Protocol J2A-MC-GZGE(b)

A Phase 2 Study of Once-Daily LY3502970 Compared with Placebo and Once-Weekly Dulaglutide in Participants with Type 2 Diabetes Mellitus

NCT05048719

Approval Date: 27-Oct-2021

Title Page

Protocol Title: A Phase 2 Study of Once-Daily LY3502970 Compared with Placebo and Once-Weekly Dulaglutide in Participants with Type 2 Diabetes Mellitus

Protocol Number: J2A-MC-GZGE

Amendment Number: b

Compound: LY3502970

Brief Title: Effect of LY3502970 Versus Placebo and Dulaglutide in Participants with Type 2 Diabetes Mellitus

Study Phase: 2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 142842

EudraCT: 2021-002806-29

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

Approval Date: 27-Oct-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment [a]	*30-Jun-2021*
Original Protocol	*15-Jun-2021*

Amendment [b]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Modified frequency of blood pressure collections at a visit from 3 to 2.	Typographical error. It was always planned that there would be only 2 collections and the eCRF allows for only 2 collections.
1.3. Schedule of Activities	Corrected the visit numbers for distribution of single dose pens.	Typographical error.
3. Objectives, Endpoints, and Estimands	Adjusted the wording for safety estimand.	To more precisely define safety estimand for the study.
4.1.1. Overview of Study Periods	Corrected visit number for dose escalations.	Typographical error. Dose escalations occur at Visits 4 through 10.
5.1. Inclusion Criteria	Added a note to Inclusion Criterion #3 that participants from some countries may be required to be on metformin.	To address a regulatory agency concern.
6.5. Dose Modification	Replaced text referring to contacting the IWRS help desk for dose modification.	The investigator should now work through the IWRS web site portal for dose modifications.
6.8. Concomitant Therapy	Added language stating that 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.	Oversight in original protocol.

Section # and Name	Description of Change	Brief Rationale
	Added prohibition of taking CYP3A inducers.	To address regulatory agency request.
	Added language stating that orally administered drugs with a narrow therapeutic index should not be taken simultaneously with LY3502970 due to delayed gastric emptying. Also provided examples of these drugs commonly taken by the participants with T2DM.	To address regulatory agency request.
7.1.3. Temporary Discontinuation	Removed the sentence regarding eCRF recording.	The eCRF was designed to capture any missed doses, including those associated with noncompliance. It also allows for the reason as "subject decision".
7.1.4. Restarting Study Drug after Interruption	Replaced text referring to contacting the IWRS help desk for restarting study drug.	The investigator should now work through the IWRS web site portal for restarting study drug.
8.2.3. Electrocardiograms	Deleted text referencing waiting 30 minutes between ECG and blood collection. Also, deleted text referencing ECG collection immediately prior to PK specific visit collection.	Typographical errors. There is no reason to wait 30 minutes between ECG and blood collection. Also, there are no ECG collections immediately prior to PK specific visit collection.
9.3.1. Statistical Analyses: General Considerations	Clarified HbA1c stratum.	Fixed the language to be less cumbersome.
	HbA1c stratum will be included in the model for the analysis of HbA1c.	Inclusion of discretized strata based on the continuous variable.
	Removed language about SAS computation procedure.	The analysis software may not be limited to SAS.
	Added that additional supplemental estimands may be explored for the primary and secondary efficacy endpoints.	Oversight in original protocol.

Section # and Name	Description of Change	Brief Rationale
	Changed longitudinal logistic regression model to logistic regression model.	A simulation has shown that logistic regression with missing values imputed with multiple imputations can lead to smaller variance estimates than longitudinal logistic regression and the analysis was updated accordingly.
9.3.2. Primary Endpoint(s)/Estimand(s) Analysis	Corrected visit number for Week 26.	Typographical error. Visit number for Week 26 is Visit 15.
9.3.3. Secondary Analyses	Changed longitudinal logistic regression to logistic regression with multiple imputation.	A simulation has shown that logistic regression with missing values imputed with multiple imputations can lead to smaller variance estimates than longitudinal logistic regression and the analysis was updated accordingly.
9.3.7. Subgroup Analyses	Corrected “efficacy stand” to “estimand”	Typographical error.
	HbA1c stratum will be included in the model for the subgroup analysis of HbA1c.	Inclusion of discretized strata based on the continuous variable.
10.10. Appendix 10: Provisions for Changes in Study Conduct During Exceptional Circumstances	Corrected visit numbers that need centralized laboratory collections rather than local laboratory collections.	Typographical error. Visits 3, 10, and 15 need to have blood collection through the central laboratory.
	Corrected table with adjustments to visit windows.	Typographical error.
Throughout the protocol	Minor editorial changes made throughout the protocol.	Correction.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2 Study of Once-Daily LY3502970 Compared with Placebo and Once-Weekly Dulaglutide in Participants with Type 2 Diabetes Mellitus

Brief Title: Effect of LY3502970 Versus Placebo and Dulaglutide in Participants with Type 2 Diabetes Mellitus

Rationale:

LY3502970 is a non-peptide glucagon-like peptide-1 (GLP-1) receptor agonist that is being developed as a daily oral adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Unlike the peptide GLP-1 receptor agonists approved by regulators to-date, LY3502970 is a small molecule being developed for daily oral administration.

Study J2A-MC-GZGE (GZGE) is a Phase 2, multicenter, randomized, double-blind, parallel, placebo- and active comparator (1.5 mg dulaglutide QW) -controlled 26-week study that will investigate glucose-lowering and body weight-lowering efficacy, as well as tolerability and safety of LY3502970 in participants with T2DM who failed to achieve adequate glycemic control on diet and exercise alone or when treated with a stable dose of metformin. This study is designed to inform dose selection and dose escalation scheme for Phase 3.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To demonstrate that at least one dose level of QD oral doses of LY3502970 is superior in change from baseline for HbA1c relative to placebo at Week 26, in participants with T2DM inadequately controlled with diet and exercise alone or treated with a stable dose of metformin.	Difference between LY3502970 and placebo in change from baseline in HbA1c at Week 26
Secondary	
To compare the effect of QD LY3502970 versus placebo and versus dulaglutide on glucose control at Week 26	• Difference between LY3502970 and dulaglutide in change from baseline in HbA1c at Week 26 • Percentage of participants with HbA1c ≤6.5% and of <7.0% at Week 26 • Change from baseline in fasting blood glucose at 26 weeks
To compare the effect of QD LY3502970 versus placebo and versus dulaglutide on body weight at Week 26	• Change from baseline in body weight at Week 26 • Percent change in body weight from baseline at Week 26

Objectives	Endpoints
	• Percentage of participants with ≥5%, ≥10% body weight loss from baseline at Week 26
To assess safety and tolerability of LY3502970	• Adverse events overall • Adverse events of special interest • Laboratory parameters • Electrocardiogram • Vital signs
To assess the PK of LY3502970 and potential participant factors that may influence its PK	• Population PK Parameters

Abbreviations: HbA1c = hemoglobin A1c; PK = pharmacokinetics; QD = once daily; T2DM = type 2 diabetes mellitus.

Overall Design

Brief Summary:

The purpose of this study is to measure the change in hemoglobin A1c (HbA1c) with oral daily LY3502970 compared with placebo and compared with once-weekly subcutaneously delivered dulaglutide 1.5 mg in participants with T2DM who failed to achieve adequate glycemic control on diet and exercise alone or when treated with a stable dose of metformin.

Study details include:

- The study duration will be up to 30 weeks.
- The treatment duration will be up to 26 weeks.

Number of Participants:

Approximately 530 participants will be screened to achieve 370 randomly assigned to study intervention.

Intervention Groups and Duration:

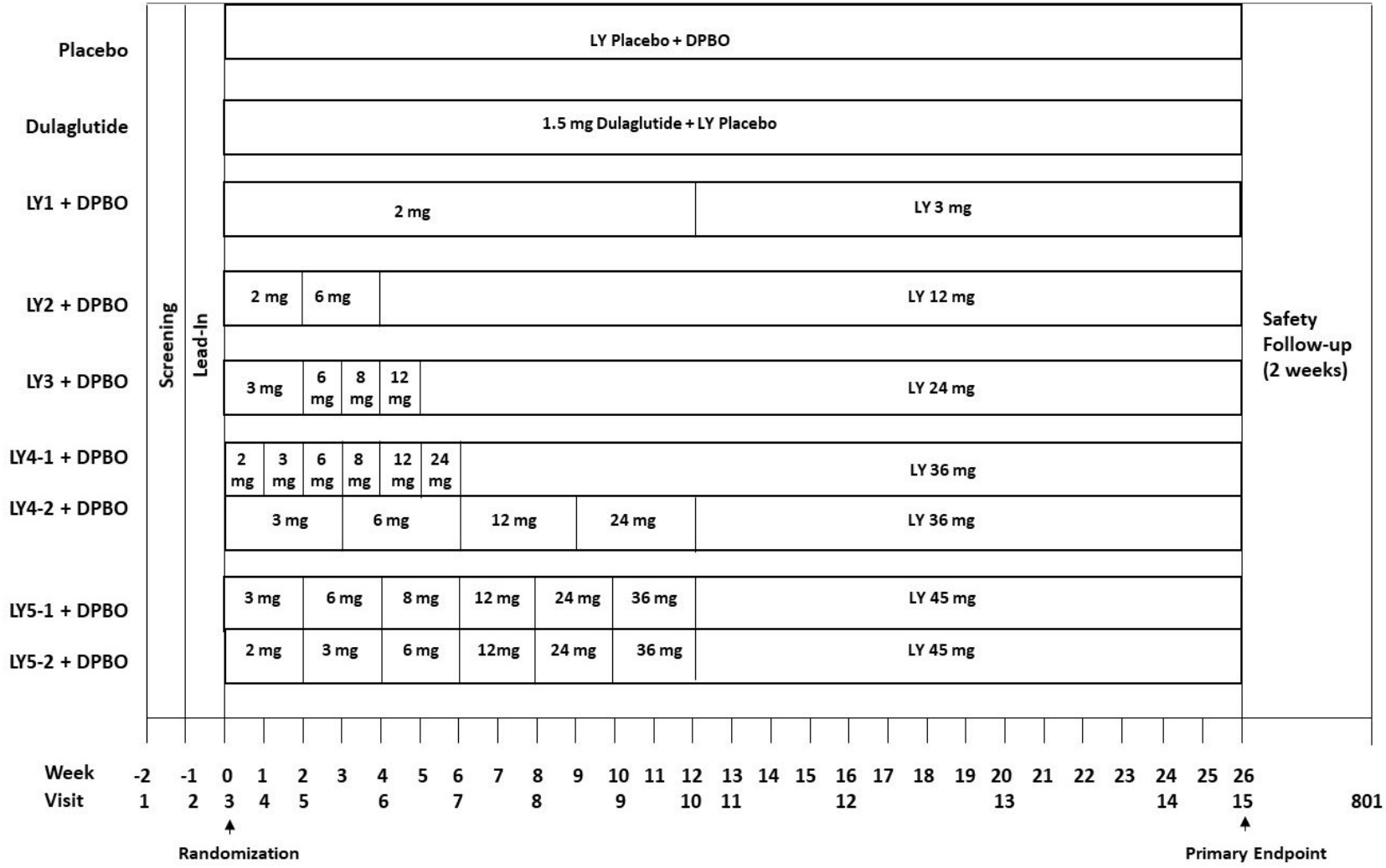
The duration of study participation for each participant will be approximately 30 weeks. The study will consist of an approximately 2-week screening/lead in period followed by a 26-week treatment period. There will also be a 2-week off-drug safety follow-up period.

During the treatment period, LY3502970 doses will be escalated for some treatment groups. The dose escalation period will range from 0 to 12 weeks depending on the dose group. LY3502970 or matching placebo will be administered daily by oral capsule and dulaglutide 1.5 mg or matching placebo will be administered once weekly by subcutaneous injection.

Please see Section 6.5 regarding dose adjustments for participants who are having difficulty tolerating a specific dose.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: DPBO = dulaglutide placebo; LY = LY3502970; LY1 = LY 3 mg; LY2 = LY 12 mg; LY3 = LY 24 mg; LY4 = LY 36 mg; LY5 = LY 45 mg.

1.3. Schedule of Activities (SoA)

The Schedule of Activities (SoA) described below should be followed for all participants enrolled in Study GZGE. However, for those participants whose participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Section 10.10 (Appendix 10) for additional guidance.

