3 Strong CYP3A Inhibitors or Inducers, P-gp or BCRP Substrates with a Narrow Therapeutic Index, and Strong OATP Inhibitors	Added “Strong” to CYP3A inhibitors and OATP inhibitors in title	Clarification
10.12. Abbreviations and Definitions	• Added “BCRP” • Revised the definition of “CEC”	Per protocol revision and correction
11. References	Added a reference.	Per protocol revision

11. References

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