Protocol: J1I-MC-GZBD(c)

A Phase 2 Study of Once-Weekly LY3437943 Compared with Placebo and Dulaglutide in Participants with Type 2 Diabetes

NCT04867785

Approval Date: 29-Aug-2022

Title Page

Protocol Title: A Phase 2 Study of Once-Weekly LY3437943 Compared with Placebo and Dulaglutide in Participants with Type 2 Diabetes

Protocol Number: J1I-MC-GZBD

Amendment Number: c

Compound: LY3437943

Study Phase: Phase 2

Short Title: Effect of LY3437943 Versus Placebo and Dulaglutide in Participants with Type 2 Diabetes

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 145825

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

Document ID: VV-CLIN-072318

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment b	*10-May-2021*
Amendment a	*1-Mar-2021*
Original Protocol	*19-Feb-2021*

Amendment [c]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The overall changes and rationale for the changes made in this amendment are described in the following table.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Pharmacokinetic (PK) sample row: Updated sample taken at Visit 13 from Predose to Postdose	Dosing does not occur at Visit 13 (Week 36); therefore, time point is now described as approximately 1 week post the last dose (Week 35).
	Pharmacokinetic Schedule of Events table Sample #11 row: Updated collection time point from "Predose (up to 8 hours)" to "Postdose (approximately 1 week)"	Dosing does not occur on Week 36. This sample collection time point is approximately 1 week following the last dose.
	Pharmacokinetic Schedule of Events table Sample #12 row: Updated collection time point from "4 weeks post last dose" to "5 weeks post last dose"	Since last dose is on Week 35, the Sample #12 collected at the Safety Follow-up visit is 5 weeks post the last dose.
Section 7.1 Discontinuation of Study Intervention	Information about inadvertent enrollment has been removed.	Deleted as internal process will be followed for inadvertent enrollment.
Section 7.2.1 Discontinuation of Inadvertently Enrolled Participants	This section has been removed.	Deleted as internal process will be followed for inadvertent enrollment.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2 Study of Once-Weekly LY3437943 Compared with Placebo and Dulaglutide in Participants with Type 2 Diabetes

Short Title: Effect of LY3437943 Versus Placebo and Dulaglutide in Participants with Type 2 Diabetes

Rationale:

Epidemiological studies have shown that type 2 diabetes (T2D) and obesity are tightly associated (Verma and Hussain 2017; Marreno 2009). The ongoing global obesity epidemic increases the incidence of T2D and other comorbidities, including hyperlipidemia and hypertension resulting in an increased incidence of micro- and macrovascular complications (Garber 2012; Neeland et al. 2019; Dwivedi et al. 2020). In addition, obesity complicates treatment of T2D by worsening insulin resistance, preventing many patients from achieving their treatment goals (Kahn et al. 2006; Scheen and Van Gaal 2014; Barazzoni et al. 2018). Glucose-lowering therapeutic interventions that encompass weight loss may have a potential to slow the progression of T2D and reduce the risk of chronic complications (Lau and Teoh 2015; Aroda 2018; Pereira and Eriksson 2019; Chun and Butts 2020). Treatments that simultaneously target T2D and obesity are considered an important unmet medical need.

LY3437943 is a novel synthetic long-acting peptide, which shows potent agonist action at glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and glucagon (Gcg) receptors (GIPR, GLP-1R, and GcgR). It includes a linear peptide component of 39 amino acid residues conjugated to a C20 fatty acid moiety. In nonclinical pharmacology models, LY3437943 demonstrated equal or greater activity in glucose-dependent insulin secretion compared with an existing GLP-1 receptor agonist (GLP-1 RA), as demonstrated by intravenous glucose tolerance test in lean rat. In addition, LY3437943 demonstrated greater weight loss in diet-induced obese (DIO) mice compared with an existing GLP-1 receptor agonist (GLP-1 RA). The body weight reduction in DIO mice was primarily due to loss of fat mass and was associated with lowered total plasma cholesterol and reduced liver fat content.

Pharmacokinetic data from Phase 1 clinical studies support once-weekly administration of LY3437943. In these trials, LY3437943 was found to be safe and well tolerated, thereby justifying further investigation in a Phase 2 study.