Study Period I Screening/Lead-in			**Study Period II Treatment period** For early terminations that occur before the last visit in treatment period, see the activities listed for ET in this table. Shaded columns represent the dose escalation period Weeks 0-12.														**Study Period III Safety Follow-Up**
	Screening	**Lead-In**															
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**ET**	**801**
Week Relative to Randomization	**-2**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**13**	**16**	**20**	**24**	**26**	**-**	**2 Wks post end of TXP**
Allowable interval tolerance (days)			**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**
Fasting Visit	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Administrative																	
Informed consent	X																
Inclusion and exclusion criteria review	X		X														
Demographics	X																
Preexisting conditions and medical history, including surgical history	X		X														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-diabetic medication	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Allowable interval tolerance (days)			**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**
Fasting Visit	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Substance use (alcohol, caffeine, tobacco use)	X	X															
Adverse events (AEs) and Product Complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Evaluation																	
Height	X																
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X		X			X		X		X			X		X	X	X
Vital signs (2 sitting BP and PR measurements)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Vital signs include pulse rate, blood pressure, and temperature. Vital sign measurements should be measured after participant has been sitting for at least 5 minutes and before obtaining ECG tracings and before collection of blood samples for laboratory testing (See Section 8.2.2).																
Physical examination	X																

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Fasting Visit	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Symptom-directed physical examination			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	As indicated based on participant status and standard of care. May be performed by qualified personnel per local regulations.																
12-Lead ECGs	X		X			X		X		X			X		X	X	X
	Central ECGs should be collected prior to collection of blood samples, including PK samples. ECG measurements should be obtained per the instructions in Section 8.2.3.																
Participant Education and Supplies																	
Blood glucose (BG) meter, instructions		X															
Dispense BG meter/supplies (if needed)		X	X	X	X	X	X	X	X	X	X	X	X	X			
Diabetes education		X	X														
	Diabetes education to be performed by site personnel to educate participants on symptoms and management of hyperglycemia and hypoglycemia, SMBG, self-injection, and diabetes management. All trainings should be repeated as needed to ensure participant compliance.																

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Fasting Visit	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood Glucose Monitoring																	
Remind participants about 7-point SMBG		X			X				X			X		X			
	The 7-point SMBG will be required prior to randomization and randomization can occur any time after the 7-point SMBG is completed. At all other times, the participant should be instructed to collect the 7-point SMBG during the week prior to the visit in which the 7-point SMBG is required. All 7-points of the SMBG should be completed in a single day.																
7-point SMBG			X			X				X			X		X		
	Baseline 7-point SMBG to be explained to the participant at Visit 2 with participant completing the 7-point SMBG during the week prior to Visit 3. All other 7-point SMBGs should be completed during the week prior to the visit in which the 7-point SMBG is required.																
Review SMBG values and hypoglycemic events collected in the diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Participant diary dispensed		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Diary compliance check			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary return			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Fasting Visit	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Patient-Reported Outcomes (paper)																	
SF-36 v2 acute form			X									X		X		X	
DTSQs			X									X		X		X	
DTSQc												X		X		X	
Participant Survey														X		X	
Laboratory Tests and Sample Collections																	
Hematology	X		X							X					X	X	X
Hemoglobin A1c (HbA1c)	X		X			X		X		X		X	X		X	X	X
Clinical chemistry	X		X			X				X					X	X	X
Glucose	X		X			X		X		X		X	X		X	X	X
Glucagon			X												X		
Lipid panel	X		X			X				X					X		
Calcitonin	X		X							X					X		
Pancreatic Amylase	X		X			X				X			X		X		X
Lipase	X		X			X				X			X		X		X
Urinalysis	X									X					X		

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Fasting Visit	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Serum pregnancy	X																
Follicle stimulating hormone (FSH)	X																
	Collect serum estradiol, FSH, and LH in women whose menopausal status needs to be determined. For participants known to be either premenopausal or postmenopausal, these tests do not need to be collected.																
Luteinizing Hormone (LH)	X																
Estradiol	X																
Insulin			X			X				X					X		
C-peptide			X			X				X					X		
HIV screening tests	X																
Hepatitis C Virus (HCV) screening tests	X																
Hepatitis B Virus (HBV) screening tests	X																
Cytokeratin 18			X							X					X		
Pro-C3			X							X					X		
eGFR (CKD-EPI)	X									X					X		

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Fasting Visit	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Urinary albumin/creatinine ratio (UACR)	X									X					x	X	
Pharmacokinetic (PK) sample	Predose		X					X		X					X		
	Postdose					X		X				X	X			X	
	PK Predose sample should be collected predose (~up to 1 hour predose). PK Postdose sample time windows: 3-6 hours postdose (Week 4), 6-12 hours postdose (week 8), 1-3 hours postdose (Week 16), 3-6 hours postdose (Week 20). Participants may need to return to clinical site for additional PK-specific visits to provide Postdose PK samples.																
Stored Samples																	
Exploratory biomarker samples			X			X				X		X			X		
Randomization and Dosing																	
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X														
Injection training		X	X														

Study Period I Screening/Lead-in			**Study Period II Treatment period** For early terminations that occur before the last visit in treatment period, see the activities listed for ET in this table. Shaded columns represent the dose escalation period Weeks 0-12.														**Study Period III Safety Follow-Up**
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Fasting Visit	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Dispense study intervention capsules			X	X	X	X	X	X	X	X		X	X	X			
			One bottle of capsules is to be dispensed at Visits 3 and 4. Two bottles of capsules are to be dispensed at Visits 5-9 (during the dose escalation period). The site pharmacy should clearly label which bottle to take first. At Visits 10-13, 4 bottles of capsules should be dispensed. At Visit 14, 2 bottles should be dispensed.														
Dispense study intervention injection and supplies			X			X		X		X		X	X	X			
			One package of 4 single dose pens should be dispensed at Visits 3-14.														
Participant returns unused study intervention and injection supplies				X	X	X	X	X	X	X		X	X	X	X	X	
Assess drug compliance				X	X	X	X	X	X	X		X	X	X	X	X	

Abbreviations: AEs = adverse events; BG = blood glucose; BP = blood pressure; CKD-EP I =chronic kidney disease epidemiology; DTSQc = Diabetes Treatment Satisfaction Questionnaire-Change Version; DTSQs = Diabetes Treatment Satisfaction Questionnaire-Status Version; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; FSH = follicle stimulating hormone; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IWRS = interactive web response systems; PK = pharmacokinetic; LH = luteinizing hormone; PR = pulse rate; Pro-C3 = biomarker for liver fibrosis; SF-36 v2 acute form = Short Form 36 version 2 health survey acute form; SMBG = self-monitoring of blood glucose; TXP = treatment; UACR = urinary albumin creatinine ratio; Wks = weeks.

Note: If the time between Visit 1 (Screening), Visit 2 (Lead In) and Visit 3 (Randomization) takes longer or less time than 2 weeks, it is not considered a protocol deviation.

2. Introduction

2.1. Study Rationale

LY3502970 is an oral non-peptide GLP-1 receptor agonist that is being developed as a daily oral adjunct therapy to diet and exercise to improve glycemic control in adults with T2DM. Unlike the peptide GLP-1 receptor agonists approved by regulators to-date, LY3502970 is a small molecule being developed for daily oral administration.

Study J2A-MC-GZGE (GZGE) is a Phase 2, multicenter, randomized, double-blind, parallel, placebo- and active comparator (1.5 mg dulaglutide QW) -controlled 26-week study that will investigate glucose-lowering and body weight-lowering efficacy, as well as tolerability and safety of LY3502970 in participants with T2DM who failed to achieve adequate glycemic control on diet and exercise alone or when treated with a stable dose of metformin. This study is designed to inform dose selection and dose escalation scheme for Phase 3.

2.2. Background

LY3502970 is being investigated for its potential use in the treatment of T2DM. LY3502970 is a chemically synthesized molecule that shows agonist activity for GLP-1 receptor. To date no off-target toxicity has been identified in clinical trials.

The GLP-1 receptor agonists (GLP-1 RA) are highly effective peptide drugs that mimic the incretin hormone GLP-1 (Werner et al. 2010; Lau et al. 2015; Scheen 2017). The hormone is secreted from the intestine upon food consumption, and its effects include augmented glucose-dependent insulin secretion, prolonged satiety, reduced glucagon release, and delayed gastric emptying (Bayless et al. 1902; Baggio et al. 2007; Nauck et al. 1997). The GLP-1RAs have good glucose-lowering effects with the additional benefits of low risk of hypoglycemia and weight loss (Pratley et al. 2018).

Dulaglutide was chosen as the active comparator in this study. It is a subcutaneously delivered QW GLP-1 RA, which is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Dulaglutide 1.5 mg treatment alone is also associated with modest weight loss (approximately 2.3 kg mean weight loss at 26 weeks) in T2DM patients (Trulicity® United States Package Insert [USPI], 2020; Trulicity® Summary of Product Characteristics [SmPC], 2021).

The safety, tolerability, and pharmacokinetics/pharmacodynamics (PK/PD) of LY3502970 have been evaluated in 2 Phase 1 clinical pharmacology studies, J2A-MC-GZGA and J2A-MC-GZGC. Study GZGA was a single ascending dose (SAD) and a 4-week multiple ascending dose (MAD) study in healthy volunteers that evaluated the safety, tolerability, PK, and PD of LY3502970. Study GZGC was a multiple dose study in participants with T2DM designed to evaluate the safety, tolerability, PK, and PD of LY3502970 following 12 weeks of treatment.

In **Study GZGA** the SAD part of the study evaluated single oral doses 0.3-, 1-, 3-, and 6 mg. The MAD part of the study evaluated 28 daily LY3502970 doses of 2 mg and weekly dose

escalation evaluating different dose escalation schemes that ranged from 2 mg through 24 mg with terminal doses of 6-, 16-, or 24-mg. In both the SAD and MAD, gastrointestinal (GI)-related adverse events (AEs) were the most commonly reported AEs, consistent with GLP-1 receptor agonist pharmacology (Nauck et al. 2009; Dungan et al. 2014; Giorgino et al. 2015; Jendle et al. 2016; Nauck et al. 2016). All AEs were mild to moderate in severity. The incidence of GI AEs decreased with continued dosing in the MAD, thus demonstrating tachyphylaxis to the GI AEs. The MAD showed that LY3502970 initially delayed gastric emptying, an effect that was greatly diminished with continued LY3502970 exposure. Furthermore, LY3502970 showed a decrease in glucose and body weight. All the findings were similar to those observed with marketed GLP-1 receptor agonist peptide drugs.

This study also assessed the effect of food on the PK of LY3502970. The effect of food on the PK of LY3502970 was a slight decrease in the area under the curve (AUC) and the maximum plasma concentration Cmax.

There has been no apparent concentration-dependent increase in systolic or diastolic blood pressure (BP) after single or multiple doses or pulse rate (PR) after single doses. There has been a trend in concentration-dependent increase in PR after multiple doses of LY3502970, similar to that observed with other GLP-1 receptor agonists.

LY3502970 PK was studied across a range of doses administered as single doses or multiple doses (28 doses) via a once daily (QD) dosing regimen. LY3502970 PK appeared approximately dose proportional over the dose range studied after a single and multiple doses from 0.3 to 24 mg. Peak concentrations were observed at approximately 4-12 hours postdose, and the half-life was approximately 24.6-67.5 hours.

Study GZGC evaluates LY3502970 treatment for 12 weeks in participants with T2DM controlled with diet and exercise with or without a stable dose of metformin. Study GZGC included 5 dosing cohorts evaluating different target doses and dose escalations. Dose escalations occurred weekly until the target dose was reached and then maintained at the target dose for the duration of the study. The following were the dosing cohorts :

- Cohort A: 3, 6, 12, and 21 mg
- Cohort B: 3, 6, and 9 mg
- Cohort C: 3, 6, 12, and 15 mg
- Cohort D: 3, 6, 12, 21, and 27 mg
- Cohort E: 3, 6, 9, 21, 36, and 45 mg

Preliminary data indicate that the most frequently reported AEs in Study GZGC are nausea, decreased appetite, and vomiting. Consistent with other GLP-1 receptor agonists, the AEs are more frequent early in the study and at the initiation of each dose escalation but diminished with continued dosing. No off-target AEs have been observed to date. LY3502970 treatment has also demonstrated a decrease in fasting plasma glucose and a decreased in 7-point self-monitoring blood glucose levels. There has been a decrease in HbA1c and body weight. An increase in PR has been observed, which is of a similar magnitude as seen in other early phase studies of GLP-1

RAs. There have been no clinically significant effects on electrocardiogram (ECG) parameters or other laboratory parameters.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3502970 may be found in the Investigator's Brochure (IB) and Development Safety Update Reports.

2.3.1. Risk Assessment

Study Intervention

The Sponsor has evaluated the preclinical and clinical risks associated with LY3502970.

Nonclinical safety of LY3502970 was evaluated in 6-month and 9-month repeat-dose toxicology studies in rats and monkeys, respectively. Monkey doses were 0, 1.35, and 3 mg/kg/day and were administered via oral gavage QD at a volume of 1 mL/kg. Rat doses were 0, 5, 30, and 200 mg/kg/day given by oral gavage QD at a volume of 10 mL/kg. Important LY3502970-related findings in the monkey included vomiting, decreased body weight, and decreased food consumption. Additional findings from the monkey studies include changes in CV parameters (such as increases in HR and decreased blood pressure), and ECG changes (PR interval prolongation). The No-observed-adverse-effect level (NOAEL for target organ toxicity in the monkey 9-month toxicology study was 3.0 mg/kg. The monkey exposure multiples for the LY3502970 45-mg dose: males = 0.773-fold; females = 0.875-fold.

The only clinically relevant observation in the rat 6-month repeat toxicology study was LY3502970 dose-related minimally higher total bilirubin in both sexes at ≥30 mg/kg, and minimally higher bile acid in both sexes at 200 mg/kg/day. These differences likely indicated a hepatobiliary effect but lacked any correlative microscopic findings in the liver. The NOAEL for target organ toxicity in the 6-month rat toxicology study was 200 mg/kg. The rat exposure multiples for the LY3502970 45-mg dose: males = 16.5-fold; females = 31.1-fold.

In the Phase 1 Study GZGA, most findings were associated with the pharmacology of LY3502970 and include:

- nausea
- vomiting
- loss of appetite, and
- increased HR.

Of note, there have not been any liver transaminase or bilirubin changes observed in any of the Phase 1 clinical trials.

All identified risks from preclinical and clinical studies to date are associated with LY3502970 pharmacology and are considered monitorable and manageable at the planned dose range of 2 to 45 mg of LY3502970. These risks are similar to those noted during development of marketed GLP-1 receptor agonists. Participants will be closely monitored with scheduled medical assessments, vital signs, laboratory evaluations, and triplicate ECG measurements.

For the dulaglutide comparator, refer to the Prescribing Information for Trulicity (Trulicity United States Prescribing Information, 2021, Trulicity® Summary of Product Characteristics [SmPC], 2021) for more information about the known and expected benefits and risks of dulaglutide.

Benefit Assessment

Data from the Phase 1 studies indicate that LY3502970 may lower glucose, which should result in lowered HbA1c in participants with T2DM. The data also showed that LY3502970 treatment resulted in a decrease in body weight. Taken together these data support improved glycemic control in participants with T2DM.

Overall Benefit Risk Conclusion

LY3502970 is being investigated as a daily oral therapy as an adjunct to diet and exercise to improve glycemic control in adults with T2DM who may or may not be taking metformin. At this time, no safety or efficacy issues that would reflect a significant risk to clinical trial subjects have been identified which would constitute undue risk to study participants. The safety profile continues to be refined as more clinical safety data become available. The benefit-risk profile continues to support further development of LY3502970.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate that at least one dose level of QD oral doses of LY3502970 is superior in change from baseline for HbA1c relative to placebo at Week 26, in participants with T2DM inadequately controlled with diet and exercise alone or treated with a stable dose of metformin.	Difference between LY3502970 and placebo in change from baseline in HbA1c at Week 26
Secondary	
To compare the effect of QD LY3502970 versus placebo and versus dulaglutide on glucose control at Week 26	• Difference between LY3502970 and dulaglutide in change from baseline in HbA1c at Week 26 • Percentage of participants with HbA1c ≤6.5% and of <7.0% at Week 26 • Change from baseline in fasting blood glucose at 26 weeks
To compare the effect of QD LY3502970 versus placebo and versus dulaglutide on body weight at Week 26	• Change from baseline in body weight at Week 26 • Percent change in body weight from baseline at Week 26 • Percentage of participants with ≥5%, ≥10% body weight loss from baseline at Week 26
To assess safety and tolerability of LY3502970	• Adverse events overall • Adverse events of special interest • Laboratory parameters • Electrocardiogram • Vital signs
To assess the PK of LY3502970 and potential participant factors that may influence its PK	• Population PK Parameters
Exploratory	
To assess the relationship between QD LY3502970 dose and/or exposure and key efficacy and safety measures and potential participant factors that may influence these relationships	• Dose-response and concentration-response analyses for key efficacy and safety parameters
To evaluate the effect of QD LY3502970 versus placebo and versus dulaglutide on body weight as measured by BMI and waist circumference at Week 26	• Change from baseline in BMI at 26 weeks • Change from baseline in waist circumference at 26 weeks
To evaluate the effects of QD LY3502970 versus placebo and versus dulaglutide on 7-point SMBG profile	• Change from baseline in 7-point SMBG values at Week 26

Objectives	Endpoints
To evaluate the effects of QD LY3502970 versus placebo and versus dulaglutide on biomarkers	• Change from baseline in mechanistic biomarkers (Section 1.3) at Week 26
To evaluate the effects of QD LY3502970 versus placebo and versus dulaglutide on patient-reported outcomes	
• Health-related quality of life	• Change from baseline in SF-36v2 acute form domains and summary scores at Week 24
• Diabetes treatment satisfaction	• Change from baseline in DTSQs at Week 24 • Actual responses to DTSQc at Week 24
• Participant experience	• Summary statistics of actual responses to Participant survey at Week 24

Abbreviations: BMI = body mass index; DTSQc = Diabetes Treatment Satisfaction Questionnaire-Change Version; DTSQs = Diabetes Treatment Satisfaction Questionnaire-Status Version; HbA1c = hemoglobin A1c; PK = pharmacokinetics; QD = once daily; SF-36v2 = Short Form 36 version 2 health survey acute form; SMBG = self-monitoring of blood glucose; T2DM = type 2 diabetes mellitus.

Primary Estimand

The primary clinical question of interest is: What is the treatment difference in HbA1c change from baseline after 26 weeks of treatment in participants who meet the inclusion criteria and would have completed the treatment period without additional anti-hyperglycemic rescue medication?

The "efficacy estimand" is described by the following attributes:

- Population: participants who meet the inclusion criteria. Further details can be found in Section 5 and Section 9.
- Endpoint: change from baseline in HbA1c at Week 26.
- Treatment condition: the randomized treatment with allowance for down-titration based on GI tolerability.

The two intercurrent events "permanent discontinuation of study drug" and "initiation of rescue medication" are handled by the hypothetical strategy and the potential outcome of interest is the response in the efficacy measurement if participants had adhered to the randomized treatment without using additional anti-hyperglycemic rescue medication. There are no other defined intercurrent events. Down-titration will not be considered as intercurrent events for the definition of estimand in this study. Further details on study interventions and concomitant, including rescue, interventions may be found in Section 6.

Population-level summary: difference in mean changes in HbA1c at Week 26 between QD LY3502970 and placebo.

Rationale for "efficacy estimand": This phase 2 study aims to study the efficacy of LY3502970 under the ideal condition that all participants adhere to the randomized treatment without using additional anti-hyperglycemic rescue medication.

Estimand(s) for Secondary Objectives

The same estimand for the primary objective will be used for the following efficacy endpoints for the secondary objectives:

- Difference between LY3502970 and dulaglutide in change from baseline in HbA1c at Week 26
- percentage of participants with HbA1c ≤6.5% and of <7.0% at Week 26
- change from baseline in fasting blood glucose at 26 weeks
- Change from baseline in body weight at Week 26
- Percent change in body weight from baseline at Week 26
- Percentage of participants with ≥5%, ≥10% body weight loss from baseline at Week 26

Unless specified otherwise, safety and tolerability assessments will be guided by an estimand comparing safety of LY3502970 doses with placebo and dulaglutide for the entire study period (the treatment period plus safety follow-up period) irrespective of adherence to study intervention for all study population (including advertently enrolled participants).

4. Study Design

4.1. Overall Design

Study GZGE is a Phase 2, multicenter, randomized, double-blinded, parallel, placebo- and active comparator (1.5 mg dulaglutide QW)-controlled 26-week study, to investigate the safety and efficacy of LY3502970 in participants with T2DM who failed to achieve adequate glycemic control on diet and exercise alone or on a stable dose of metformin for at least 3 months prior to Visit 1) (see Section 1.2).

4.1.1. Overview of Study Periods

Screening Period

Visit 1

The purpose of screening procedures at Visit 1 is to establish initial eligibility and to obtain blood samples for laboratory assessments needed to confirm eligibility. The participant must sign the informed consent form (ICF) before the study procedures are performed, as outlined in the SoA, Section 1.3. Screening procedures will be performed according to the SoA (Section 1.3).

Visit 2

At Visit 2, the screening laboratory results will be reviewed to confirm eligibility.

Participants will be provided with paper diaries and will be trained on how to record key study information, as appropriate. Participants will start recording their self-monitoring of blood glucose (SMBG) values and hypoglycemic events immediately after Visit 2 and will perform these procedures until the last study visit.

Participants will receive training on the routine BG monitoring and paper diary completion required during the study. Participants should follow the investigator's instructions related to frequency of SMBG but should test their glucose a minimum of 3 times per week and as specified for determination of 7-point glucose profiles (see Section 10.8). Eligible participants will return to the site for some baseline procedures during the lead-in phase (Visit 2) and again for randomization to treatment and to receive their first dose of study drug at Visit 3.

Diabetes education will be performed by site personnel to educate participants on symptoms and management of hyperglycemia and hypoglycemia, SMBG, self-injection, and diabetes management according to American Diabetes Association Standards of Medical Care in Diabetes (ADA 2020) or local standards. Participants will be trained on how to utilize BG meters and how to collect SMBG, including 7-point measurements as appropriate. Blood glucose meters or supplies will be provided to measure SMBG values (see Section 10.8).

Of note, if the screening period between Visit 1 and Visit 3 (randomization) takes less or more time than 2 weeks, it is not a protocol deviation.

Randomization

Visit 3

At Visit 3, eligible participants, those who meet all applicable inclusion criteria and none of the applicable exclusion criteria, will perform all required study procedures prior to randomization.

Patient-reported outcomes questionnaires should be administered according to the SoA (Section 1.3), as early as possible during the visit. Preferred administration order of these questionnaires throughout the trial is

1. SF-36 v2 acute form
2. DTSQs

Following randomization, study site personnel will train participants on how to use the single-dose pen and observe the study participant inject the first dose of study comparator/placebo according to the randomized treatment group. Site personnel will also observe the study participant take the first oral dose of study drug capsule. The date and time of the first dose of study drugs will be recorded on the electronic case report form (eCRF). Beginning at randomization, all participants will receive study drugs according to the randomized treatment arm for the duration of the 26-week treatment period as per the SoA (Section 1.3).

Treatment Period

During the Treatment Period, study drugs and injection supplies will be returned per the SoA (Section 1.3) and according to local requirements. New supplies will be dispensed as needed. Participants should be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties taking or administering their study drugs. Whenever possible, participants should take their study medication (both capsule and injection) at the study site during a visit.

Participants should also be advised about the appropriate course of action if study drugs are not taken at the required time (late/missing doses) (see Section 6.5). Study participants will be permitted to use concomitant medications that they require during the study, except certain excluded medications (see Section 6.8) that may interfere with the assessment of efficacy and safety characteristics of the study treatments.

Dose-Escalation Period (Visits 4-10)

For maintenance doses of LY3502970 starting at 3 mg, the initial dose will be 2 or 3 mg followed by additional escalation steps as appropriate. The dose will be increased until the maintenance dose is achieved (see Section 1.2 for dosing details and the LY3502970 Treatment Group Dose Escalation Regimen table below).

The maintenance doses of LY3502970 or dulaglutide 1.5 mg will be continued for the remainder of the study. For participants who experience intolerable GI symptoms or may need dose adjustment for other reasons, the dose modification procedures are described in Section 6.5.

LY3502970 Treatment Group Dose Escalation Regimen

W	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
V	3	4	5		6		7		8		9		10	11			12				13				14		15
LY1	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
LY2	2	2	6	6	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	
LY3	3	3	6	8	12	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	
LY4-1	2	3	6	8	12	24	36	36	36	36	36	36	36	36	36	36	36	36	36	36	36	36	36	36	36	36	
LY4-2	3	3	3	6	6	6	12	12	12	24	24	24	36	36	36	36	36	36	36	36	36	36	36	36	36	36	
LY5-1	3	3	6	6	8	8	12	12	24	24	36	36	45	45	45	45	45	45	45	45	45	45	45	45	45	45	
LY5-2	2	2	3	3	6	6	12	12	24	24	36	36	45	45	45	45	45	45	45	45	45	45	45	45	45	45	

Abbreviations: LY = LY3502970; V = Visit; W = week.

Note: Gray area represents the dose escalation period.

Maintenance Period (Visits 11-15)

During the maintenance period, visits will occur approximately every 3-4 weeks until 24 weeks and then 2 weeks from Weeks 24 to 26. Visit procedures should be conducted according to the SoA (Section 1.3).