Study J1I-MC-GZBD (GZBD) is a Phase 2, multicenter, randomized, double-blind, parallel, placebo- and active comparator-controlled 36-week study, with the primary outcome at 24 weeks, that will investigate glucose-lowering and body weight-lowering efficacy, as well as tolerability and safety of LY3437943 in participants with T2D who failed to achieve adequate glycemic control on diet and exercise alone or on a stable dose of metformin (≥1000 mg/day for at least 3 months prior to Visit 1). The primary objective will be to assess the effect on hemoglobin A1c (HbA1c) after 24 weeks of treatment. Participants will be studied for a total of 36 weeks of treatment to provide sufficient follow-up time to obtain additional weight loss

efficacy data over a longer time period. This study is designed to support dose selection for Phase 3.

Objectives and Endpoints

Objectives	Estimands/Endpoints
Primary	
To demonstrate superiority of QW LY3437943 (0.5, 4.0, 8.0, or 12.0 mg) in change from baseline for HbA1c relative to placebo, in participants with T2D inadequately controlled with diet and exercise with or without a stable dose of metformin	Change in HbA1c (%) from baseline to 24 weeks
Secondary	
To compare the effect of QW LY3437943 versus placebo and versus dulaglutide on: • Glucose control	• Change in HbA1c from baseline to 24 (dulaglutide comparison only) and 36 weeks • Percentage of participants reaching HbA1c <7.0% at 24 and 36 weeks • Change in FBG from baseline to 24 and 36 weeks (mg/dL, mmol/L)
Body weight control	Change in body weight (kg) from baseline to 24 and 36 weeks
To assess safety and tolerability of study interventions	• Adverse events overall • Adverse events of special interest • Laboratory parameters • Electrocardiogram • Vital signs • Number of participants testing positive for anti-LY3437943 antibodies
To assess PK of LY3437943 and potential participant factors that may influence its PK	• LY3437943 plasma concentration

Abbreviations: FBG = fasting blood glucose; HbA1c = hemoglobin A1c; PK = pharmacokinetics; QW = once-weekly; T2D = type 2 diabetes.

Overall Design

Study GZBD is a Phase 2, multicenter, randomized, double-blind, parallel, placebo- and active comparator-controlled 36-week study, with the primary outcome at 24 weeks, to investigate the safety and efficacy of LY3437943 in participants with T2D who failed to achieve adequate glycemic control on diet and exercise alone or on a stable dose of metformin (≥1000 mg/day for at least 3 months prior to Visit 1).

Disclosure Statement: This is a parallel group treatment study that is participant and investigator blinded.

Number of Participants:

A total of approximately 300 participants will be randomized in a 2:2:2:1:1:1:1:2 ratio to either placebo, dulaglutide 1.5 mg, LY3437943 0.5 mg, LY3437943 4 mg (with starting dose at 2 mg; slow escalation), LY3437943 4 mg (with starting dose at 4 mg; no escalation), LY3437943 8 mg (with starting dose at 2 mg; slow escalation), LY3437943 8 mg (with starting dose at 4 mg; rapid escalation) or LY3437943 12 mg (starting dose at 2 mg; slow escalation).