Patient-reported outcomes questionnaires should be administered at Week 16 (Visit 12) and Week 24 (Visit 14), as early as possible during the visit. Preferred administration order of these questionnaires is

1. SF-36v2 acute form
2. DTSQs
3. DTSQc
4. Participant survey (Week 24)

Early Termination Visit

Participants unable or unwilling to continue the study for any reason will perform an early termination (ET) of treatment visit (Section 7.1). If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as an ET visit. Procedures should be completed according to the SoA (Section 1.3). Participants who withdrawal from the study after signing the informed consent but who have not taken a dose of study drug prior to randomization do not need to complete ET procedures.

Patient-reported outcomes questionnaires should be administered at ET visit. Preferred administration order of these questionnaires is

1. SF-36v2 acute form
2. DTSQs
3. DTSQc
4. Participant survey

Safety Follow-up Period

Visit 801

A safety follow-up visit will occur approximately 2 weeks following the last treatment period visit. All participants who have taken at least one dose of study drug should complete a safety follow-up visit (Visit 801), according to the SoA (Section 1.3).

For participants who discontinue from investigational product (IP) early but remain in the study, all remaining visits should be completed per SoA (Section 1.3).

For participants who discontinue from the study early (regardless of whether they discontinue IP at the same time or have discontinued IP at an earlier visit), an ET visit followed by the safety follow-up visit (Visit 801) should be completed as per the SoA (Section 1.3).

Participants are also required to return any remaining study diaries to the study site at the end of this period.

4.2. Scientific Rationale for Study Design

Study GZGE is a Phase 2 study designed to examine the efficacy on glycemic control, decreasing body weight, and safety of QD LY3502970 compared with placebo and QW

dulaglutide 1.5 mg in participants with T2DM who have inadequate glycemic control with diet and exercise alone or in combination with a stable dose of metformin.

Inclusion of an active comparator (dulaglutide 1.5 mg) in Study GZGE will allow for a direct comparison of the safety and efficacy of QD LY3502970 to an injectable GLP-1 RA (as well as to placebo) over a 6-month time period. In addition, effects of the medication on other parameters such as other measures of glycemic control and various other safety-related assessments will also be determined. The planned duration of 6 months will allow for a more robust evaluation of the body weight effects of the 2 drugs, as the putative mechanism of action of LY3502970 suggests that treatment with LY3502970 will result in continued weight loss over a 6-month period. The data from this trial will form the primary basis to assess dose/exposure–response of LY3502970 efficacy for selection of doses to be included in Phase 3 testing. The data will also provide information to select the dose escalation scheme to reach the target doses in Phase 3. In addition, safety and tolerability over a wide dose range of LY3502970 versus placebo and dulaglutide 1.5 mg will be assessed to enable robust benefit–risk characterization in T2DM.

The placebo arm is included to determine whether any efficacy or safety effects of LY3502970 are different in magnitude from those of dulaglutide 1.5 mg, equivalent to or are also different from no treatment (i.e., placebo).

Dulaglutide 1.5 mg was chosen to be the active comparator because it is a marketed GLP-1RA and has a great deal of data on its effects on HbA1c, glucose, body weight, and AEs in the population chosen for this study.

The current study will enroll participants with inadequate glycemic control based on HbA1c values ranging from 7.0% to 10.5%, inclusive. The study population, as defined by inclusion and exclusion criteria, is expected to include participants with modestly advanced T2DM and partially preserved pancreatic β cell function, the key prerequisite for glucose-lowering efficacy of incretins.

To minimize the potential confounding effect of changes in concomitant medications, participants will be permitted to use concomitant medications that do not interfere with the assessment of efficacy or safety characteristics of the study treatments.

4.3. Justification for Dose

LY3502970 maintenance doses of 3, 12, 24, 36, and 45 mg administered orally QD, were selected based on the points below.

- In the single and a 4-week multiple dose study in healthy volunteers, GZGA, LY3502970 doses through 24 mg were safe and well tolerated following dose escalation.
- Although data are limited, in the 12-week study, GZGC, in participants with T2DM, LY3502970 doses through 45 mg appear to be safe and tolerated following dose escalation. Furthermore, LY3502970 treatment through 45 mg appears to reduce glucose, HbA1c, and body weight in the 12-week study.
- The selected dose levels and dose range will evaluate various dose escalation schemes and support dose exposure-response analysis of multiple safety and efficacy measures to support selection of dose(s) of LY3502970 with optimal benefit-risk ratio for further clinical development.

High acute doses of GLP-1 RAs, including LY3502970 are often poorly tolerated due to GI symptoms, whereas a more gradual dose escalation scheme to reach a high dose has been shown to improve GLP-1RA tolerability. Therefore, different dose escalation schemes are also being evaluated within dose groups to provide information on starting doses, dose increments and duration of increments, on tolerability to support a dose escalation scheme in further clinical development.

4.4. End of Study Definition

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

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

5. Study Population

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. Participant must be 18 or the legal age of consent in the jurisdiction in which the study is taking place to 75 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Have been diagnosed with T2D based on the World Health Organization (WHO) classification (see Section 10.6) or other locally applicable diagnostic standards for at least 6 months prior to screening
3. Have an HbA1c value at screening of ≥7.0% and ≤10.5% and treated with diet and exercise alone or with a stable dose of metformin (and not more than the locally approved dose) for at least 3 months prior to screening/Visit 1. ***Note***: Participants from some countries may be required to be on metformin in order to enroll in this study.

Weight

4. Have a body mass index (BMI) of ≥ 23 kg/m^2 at Visit 1
5. Have had a stable body weight for the 3 months prior to randomization (≤5 % body weight gain and/or loss)

Sex and Contraceptive/Barrier Requirements

6. Male and/or female

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

Women not of childbearing potential (for definitions, see Section 10.4) and men can participate in this study considering the following:

- Male participants:
  - Males who agree to use highly effective/effective methods of contraception may participate in this trial.
  - Please refer Section 10.4 to for definitions and additional guidance related to contraception.
- Female participants:
  - Women not of childbearing potential (WNOCBP) may participate in this trial.
  - Please refer to Section 10.4 for definitions and additional guidance related to contraception.

Note: Hormone replacement therapy in post-menopausal women is allowed but women must be on stable therapy for 3 months prior to screening/Visit 1.

Informed Consent

7. Capable of giving signed informed consent as described in Section 10.1 (Appendix 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

8. Have type 1 diabetes mellitus (T1DM) or history of ketoacidosis or hyperosmolar coma
9. Have a history of proliferative diabetic retinopathy, diabetic maculopathy, or severe non-proliferative diabetic retinopathy that requires immediate treatment intervention
10. Have had more than 1 episode of severe hypoglycemia, as defined by the occurrence of neuroglycopenic symptoms requiring the assistance of another person for recovery, within 6 months prior to Visit 1, or has a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms. Any participant that the investigator feels will not be able to communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia should also be excluded.
11. Have a history of acute or chronic pancreatitis or elevation in serum lipase/amylase (greater than 3 times the upper limit of normal [ULN]) or fasting serum triglyceride level of >500 mg/dL at screening

Obesity Related

12. Have obesity induced by other endocrine disorders (such as Cushing's syndrome or Prader-Willi syndrome)

Other Medical

13. 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 medications that directly affect GI motility
14. Have poorly controlled hypertension (in other words, mean seated systolic BP ≥160 mm Hg or mean seated diastolic BP ≥100 mm Hg) at screening, renal artery stenosis, or symptomatic postural hypotension. For participants with uncontrolled hypertension at the screening visit, antihypertensive medication may be started, and BP must meet the protocol criterion for hypertension control by the randomization visit.

15. Have a known self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma
16. Evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone that, in the opinion of the investigator, would pose a risk to participant safety. Participants on a stable dose of thyroid replacement therapy for at least the prior 3 months who are clinically euthyroid and who are anticipated to remain on this dose throughout the trial period may be eligible if they meet the other criteria.
17. Have had any of the following within the last 6 months prior to screening:
    - myocardial infarction (MI),
    - unstable angina,
    - coronary artery bypass graft,
    - percutaneous coronary intervention (diagnostic angiograms are permitted),
    - transient ischemic attack (TIA),
    - cerebrovascular accident (stroke) or decompensated congestive heart failure, or
    - currently have New York Health Association Class III or IV heart failure.
18. Have an ECG considered by the investigator indicative of abnormalities that may interfere with the interpretation of changes in ECG intervals at screening
19. Medical history of significant autonomic neuropathy as evidenced by urinary retention, resting tachycardia, orthostatic hypotension, or diabetic diarrhea
20. Have a personal or family history of long QT syndrome, family history of sudden death in a first-degree relative (parents, sibling, or children) before the age of 40 years, or a personal history of unexplained syncope within the last year. Use of prescription or over-the-counter medications known to significantly prolong the QT or QTc interval at screening.
21. Have an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, as determined by the central laboratory at Visit 1, or a level of eGFR that would contraindicate the use of metformin per the label in the respective country. Participants on metformin must meet local label requirements.
22. Have signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or any of the following, as determined by the central laboratory during screening
    - Alanine aminotransferase (ALT) level >3.0X upper limit of normal (ULN) for the reference range (as determined by the central laboratory at study entry)
    - alkaline phosphatase (ALP) level >1.5X ULN for the reference range, or
    - total bilirubin level (TBL) >1.5X ULN for the reference range (except for cases of known Gilbert's Syndrome)

23. Have a serum calcitonin level (at Visit 1) of
    - ≥ 20 ng/L, if eGFR ≥ 60 mL/min/1.73 m^2 or
    - ≥35 ng/L if eGFR < 60 mL/min/1.73 m^2 (as determined by central laboratory at Visit 1)
24. Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years prior to screening
25. Have evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies historically or at screening
26. Evidence of hepatitis B and/or positive hepatitis B surface antigen.
27. Hepatitis C as defined by presence of hepatitis C virus (HCV) ribonucleic acid (RNA) or positive hepatitis C antibody (anti-HCV). Participants treated for hepatitis C (and diagnosed as cured) must have an RNA test at screening and also be RNA negative for at least 3 years prior to screening in order to be eligible for the study.
28. Have a history of a transplanted organ (corneal transplants [keratoplasty] allowed).
29. Have any other condition (including known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol
30. Have had a blood donation of ≥500 mL within the previous 8 weeks of study screening or a blood transfusion or severe blood loss within the prior 3 months, or have known hemoglobinopathy (for example, hemolytic anemia or sickle cell anemia), or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with HbA1c measurements
31. Have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 6 months
32. Have evidence of a significant active, uncontrolled medical condition or a history of any medical problem capable of constituting a risk when taking the study medication or interfering with the interpretation of data, as judged by the screening investigator at screening
33. Have difficulty swallowing capsules

Prior/Concomitant Therapy

34. Unless otherwise specified, all concomitant medications should be at a stable dose for at least 3 months prior to randomization

35. With the exception of stable doses of metformin, participants on another OAM (including, but not limited to, sulfonylureas, DPP-4i, sodium–glucose cotransport 2 inhibitors, alpha-glucosidase inhibitors, meglitinides) may be randomized if the additional OAM treatment was discontinued at least 3 months prior to screening
36. Have used insulin for diabetic control within the prior year. However, short-term use of insulin for acute conditions is allowed (≤14 days) in certain situations, such as during a hospitalization or perioperatively.
37. Have had any exposure to dulaglutide, other GLP-1 analogs, or other related compounds within the prior 3 months or any prior history of hypersensitivity/allergies to these medications. Have known or suspected hypersensitivity to trial product(s), to selective GLP-1 RAs or GIP/GLP-1 or GLP-1/GCG dual receptor agonists.
    - Participants who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability or lack of efficacy should not be randomized.
38. Have taken within 3 months prior to screening medications (prescribed or over the counter) or alternative remedies (including herbal/nutritional supplements) intended to promote weight loss

    Examples include, but are not limited to:

    - Saxenda® [liraglutide 3.0 mg] or other GLP-1RA
    - Xenical® [orlistat]
    - Meridia® [sibutramine]
    - Acutrim® [phenylpropanolamine]
    - Sanorex® [mazindol]
    - Adipex® [phentermine]
    - BELVIQ® [lorcaserin]
    - Qsymia™ [phentermine/topiramate combination]
    - Contrave® [naltrexone/bupropion]
    - Wegovy™ (semaglutide 2.4 mg), and
    - other similar body weight loss medication, including over-the-counter (OTC) medications, for example, allī®
39. Are receiving or have received within 3 months prior to screening chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, single intraarticular injection, or inhaled preparations) or have received such therapy within 4 weeks immediately prior to screening
40. Are receiving strong CYP3A inhibitors and drugs that are P-glycoprotein/breast cancer resistant protein (P-gp/BCRP) substrates with narrow therapeutic index. Please see Section 6.8 concomitant medications for details.

41. Have a history of use of marijuana or tetrahydrocannabinol (THC)-containing products within 3 months of enrollment or unwillingness to abstain from marijuana or THC-containing products use during the trial

    Note: If a participant has used cannabidiol oil during the past 3 months but agrees to refrain from use for the duration of the study, the participant can be enrolled.

42. Are currently taking a central nervous system stimulant (for example, Ritalin-SR®) with the exception of caffeinated beverages at screening
43. Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) [1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits].
44. Evidence of regular use of known drugs of abuse in the opinion of the investigator

Prior/Concurrent Clinical Study Experience

45. Are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study
46. Have participated, within the last 90 days, in a clinical study and received treatment, whether active or placebo. If the study involved an IP; at least 5 elimination half-lives or 90 days, whichever is longer, should have passed
47. Have previously completed or withdrawn from this study or any other study investigating LY3502970

Other Exclusions

48. Are women of child-bearing potential
49. Are women, acting as a surrogate, who are currently pregnant or breastfeeding, or who intend to become pregnant or to breastfeed at any time during the study or within 20 weeks after receiving the last dose of study drug
50. Are investigative 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.
51. Are employees of Eli Lilly and Company (Lilly) or are employees of a third-party organization involved in the study which requires exclusion of their employees
52. Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study

5.3. Lifestyle Considerations

Throughout the study, participants may undergo medical assessments and review of compliance with requirements before continuing in the study. Participants will report to the clinical research site for safety assessments and will remain in the clinic until all procedures for that visit are complete and the investigator has deemed it safe to release the participant from the clinic.

Per the SoA (Section 1.3), personnel will provide diabetes management counseling, which will include instructions on diet and exercise and education about the signs, symptoms, and management of hyperglycemia and hypoglycemia, SMBG, and self-injection.

Prescription or OTC medications that promote weight loss are exclusionary if used within 3 months prior to screening or between screening and randomization. These medications are also not allowed at any time during the treatment period. If started after randomization, the medications should be immediately withdrawn. Participants who refuse to withdraw the weight loss medications must be discontinued from study drug.

Throughout the study, participants may undergo medical assessments and review of compliance with requirements before continuing in the study.

Meals/Diet-Participants should not initiate a structured diet and/or exercise program for weight reduction during the study other than the lifestyle and dietary measures for diabetes treatment.

For certain assessments, the participants will be required to come to the site in a fasting state, after an overnight fast (except for water) of at least 8 hours when clinical laboratory assessments and/or weight measures are performed as specified in the SoA (Section 1.3).

Caffeine, Alcohol, and Tobacco-Participants will be allowed to maintain their regular caffeine consumption throughout the study period.

Alcohol will not be permitted at least 24 hours prior to the study site visits, until the participant has been discharged from the clinical research site. Daily alcohol should not exceed 3 units for males and 2 units for females.

Participants should consume no more than 10 cigarettes or equivalent vaping products per day.

Physical Activity-Participants will be advised to maintain their regular levels of physical activity/exercise during the study; strenuous exercise within 24 hours prior to all visits should be avoided if possible. When certain study procedures are in progress at the site, participants may be required to remain recumbent or seated.

Blood Donation –Study participants should be instructed not to donate blood or blood products during the study and for 8 weeks 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 randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

If, in the opinion of the investigator, an ineligible lab test result is the result of an error or extenuating circumstance, then that parameter can be retested without the participant having to be rescreened. However, screen failures for HbA1c may not be retested or rescreened.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

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

All participants will take one capsule orally each day and one subcutaneous injection each week. All capsules are the same size and placebo capsules match LY3502970 capsules. Furthermore, the dulaglutide placebo injection device matches the active dulaglutide injection device. Therefore, participants will not know whether they are receiving active LY3502970 or LY3502970 placebo to match, the dose of LY3502970, or dulaglutide 1.5 mg or dulaglutide placebo to match.

LY3502970 will be supplied in weekly bottles with 10 capsules per bottle. Bottles contain 10 capsules to account for visit windows and preventing participants from missing doses even if it delays the dose escalation. Participants should be instructed to return unused capsules.

Disposition of Study Drug Bottles

Visit	Number of Bottles of Capsules to be Dispensed
3	1
4	1
5-9*	2
10-13	4
14	2

*Visits 5-9 take place during the dose escalation period. The site pharmacy should clearly label which bottle to take first.

Dulaglutide or matching placebo will be supplied at the monthly visits as 4 single-dose pens.

6.1. Study Intervention(s) Administered

ARM Name	LY3502970	LY-Placebo	Dulaglutide	Dulaglutide-Placebo
Intervention Name	LY3502970	LY3502970-Placebo	dulaglutide	dulaglutide-placebo
Type	Drug		Drug	
Dose Formulation	capsule	capsule	Injectable	Injectable
Unit Dose Strength(s)	2 mg capsule LY 3 mg capsule LY 6 mg capsule LY 8 mg capsule LY 12 mg capsule LY 24 mg capsule LY 36 mg capsule LY 45 mg capsule LY	capsule of LY-placebo to match	1.5 mg/0.5 mL single-dose pen	placebo to match dulaglutide in a 0.5 mL single-dose pen
Route of Administration	oral	oral	SC	SC
Use	experimental	placebo	active-comparator	placebo- active-comparator

Abbreviations: LY = LY3502970; SC = subcutaneous.

6.1.1. Medical Devices

The medical devices provided for use in the study are marketed prefilled single-use pens for dulaglutide and prefilled single-dose placebo pens for dulaglutide placebo. Any medical-device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 10.3.3).

6.2. Preparation, Handling, Storage, and Accountability

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

The study site must store the study drug in a locked and secure environment. The study drug capsules may be stored at room temperature. Participants will also be provided with single dose pens (SDPs) containing dulaglutide or dulaglutide placebo at clinic visits according to the Study Schedule. Dulaglutide/matching placebo SDPs should be stored refrigerated (not frozen) at 2°C to 8°C. Dry ice should not be used for cooling. Participants will also receive insulated bags with cooling gel packs for use in transporting the SDPs from the site to the home. Study drug in each participating country will be labeled according to the country's regulatory requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an interactive web-response system (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

Participants will be randomly assigned to study intervention in a randomization ratio of 5:5:5:5:5:3:3:3:3, including 50 participants per treatment group to placebo, dulaglutide, LY1, LY2 and LY3 treatment groups, and 30 participants per treatment group to LY4-1, LY4-2, LY5-1 and LY5-2 treatment groups.

This is a double-blind study. All participants will take daily oral blinded study drug and weekly subcutaneously injected study drug. Participants will not know if they are receiving active or matching placebo oral study drug or active or matching placebo injectable study drug.

Stratification will be by country and HbA1c stratum (≤8.0%, >8.0%) at Visit 1.

Study intervention will be dispensed at the study visits summarized in SoA (Section 1.3).

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

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

Emergency codes will be available to the investigator and pharmacy. A code, which reveals the study intervention (group) for a specific study participant, may be opened during the study only if the participant's well-being requires knowledge of the participant's treatment assignment.

If a participant's study treatment assignment is unblinded, the participant must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical research physician/clinical research scientist (CRP/CRS) for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

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

6.4. Study Intervention Compliance

Participant compliance with study drug will be assessed at each visit. Compliance will be assessed by direct questioning and counting of unused study drug (capsules/single dose pens). Study drug compliance will be determined by the following:

- Study drug administration data will be recorded by the participant and reviewed by the investigator at each study visit.
- The participants will be instructed to return any unused study drug and/or empty vials at the next visit to the study site for the purpose of performing drug accountability.

In addition to the assessment of a participant's compliance with the study drug administration, other aspects of compliance with the study treatments will be assessed at each visit based on the participant's adherence to the visit schedule, completion of study, study drug administration logs, and any other parameters the investigator considers necessary.

Participants considered to be poorly compliant with their medication, 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. Additional unscheduled visits may be scheduled if study site personnel determine that a participant requires additional training for the study drug preparation and injection techniques.

6.5. Dose Modification

Participants who do not tolerate the first capsule dose escalation, in other words from 2 mg or 3 mg to 6 mg (or placebo equivalent), will need to discontinue from study treatment. If a participant does not tolerate a dose level higher than 6 mg for 1 week (for example, moderate-to-severe nausea, vomiting, or diarrhea) and the investigator does not believe that the participant will tolerate the dose with further exposure, then the investigator may reduce the dose to the next lower target dose (for example, 3 mg, 12 mg, 24 mg, or 36 mg). If this dose is tolerated after 2 weeks, the dose should be increased per original protocol dose escalation until the target dose is achieved. If this dose escalation is not tolerated, the dose should be reduced to the next lower target dose that was tolerated (for example, 3 mg, 12 mg, 24 mg, or 36 mg). The participant will remain at that dose level for the duration of the study. Maintenance doses of 2 mg, 6 mg, or 8 mg will not be allowed. The injectable study treatment should be maintained during dose modification of the capsule treatment.

Participants who do not tolerate the injectable study treatment, such as participants who have moderate to severe nausea and/or vomiting following 2 injections (2 weeks of treatment) and the investigator believes the participant will not tolerate the injectable treatment with further dosing will need to discontinue the injectable study treatment. The participant should continue taking the capsule study treatment.

In order to maintain blinding to study drug, the site should work through the IWRS web site portal for dose modifications.

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

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

6.7. Treatment of Overdose

Capsule Study Drug

For this study, any total dose estimated from where the participant is in the dose-escalation regimen or treatment-maintenance regimen within a 48-hour time period that is greater than 100 mg will be considered an overdose and should be reported per criteria described in Section 10.3.1. For example, if a participant takes 3 45-mg capsules within 48 hours or all of the capsules in a bottle at one time for dose escalations beginning with the 12 mg dose, those would be considered overdoses. The investigator should assume that all participants are assigned to LY 4-1 treatment group if the event occurs during Week 2 through Week 11, and to the LY 5 treatment group after Week 11 considering where the participant would be in the dose escalation and how many capsules were taken for calculation of the potential overdose.

Injectable Study Drug

For this study, taking more than 1 injection within a 72-hour period is considered an overdose.

Overdose Treatment

In the event of an overdose for either the capsule or the injectable study treatment, the investigator should

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 1 week. Based on the known AE profile of LY3502970, the following are the possible AEs related to an overdose:
    - Severe GI events that lead to dehydration and require medical intervention
    - CV abnormalities such as increase in heart rate, decrease in BP, supraventricular arrhythmias/cardiac conduction disorders
    - Hypoglycemia

Implement medical intervention/monitoring according to the clinical presentation.

Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).

Document the quantity of the excess dose as well as the duration of the overdose in the case report form (CRF).

6.8. Concomitant Therapy

Allowed concomitant medications should be taken according to label instructions. Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- reason for use
- dates of administration including start and end dates
- 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 drug administration by at least 2 to 4 hours.

Participants cannot be taking strong CYP3A inducers or inhibitors and drugs that are sensitive P-glycoprotein/breast cancer resistant protein (P-gp/BCRP) substrates with a narrow therapeutic index. In order to be eligible for screening into this study, those drugs need to be washed out for at least 2 weeks and the participant should be on a stable dose of alternative medications for at least 2 weeks prior to screening.

The FDA has provided a list of strong CYP3A4 inhibitors, which are listed below:

- boceprevir
- cobicistat
- danoprevir and ritonavir
- elvitegravir and ritonavir

- grapefruit juice
- indinavir and ritonavir
- itraconazole
- ketoconazole
- lopinavir and ritonavir
- paritaprevir and ritonavir
- ombitasvir and/or dasabuvir
- posaconazole
- ritonavir
- saquinavir and ritonavir
- telaprevir
- tipranavir and ritonavir
- telithromycin
- troleandomycin
- voriconazole
- clarithromycin
- nefazodon,
- nelfinavir

In order to be eligible for screening into this study, participants taking the following anti-fungal agents

- 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 prescribed clarithromycin or telithromycin, azithromycin may be considered as an alternative option. Participants who chronically use these drugs should be excluded.

Examples of sensitive P-gp substrates are:

- digoxin
- fexofenadine
- loperamide
- quinidine
- talinolol, and
- vinblastine

Participants taking these drugs are excluded from being screened for this study.

Examples of sensitive BCRP substrates are:

- coumestrol,
- daidzein,
- genistein,
- prazosin, and
- sulphasalazine.

Participants taking these drugs are excluded from being screened for this study.

Initial doses of LY3502970 may delay gastric emptying and have the potential to transiently impact the rate of absorption of concomitantly administered oral medicinal products. If an orally administered drug has a narrow therapeutic index and its oral absorption is sensitive to gastric emptying time, then LY3502970 and that drug should not be administered simultaneously because exposure to the non-study drug may be affected. It is recommended that the drugs are administered at least 2 to 4 hours apart.

Examples of drugs with narrow therapeutic indexes that may have increased exposure due to delayed gastric emptying and are commonly used in participants with T2DM:

- levothyroxine
- sulfonylureas
- warfarin/coumarins
- ethinyl estradiol
- oxycodone

6.8.1. Management of Participants with Gastrointestinal Symptoms

In the Phase 1 program, the most commonly reported treatment-emergent adverse events (TEAEs) for participants receiving LY3502970 were nausea, vomiting, and diarrhea. To mitigate GI symptoms and manage participants with intolerable GI AEs, the investigator should:

- 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. Also, participants may be informed that lower-fat meals could be better tolerated.
- Prescribe symptomatic medication (for example, anti-emetic or antidiarrheal medication) per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the eCRF.
- Temporarily interrupt study drug (omit 1 to 3 doses). The data related to temporary interruption of study treatment should be documented in source documents and entered on the eCRF.
- After the interruption, restart at the same dose with the participant taking medication to alleviate their GI symptoms.

If intolerable GI symptoms or events persist despite the above measures, see Section 6.5.

6.8.2. Hyperglycemia Rescue Medicine

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 26-week treatment period. An additional therapeutic intervention should be considered in participants who meet the following criteria:

- The participants are fully compliant with assigned therapeutic regimen.

  AND

- In the absence of any acute condition that raises BG either of the following occurs:
  - During the first 6 weeks post-randomization: An average fasting glucose level above 270 mg/dL (15.0 mmol/L) occurs over at least a 2-week period (at least 4 values/week must be available);
    Or
  - Average FBG >240 mg/dL (>13.3 mmol/L) over any 2-week period or longer from Week 6 to Week 12 postrandomization;
    Or
  - Average FBG >200 mg/dL (>11.1 mmol/L) over any 2-week period or longer after Week 12.

If these conditions are met, then participants may begin treatment with another antihyperglycemic agent as determined by their physician. If treatment with another antihyperglycemic agent is instituted, then study drug (both oral and injectable) should be permanently discontinued. Participants may remain in the study for safety follow-up, but the date at which they begin rescue therapy will be the last date for collection of efficacy measures.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

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

Possible reasons leading to permanent discontinuation of IP:

- Participant Decision
- The participant or the participant's designee (for example, parents or legal guardian) requests to discontinue IP.
- Investigator Decision
    - the investigator decides that the participant should be discontinued from the study medication
- Any medication for weight loss is given for more than 1 week
- Participants will be discontinued from the IP in the following circumstances:
    - Diagnosis of cirrhosis after randomization (refer to Section 8.3.3.7 for details)
    - Pancreatitis or pancreatic cancer (refer to Section 8.3.3.2 for details)
    - Diagnosis of medullary thyroid carcinoma (MTC) after randomization
    - Diagnosis of an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
    - Any TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
    - A female participant becomes pregnant
    - Diagnosis of T1DM or latent autoimmune diabetes in adults
- If the participant develops any exclusion criteria during the course of the study, the investigator should call the sponsor to determine whether discontinuation of study drug is necessary
- Significant non-compliance with the protocol

Study drug should be temporarily discontinued in any individual suspected of having a severe or serious allergic reaction to study drug or other serious safety concerns. Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator.

If study drug is permanently discontinued, the participant should remain in the study. The participant should continue participation in the study, attend all visits, and undergo most protocol procedures.

Participants discontinuing from the IP prematurely for any reason should complete AE and other follow-up procedures per Section 1.3 (SoA), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

7.1.1. Liver Chemistry Stopping Criteria

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

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/ discontinuation decisions rather than TBL>2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL > 2x ULN	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/ discontinuation decisions rather than TBL>2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.	

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

7.1.2. QTc Stopping Criteria

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

7.1.3. Temporary Discontinuation

After randomization, the investigator may interrupt study drug, for example, due to an AE (for example, nausea of moderate severity or vomiting), or a clinically significant laboratory value. If

study drug interruption is due to an AE, the event is to be followed and documented. Every effort should be made by the investigator to maintain participants in the study and to restart study drug promptly after any interruption, as soon as it is safe to do so (See Section 7.1.4 for restarting study drug). The dates of study drug interruption and restart must be documented. The data related to interruption of study treatment will be documented in source documents and entered on the eCRF.

7.1.4. Restarting Study Drug after Interruption

Capsule Study Drug

If the number of consecutive missed capsule doses is ≤7, the treatment can be restarted at the same dose.

Participants who have missed >7 days of capsule study drug will need to restart the study drug at the 8 mg dose (LY3502970 treatment groups 2, 3, 4-1, 4-2, 5-1, and 5-2) and dose escalate according to the protocol. LY3502970 treatment group 1 (2/3 mg group) will restart study drug at 3 mg and remain at that level for the duration of the study.

In order to maintain blinding of the investigator and participant, the investigator should work through the IWRS web site portal for restarting study drug and IWRS will provide dispensing information. Dose reductions may occur at unscheduled visits.

Injectable Study Drug

Participants who have missed any amount of injectable study drug may restart the injectable study drug at any time. There is no dose escalation procedure associated with the injectable study drug.

The investigator will use the IWRS web site portal to receive the appropriate study drug dispensing information to preserve blinding of the study drug.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from both the study intervention and the study at that time.

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically advisable for the participant to continue on study treatment. If the investigator and the Lilly CRP/CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled participant to continue in the study with or without treatment with IP. Safety follow-up should be performed as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events, Serious Adverse Events, and Product Complaints) of the protocol.

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (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.

8.1. Efficacy Assessments

Primary:

The primary efficacy measure is change from baseline in HbA1c, as determined by the central laboratory.

Secondary:

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

- HbA1c as determined by the central laboratory
- Fasting blood glucose (FBG) as determined by the central laboratory
- Body weight (see Section 10.8 for measurement procedure)

Exploratory:

- BMI (see Section 10.8 for measurement procedure)
- Waist circumference (see Section 10.8 for measurement procedure)
- Seven-point SMBG (see Section 10.8 for measurement procedure)
- Mechanistic biomarkers: to explore potential mechanisms of action related to changes in glucose, lipid, and/or nutrient metabolism, markers will be assessed.
- Patient-reported outcomes (see Section 10.9 for details)
    - Short Form-36 version 2 Health Survey acute form, 1-week recall version
    - Diabetes Treatment Satisfaction Questionnaire-Status Version
    - Diabetes Treatment Satisfaction Questionnaire-Change Version
    - Participant Survey

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the CV, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded as per the SoA Section 1.3. Refer to Section 10.8 for further details on weight measurements.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, CV system, and abdomen (liver and spleen).

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

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the Schedule of Activities (Section 1.3) and following the study-specific recommendations included in Section 10.8).

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

8.2.3. Electrocardiograms

For each participant, 12-lead ECGs should be collected according to Section 1.3.

- All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory.
- 12-lead ECGs should be obtained after the subject has rested in a supine position for at least 10 minutes.

Electrocardiograms should be collected prior to collection of blood samples for laboratory testing, including PK trough level samples.

Screening and early termination ECGs may be collected as single ECGs. All other ECGs are to be recorded in triplicate; consecutive replicate ECGs will be obtained at approximately 1-minute intervals.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

Electrocardiograms will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria and for immediate participant management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE. The investigator (or qualified designee) is responsible for determining if any change in participant management is needed, and must document his/her review of the ECG printed at the time of evaluation.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the

participant will be assessed by the investigator for symptoms (for example, palpitations, near syncope, and syncope) and to determine whether the participant can continue in the study. The investigator or qualified designee is responsible for determining if any change in participant. management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

All digital ECGs will be obtained using centrally provided ECG machines and 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 over-read 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 HR may be used for data analysis and report-writing purposes, unless a cardiologist over-reading of the ECGs is conducted prior to completion of the final study report (in which case, the over-read data would be used).

Any treatment-emergent clinically significant ECG finding resulting in a diagnosis should be reported as an AE in the eCRF.

8.2.4. Clinical Safety Laboratory Tests

- See Section 10.2 (Appendix 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 or within 2 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA (Section 1.3), standard collection requirements.

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

8.2.5. Pregnancy Testing

Female participants will undergo a serum pregnancy test at screening.

8.2.6. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. The study team will review safety reports in a blinded fashion (for applicable blinded study period) according to the schedule provided in the Trial-Level Safety Review plan. Lilly will also review SAEs within time frames mandated by company procedures. The Lilly CRP/CRS will, as appropriate, consult with the functionally independent Global Patient Safety (GPS) therapeutic area physician or clinical scientist. Safety monitoring will include review of hepatic, pancreatic, CV, thyroid c-cell function, and renal safety data. The hepatic safety monitoring plan is provided below; for additional information, please see also Section 10.5.

8.2.6.1. Hepatic Safety Monitoring

Close hepatic monitoring

Laboratory tests (Section 10.2), including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

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

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

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

Comprehensive hepatic evaluation

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

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

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computerized tomography [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 (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

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

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

1. Elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests (if baseline ALT <1.5X ULN)

- In participants with baseline ALT ≥1.5X ULN, the threshold is ALT ≥3X baseline on 2 or more consecutive tests

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

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

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

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

- AEs
- SAEs
- Product complaints (PCs)

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

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

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

For some studies, participants are not always able to provide valid verbal responses to open-ended questions. In these circumstances, another method of detecting events must be specified.

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

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	start of study drug	participation in study has ended	Should be recorded in the eCRF as soon as possible. The sponsor will periodically evaluate safety data in the eCRF.	AE eCRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	signing of the informed consent form (ICF)	start of intervention	Within 24 hours of awareness	SAE eCRF	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 eCRF	SAE paper form
SAE*– after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	90 days or 3 months after last participant visit	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	SAE paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥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 female participant who becomes pregnant while participating in the study will discontinue study intervention. 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 are AEs that will be adjudicated by an external adjudication committee

- pancreatitis (see Section 8.3.3.2)
- major adverse CV events (see Section 8.3.3.4),
- supraventricular arrhythmias and cardiac conduction disorders (Section 8.3.3.5)
- drug-induced liver injury, and
- deaths.

The following are additional adverse events of special interest (AESI)

- hypoglycemia (Level 2 and 3)
- severe persistent hyperglycemia
- thyroid malignancies and C-cell hyperplasia
- hepatobiliary disorders
- severe GI AEs, and
- acute renal events.

Sites should collect additional details and data regarding these AEs, as instructed on the applicable eCRFs, and detailed below.

8.3.3.1. Hypoglycemia

Upon ICF signing, all participants will be educated about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia.

Participants who develop persistent or recurrent unexplained hypoglycemia during the treatment period will be asked to reduce the dose or discontinue any concomitant glucose-lowering agents other than study drug. Study drug discontinuation for recurrent hypoglycemia should be considered only if these events continue despite complete discontinuation of concomitant medications.

All hypoglycemic episodes will be recorded on a specific eCRF and should not be recorded as AEs unless the event meets serious criteria. If a hypoglycemic event meets severe criteria (see definition below), it should be recorded as serious on the AE and SAE eCRFs, and reported to Lilly as an SAE.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the BG values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips) in accordance with the 2020 American Diabetes Association position statement on glycemic targets (ADA 2020) as below. **Level 2** and **Level 3** hypoglycemia events are considered as safety topics of special interest:

Level 1 hypoglycemia:

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

Level 2 hypoglycemia:

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

Level 3 hypoglycemia:

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

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

Nocturnal hypoglycemia:

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

8.3.3.2. 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):

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

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase and lipase
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal MRI, 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 IP. In this case, the participant needs to receive an appropriate alternative glucose lowering regimen. Afterwards, if pancreatitis is confirmed by the adjudication committee, the IP must be permanently discontinued, and the participant needs to be followed throughout the duration of the study. If the case is not confirmed, then the participant can restart the IP if the investigator deems as clinically appropriate as described in Section 6.5 (Dose Modification).

Case adjudication and data entry

An independent clinical endpoint committee (CEC) will adjudicate all suspected cases of acute pancreatitis. Relevant data from participants with acute pancreatitis will be entered into a specifically designed eCRF page. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

Asymptomatic elevation of pancreatic 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.

8.3.3.3. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or MEN2 will be excluded from the study. Participants who are diagnosed with MTC and/or MEN2 during the study will have study drug stopped and should continue follow-up with an endocrinologist. Additionally, participants who have a serum calcitonin level of ≥20 ng/L, if eGFR ≥ 60 mL/min/1.73 m^2 or ≥35 ng/L if eGFR < 60 mL/min/1.73 m^2, as determined by central laboratory at Visit 1, will also be excluded.

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. These data will be captured in specific eCRFs. 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.

If an increased calcitonin value (see definitions below) 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.

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 eCRF.

Calcitonin Measurements in Participants with eGFR ≥60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR ≥60 mL/min/1.73 m^2 is defined below. If a participant's laboratory results meet these criteria, these clinically significant laboratory results should be recorded as an AE.

- *Serum calcitonin value ≥20 ng/L and <35 ng/L AND ≥50% increase from the screening value.* These participants will be requested to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the study drug should be discontinued, and the participant should undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude adverse effects on the thyroid gland.
- *Serum calcitonin value ≥35 ng/L AND ≥50% over the screening value*. In these participants, study drug should be discontinued, and the participant should be recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist.

Calcitonin Measurement in Participants with eGFR <60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR <60 mL/min/1.73 m^2 is defined as a *serum calcitonin value ≥35 ng/L AND ≥50% over the screening value.* If a participant's labs meet these criteria, these clinically significant labs should be recorded as an AE.

In these participants, 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 adverse effects on the thyroid gland.

8.3.3.4. Major Adverse Cardiovascular Events

Nonfatal CV AEs 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.

8.3.3.5. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac 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 reading center. 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.

8.3.3.6. Deaths

All deaths will be adjudicated by a committee of physicians external to Lilly. This committee will be blinded to treatment assignment.

8.3.3.7. Hepatobiliary Disorders

All events of TE biliary colic, cholecystitis, cholelithiasis or other suspected events related to acute gallbladder disease 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 8.2.6.1.

8.3.3.8. Severe Gastrointestinal Adverse Events

LY3502970 and dulaglutide 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 eCRFs, respectively. For detailed information concerning the management of GI AEs, please refer to Section 6.8.1.

8.3.3.9. 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. Gastrointestinal AEs have been reported with LY3502970 including nausea, diarrhea, and vomiting. This is consistent with other GLP-1R agonists (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.

8.4. Pharmacokinetics

Blood samples will be collected from all randomized participants in accordance with schedule provided in Section 1.3 and at ET for measurement of plasma concentrations of LY3502970. Participants may need to return to the clinical site for PK-specific visits to provide post-dose PK samples dependent on the time window of PK sampling. Only samples from participants assigned to treatment with LY3502970 will be analyzed for drug concentration.

Date and time of each sample and the most recent LY3502970 dose prior to PK blood draw must be recorded. Drug concentration information that would unblind the study will not be reported to study sites or blinded personnel while the study is blinded.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3502970 will be assayed using a validated liquid chromatography mass spectrometry method. Analyses of samples collected from participants who received placebo or dulaglutide are not planned. Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 1 year following the last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as additional metabolism, protein binding, or exploratory analyses including bioanalytical assay validation or cross-validation exercises.

Instructions for the collection and handling of blood samples will be provided by the sponsor.

8.5. Pharmacodynamics

Efficacy measures will be used as indicators of pharmacodynamic response.

8.6. Genetics

Not applicable.

8.7. Biomarkers

In addition to the planned biomarker research as indicated in the SoA (Section 1.3), biomarker research on stored nonpharmacogenetic samples may be performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including proteins, lipids, and other cellular elements.

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

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

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3502970 or after LY3502970 becomes commercially available.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The study hypothesis for the primary objective is that at least one dose level of QD oral doses of LY3502970 is superior in change from baseline for HbA1c relative to placebo at Week 26, in participants with T2DM inadequately controlled with diet and exercise alone or treated with a stable dose of metformin.

9.1.1. Multiplicity Adjustment

Treatment comparisons will be performed for the primary objective at the full significance level of 0.05. No multiplicity adjustments will be made for the analysis of secondary and exploratory objectives.

9.2. Analyses Sets

For the purposes of analysis, the following analysis population and datasets are defined:

Participant Analysis Population/Datasets	**Description**
Entered Participants	All participants who sign informed consent.
Randomized	All participants who are randomly assigned a study drug.
Efficacy Analysis Set (EAS)	Data obtained during the treatment period from all randomized participants who are exposed to at least 1 dose of study drug. Excludes data after permanent discontinuation of study drug or initiation of rescue medication. Participants will be included in the treatment group to which they were randomly assigned.
Full Analysis Set (FAS)	Data obtained during the treatment period from all randomized participants who are exposed to at least 1 dose of study drug, regardless of adherence to study drug or initiation of rescue medication. Participants will be included in the treatment group to which they were randomly assigned.
Safety Analysis Set (SS)	Data obtained during the treatment period plus safety follow-up from all randomized participants who are exposed to at least 1 dose of study drug, regardless of adherence to study drug or initiation of rescue medication. Participants will be included in the treatment group to which they were randomly assigned.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study 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 statistical analysis plan (SAP) or the clinical study report (CSR). Additional exploratory analyses of data will be conducted, as deemed appropriate.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (CIs) will be calculated at 95%, 2-sided. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

Baseline is defined as the last non-missing measurement at or before randomization visit (prior to first dosing of study drug) unless otherwise specified.

The primary estimand (a precise definition of the treatment effect to be estimated) of interest in comparing efficacy of LY3502970 doses with placebo is the "efficacy estimand" (Section 2.3.1). The primary efficacy assessment guided by the "efficacy estimand" will be conducted using the EAS (Section 9.2). To estimate the "efficacy estimand", when change from baseline is included as a response variable of analysis models, the participants will be included in the analysis only if a baseline and at least 1 postbaseline measurement are available. A restricted maximum likelihood-based, mixed-effect model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model for the analysis of the primary efficacy endpoint of change from baseline in HbA1c will include the fixed class effects of treatment (placebo, dulaglutide, LY1, LY2, LY3, LY4-1, LY4-2, LY5-1, LY5-2), strata (country, HbA1c stratum [≤8%, >8%]), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline value. An unstructured covariance structure will be used to model the within-participant errors. Significance tests will be based on least squares (LS) means and Type III tests. If this analysis fails to converge, the following covariance structures will be tested in order:

- Toeplitz with heterogeneity
- Autoregressive with heterogeneity
- Compound symmetry with heterogeneous variances
- Toeplitz
- Autoregressive
- Compound symmetry without heterogeneous variances

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Additional supplemental estimands may be explored for the primary and secondary efficacy endpoints.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3502970 doses with placebo and dulaglutide irrespective of adherence to study drug. Thus, safety analyses will be conducted using the SS.

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. LS means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons.

For categorical measures, summary statistics will include sample size, frequency, and percentages. A logistic regression model with treatment and strata as fixed effects and the continuous baseline value as a covariate will be used to examine the treatment difference in binary efficacy outcomes. Fisher's exact test or Pearson's chi-square test will be used for treatment comparisons in other categorical outcomes.

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

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

The primary efficacy assessment, guided by the "efficacy estimand", will be conducted using the EAS for the primary endpoint (change from baseline in HbA1c at Week 26).

For the "efficacy estimand", the hypothetical strategy is used to handle the intercurrent events (permanent discontinuation of study drug or initiation of rescue medication), so only data collected before the occurrence of any intercurrent events will be used in the MMRM analysis (Section 9.3.1) through which the potential efficacy measures (after the intercurrent events) had participants had not intercurrent events will be implicitly imputed.

The primary efficacy comparison will be based on the contrast between each treatment group of LY3502970 and placebo at Week 26 (Visit 15) from the MMRM analysis of change from baseline in HbA1c using the EAS (Section 9.2). The analysis model and selection of covariance structure is described in Section 9.3.1. To confirm efficacy of LY3502970 with adequate statistical power, the evaluation of the primary endpoint for LY4 (36 mg) and LY5 (45 mg) will be made by pooling two dose escalation regimens, i.e., combine LY4-1 and LY4-2 for LY4, and combine LY5-1 and LY5-2 for LY5.

Treatment comparisons will be performed for the primary objective at the full significance level of 0.05.

9.3.3. Secondary Analyses

The following secondary study objectives will be analyzed on the EAS:

- Difference between LY3502970 and dulaglutide in change from baseline in HbA1c at Week 26
- Percentage of participants with HbA1c ≤6.5% and of <7.0% at Week 26
- Change from baseline in fasting BG at 26 weeks
- Change from baseline in body weight at Week 26
- Percent change in body weight from baseline at Week 26

- Percentage of participants with ≥5%, ≥10% body weight loss from baseline at Week 26

Actual and change from baseline in HbA1c, FBG, and body weight, and percent change in body weight will be analyzed by the MMRM model for the "efficacy estimand" as described in Section 9.3.1.

Treatment comparisons for the percentage of participants with HbA1c <7.0% and ≤6.5% and percentage of participants with ≥5%, ≥10% body weight loss will be analyzed using a logistic regression with treatment and strata as fixed effects and the continuous baseline value as a covariate.

9.3.4. Tertiary/Exploratory Analysis

A Bayesian approach will be used as the dose–response model for change in HbA1c and body weight from baseline to the 26-week endpoint. The placebo group will be modeled with LY3502970 doses. Details of the prior distribution specifications along with other analyses with regards to the exploratory objectives will be provided in the SAP.

9.3.5. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3502970 doses with placebo and dulaglutide 1.5 mg irrespective of adherence to study drug. Thus, safety analyses will be conducted using the SS.

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized MedDRA Queries. Summary statistics will be provided for incidence of TEAEs, SAEs, study discontinuation due to AEs, study drug discontinuation due to AEs, deaths, and other CV endpoints. Counts and proportions of participants experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

9.3.5.1. Adverse Event of Special Interest

Summaries and analyses for incidence of AESIs will be provided by treatment. The details of analysis of AESI (as defined in Section 8.3) will be provided in the SAP.

9.3.5.2. Other Adverse Event Assessments

9.3.5.2.1. Gastrointestinal Events

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

9.3.5.2.2. Hypoglycemia Events

Hypoglycemic events will be analyzed. Incidence and rate of hypoglycemia will be reported. Some analyses may be conducted excluding data after introducing another antihyperglycemic therapy.

9.3.5.3. 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, as well as the change from baseline for these variables, will be analyzed by MMRM models as described in Section 9.3.1. The percentages of participants with treatment-emergent (TE) abnormal, high, or low measures (including laboratory, vital, and ECG parameters) will be summarized and compared between treatment groups using Fisher's exact test.

9.3.6. Pharmacokinetic/Pharmacodynamic Analyses

LY3502970 concentration data will be summarized and analyzed using a population PK approach via nonlinear mixed-effects modeling. The relationships between LY3502970 dose and/or concentration and selected efficacy, tolerability, and safety endpoints may be characterized. Additionally, the impact of intrinsic and extrinsic factors, such as age, weight, gender, and renal function on PK and/or PD parameters, may be examined as needed. Additional analyses may be conducted if they are deemed appropriate.

9.3.7. Subgroup Analyses

Subgroup analyses of the primary endpoint will be made to assess consistency of the intervention effect across the following subgroups using the "efficacy estimand":

- Age group: < 65 vs ≥ 65 years
- Sex: female vs male
- HbA1c stratum (≤8.0%, >8.0%)
- BMI (≤30 kg/m^2, >30 kg/m^2)
- Race
- Ethnicity
- Country/Region

If the number of participants is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. Further details on the statistical analysis will be provided in the SAP.

Analyses for HbA1c and change from baseline in HbA1c will be performed using an MMRM model that includes the same fixed effects given for the primary analysis model plus factors of subgroup, 2-way interaction of subgroup and treatment, 2-way interaction of subgroup and visit, and 3-way interaction of treatment, visit and subgroup. The interaction of subgroup and treatment at the primary endpoint (Week 26) will be evaluated to assess the treatment by subgroup interaction. Additional subgroup analyses may also be performed.

9.4. Interim Analysis

An interim efficacy and safety assessment after all participants complete Visit 12 (Week 16) of the treatment period may be conducted to provide information for dose escalation schemes and clinical trial material packaging for future studies. If conducted, an internal Assessment

Committee (AC) will be formed to review the interim analyses for the safety and efficacy reports in an unblinded manner. Additional interim analyses may be conducted. Details on the timing of the interim analyses, operational support, and unblinding will be specified in the AC charter and in the study unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members before the study has been unblinded for the final data base lock. Study sites will receive information about interim results only if deemed necessary for the safety of the participants. The trial will not be stopped based on the superiority of LY3502970 versus placebo or dulaglutide 1.5 mg. Therefore, there will be no inflation of the type 1 error rate and no need to employ an alpha spending function or multiplicity adjustment.

The database lock and primary data analysis for Study GZGE will occur when all participants have completed the study. Participants and investigators will remain blinded until the completion of the study.

The cancellation or addition of an interim analysis can be determined at any time during the study and will not require a protocol amendment.

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document. The SAP will describe the planned interim analyses in greater detail.

9.5. Sample Size Determination

Approximately 370 participants will be randomly assigned to study drug in a randomization ratio of 5:5:5:5:5:3:3:3:3:3, including 50 participants per treatment group to placebo, dulaglutide, LY1, LY2 and LY3 treatment groups, and 30 participants per treatment group to LY4-1, LY4-2, LY5-1 and LY5-2 treatment groups.

The sample size calculation is based on the primary efficacy estimand and its endpoint (change from baseline to Week 26 in HbA1c). Assuming a SD of 1.1%, a 2-sided alpha level of 0.05, 40 completers for one LY3502970 treatment group and 40 completers for the placebo group can provide >90% power to detect a treatment difference of -0.9% between the LY3502970 treatment group and placebo (LY3502970– Placebo) in change from baseline HbA1c at Week 26. Taking into consideration a potentially higher dropout rate due to gastrointestinal events in the higher doses of LY, 50 participants for placebo arm and 60 participants per treatment group (or 30 participants per dose escalation regimen) for LY4 and LY5 should be randomized. Assuming a same 20% dropout rate for dulaglutide, LY1, LY2, and LY3, 50 participants per treatment group should be randomized.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Informed Consent Process

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

- 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.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.3. Data Protection

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

10.1.4. Dissemination of Clinical Study Data

Report Preparation

An investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Public Access to Reports and Data

Reports

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

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK data. Data are available to request 6 months after the indication studied has been approved in the US and European Union (EU) and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once they 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, 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.clinicalstudydatarequest.com.

Publications/Publication Policy

The publication policy is described in the letters of agreement between the sponsor and the investigators and institutions.

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

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

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

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.5.

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

The first act of recruitment is the first participant to enter screening and will be the study start date.

Study or Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

Discontinuation of the Study

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

A safety investigation will be triggered to determine if the study should be terminated early based on the following criteria:

- Three study participants develop the same TEAE or SAE considered possibly or probably related to study drug that is severe or medically significant, but not immediately life threatening; or where hospitalization or prolongation of hospitalization is indicated; or is disabling; or limits self-care activities of daily living
  OR
- Two study participants develop any TEAE or SAE regardless of attribution to study drug that has life-threatening consequences or requires urgent intervention
  OR
- Death of any study participant at any time related to AE that is considered possibly or probably related to study drug study drug.

10.1.8. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.9. Investigator Information

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Clinical Laboratory Tests	**Comments**
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Differential	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	

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	
Glucose	
Lipid Panel	Assayed by Lilly-designated laboratory
High-density lipoprotein cholesterol (HDL-C)	
Low-density lipoprotein cholesterol (LDL-C)	
Very low-density lipoprotein cholesterol (VLDL-C)	
Total cholesterol	
Triglycerides	
Urinalysis	Assayed by Lilly-designated laboratory
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment (as indicated)	

Hormones (female)	Assayed by Lilly-designated laboratory
Serum pregnancy	
Follicle stimulating hormone (FSH)	
Estradiol	
Urine Chemistry	Assayed by Lilly-designated laboratory
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory
eGFR (CKD-EPI)	
Urinary albumin/creatinine ratio (UACR)	
Pharmacokinetic Samples – LY3502970 concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory storage samples:	
Serum	
Plasma (EDTA)	
Plasma (P800)	
Whole blood (EDTA)	
LY3502970 concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Hypersensitivity Tests	• Laboratory assessments should be performed if the participant experiences generalized urticaria or if anaphylaxis is suspected. • Collect sample after the participant has been stabilized, and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected. • Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

• Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. ***Note*:** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine sample for N-methylhistamine testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine N-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for N-methylhistamine testing at the next regularly scheduled visit or after 4 weeks, whichever is later.
• Drug-specific IgE	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
• Basophil activation test	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. ***Note:*** The basophil activation test is an in vitro cell-based assay that only requires a serum sample. It is a surrogate assay for drug-specific IgE, but is not specific for IgE.
• Complement (C3, C3a, and C5a)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
• Cytokine panel (IL-6, IL-1β, and IL-10)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

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

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization (ISO) 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices).

10.3.1. Definition of AE

AE Definition
a. 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.
b. An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

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

- 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 NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

• Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect • Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
f. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
g. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product Complaint
a. A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints: b. Deficiencies in labeling information, and c. Use errors for device or drug-device combination products due to ergonomic design elements of the product.

d. Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
e. Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
f. An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

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

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

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

Assessment of Intensity

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

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living,

causing discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible.

This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via 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 medical monitor by telephone.
- Contacts for SAE reporting can be found in study start up materials and from the study CRA.

SAE Reporting via Paper Form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the medical monitor or Lilly Global Patient Safety.
- 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 in study start up materials.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

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

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of child bearing potential	Females are considered a woman of childbearing potential if • they have had at least one cycle of menses, or • they have Tanner 4 breast development. Any amount of spotting should be considered menarche. If Tanner Staging of breasts is performed as part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical Trial regarding Tanner staging.
Women not of childbearing potential	Females are considered women not of childbearing potential if • they have a congenital anomaly such as Mullerian agenesis, • they are infertile due to surgical sterilization, or • they are post-menopausal. Examples of surgical sterilization include • hysterectomy, • bilateral oophorectomy, and • tubal ligation.
Postmenopausal state	The postmenopausal state should be defined as: 1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or 2. A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND With a follicle-stimulating hormone >40 mIU/mL; or 3. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or 4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy * Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.
Reproductive Toxicology Studies	Embryo-fetal studies are toxicity studies in pregnant animals designed to identify abnormalities in the development of fetuses, which could indicate potential for teratogenicity in humans. The relevant dosing period is during organogenesis.

10.4.2. Contraception Guidance

Women of childbearing potential are excluded from participation in this study.

The table below describes contraception guidance for men.

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for 90 days or 3 months after last participant visit
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study, and • for 90 days or 3 months after last participant visit
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

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

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

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

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

See protocol Section 8.2.6.1 for guidance on appropriate test selection.

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

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

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

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

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

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio.

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

10.6. Appendix 6: World Health Organization Classification of Diabetes and Diagnostic Criteria

Type 1 Diabetes: Type 1 diabetes 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: Type 2 diabetes, 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 type 2 diabetes, 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 type 2 diabetes later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998).

10.7. Appendix 7: New York Heart Association Functional Classification of Heart Failure

Class	Symptomatology
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

10.8. Appendix 8: Protocol GZGE Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, Vital Signs and 7-Point Self-Monitoring Blood Glucose (SMBG)

The following information has been adapted from standardized physical measurement protocols for the WHO's STEPwise approach to Surveillance (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.
- Body weight should be measured in fasting state. If the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting body weight measured.

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 nonstretchable 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 eCRF. 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 (blood pressure and heart rate, 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, 2 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 eCRF.
- BP must be taken with an automated blood pressure instrument.
- If blood pressure and pulse measurements are taken separately, pulse should be taken prior to blood pressure.

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

7-Point Self-Monitoring Blood Glucose

Seven-point SMBG profiles consist of measurements obtained before each meal, approximately 2 hours after each meal, and at bedtime on a day during the week before the scheduled clinic visit. Participants will record their SMBG levels in their diaries, according to instructions. The complete 7-point profile must be collected on a single day. If a participant does not complete the entire profile on a single day, all 7 points must be collected on a subsequent day.

10.9. Appendix 9: Patient-Reported Outcomes

Short Form-36 version 2 Health Survey acute form, 1 week recall version

The Short Form-36 version 2 Health Survey acute form (SF-36v2 acute), 1-week recall version is a 36-item generic, participant-completed measure designed to assess the following 8 domains

- Physical Functioning
- Role Physical
- Bodily Pain
- General Health
- Vitality
- Social Functioning
- Role Emotional, and
- Mental Health.

The Physical Functioning domain assesses limitations due to health "now" while the remaining domains assess functioning "in the past week." Each domain is scored individually and information from these 8 domains are further aggregated into 2 health component summary scores: Physical Component Summary and Mental Component Summary. Items are answered on Likert scales of varying lengths (3-point, 5-point, or 6-point scales). Scoring of each domain and both summary scores are norm based and presented in the form of T-scores, with a mean of 50 and standard deviation of 10; higher scores indicate better levels of function and/or better health (Maruish 2011).

Diabetes Treatment Satisfaction Questionnaire-Status Version

The Diabetes Treatment Satisfaction Questionnaire-Status Version (DTSQs) (Bradley and Lewis 1990; Bradley 1994) is a diabetes-specific patient-reported outcome instrument that assesses the overall treatment satisfaction and perceived frequency of hyperglycemia and hypoglycemia. It is appropriate for use in both type 1 and type 2 diabetes.

The DTSQs consists of 8 items that assess treatment satisfaction as well as concerns about hyperglycemia and hypoglycemia over the past few weeks, prior to the visit. Each item is rated on a 7-point Likert scale. Items 1, 4, 5-7, and 8 are rated from 0 (very dissatisfied) to 6 (very satisfied) and can be summed up to produce a treatment satisfaction score. 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).

Diabetes Treatment Satisfaction Questionnaire-Change Version

The Diabetes Treatment Satisfaction Questionnaire-Change Version (DTSQc) (Bradley 1999) was designed to overcome potential ceiling effects in the status version. The DTSQc 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 scale of -3 to +3. For all items except items 2 (perceived frequency of hyperglycemia) and item 3 (perceived frequency of hypoglycemia):

- the higher the score, the greater the improvement in treatment satisfaction
- the lower the score, the greater the deterioration in treatment satisfaction, and
- a score of 0 represents no change.

For items 2 and 3: the lower the score, the better the perception.

Participant Survey
The Participant Survey is a participant-completed form, which includes questions to understand participant experience with and preference for study treatments (injectable vs. oral)**,** and the factors influencing their preferences.

10.10. Appendix 10: 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, adverse events, SMBG values and concomitant medications

Mobile healthcare:

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

Other alternative locations:

During exceptional circumstances, laboratory samples may be drawn locally, if needed outside of mobile healthcare visits.

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: Visits 3, 10, and 15. 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.

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 paused due to exceptional circumstances:

- If screening is paused for less than 30 days from screening visits to randomization visit: the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within 30 days from first screening/lead-in visit.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused 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 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. 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 4 through Visit 15	within 10 days before or after the intended date per the SoA
Visit 801	within 14 days before the intended date, or up to 28 days after the intended date per the SoA

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.

10.11. Appendix 11: Abbreviations and Definitions

Term	Definition
AC	Assessment Committee
ADA	American Diabetes Association
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
blinding/masking	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BP	Blood pressure
CEC	Clinical endpoint committee
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
Cmax	maximum concentration
CMV	cytomegalovirus

complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRS	clinical research scientist
CSR	Clinical study report
CV	cardiovascular
D. bil.	Direct bilirubin
DTSQc	Diabetes Treatment Satisfaction Questionnaire-Change Version
DTSQs	Diabetes Treatment Satisfaction Questionnaire-Status Version
EAS	Efficacy analysis set
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic case report form
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.
ERCP	endoscopic retrograde cholangiopancreatography
ET	Early termination
FAS	Full analysis set
FBG	fasting blood glucose
FSH	follicle stimulating hormone
GI	gastrointestinal

GCP	good clinical practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GPS	Global Patient Safety
HbA1c	hemoglobin A1c
HAV, HBV, HCV, HDV, HEV	hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, hepatitis E virus
HIV	human immunodeficiency virus
HR	heart rate
HSV	herpes simplex virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
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.
IP	Investigational product is a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
IWRS	interactive web-response system
LH	luteinizing hormone
LS	least squares
LY	LY3502970

MAD	multiple-ascending dose
MEN2	multiple endocrine neoplasia type 2
MMRM	mixed-effect model repeated measures
MRCP	magnetic resonance cholangiopancreatography
MTC	medullary carcinoma of the thyroid
OTC	over-the-counter
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
PR	pulse rate
Pro-C3	biomarker for liver fibrosis
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PT-INR	Prothrombin time
QD	once-daily
QTc	corrected QT interval
QW	once-weekly
OTC	over the counter
SAD	Single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SS	Safety analysis set
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.
SF-36 v2 acute form	Short Form-36 version 2 health survey acute form
SDPs	single dose pens
SMBG	self-monitoring of blood glucose
SoA	schedule of activities

T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
THC	tetrahydrocannabinol
TXP	treatment
UACR	Urinary albumin creatinine ratio
ULN	Upper limit of normal
WHO	World Health Organization
Wks	weeks
WNOCBP	women not of childbearing potential

10.12. Appendix 12: 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: 30 June 2021

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

There was a typographical error in the Section 2.3 Benefit/Risk assessment. The section referred to ambulatory blood pressure monitoring (ABPM). ABPM is not being conducted in this study; however, it is being collected in a Phase 2 obesity study (J2A-MC-GZGI) that will be conducted at the same time as this study.

Section # and Name	Description of Change	Brief Rationale
2.3.1. Risk Assessment	Deleted reference to ABPM, as it will not be conducted in this study.	ABPM is not being conducted in this study but is being conducted in a Phase 2 study evaluating the effects of LY3502970 in participants with obesity or overweight with comorbidities.
Throughout the protocol	Minor editorial changes made throughout the protocol.	Correction

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Leo Document ID = 3a662cc0-d0a4-4912-b29e-a3a0309049de

Approver: PPD

Approval Date & Time: 27-Oct-2021 00:43:02 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 27-Oct-2021 00:51:01 GMT

Signature meaning: Approved