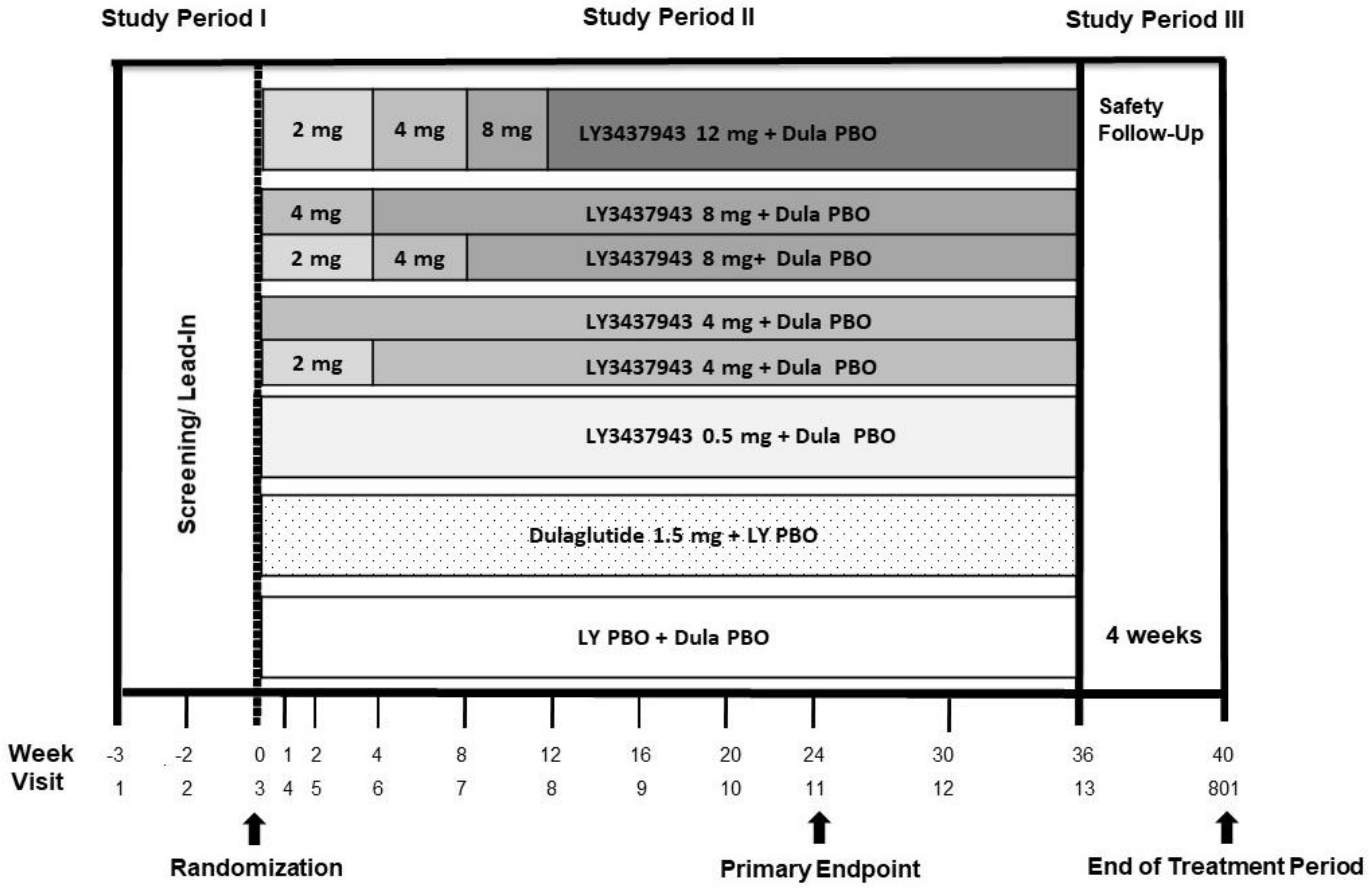
Intervention Groups and Duration:

There are 6 treatment arms, including placebo, 4 maintenance dose levels of LY3437943, and dulaglutide 1.5 mg. The maintenance doses in the 4-, 8-, and 12-mg dose range groups will be achieved using dose-escalation schemes, which will reduce the risk of tolerability issues and will occur in some LY3437943 treatment arms up to Week 12 by increasing the volume of administered study drug (or matched placebo). Participants will be blinded as to whether she or he is receiving either

- LY3437943 and dulaglutide placebo (single-dose pen; SDP) or
- Dulaglutide (SDP) and LY3437943 placebo or
- LY3437943 placebo and dulaglutide placebo.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: Dula = dulaglutide; LY = LY3437943; PBO = Placebo.

1.3. Schedule of Activities (SoA)

The Schedule of Activities described below should be followed for all participants enrolled in Study GZBD. However, for those participants whose participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Section 10.12, Appendix 12 for additional guidance.

	Study Period I Screening/ Lead-in		**Study Period II Treatment**												**Study Period III Post-Treatment Safety Follow-Up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**
Week Relative to Randomization	**-3**	**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**-**	**4 Wks post end of TXP**
Allowable Interval Tolerance (days)	**±5**	**±5**	**-**	**±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**
Administrative															
Informed consent	X														
Inclusion and exclusion criteria review	X	X	X												
Demographics	X														
Preexisting conditions and medical history, including relevant surgical history	X														
	Medical history includes assessment of relevant preexisting conditions (for example, history of gallbladder disease, cardiovascular disease, medullary thyroid carcinoma, and pancreatitis).														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events and product complaints	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
	Body weight must be measured in the fasting state. If the participant is not fasting, the participant should return at a later date within the visit window to have the fasting body weight measured.														
Waist circumference	X		X					X	X		X		X	X	
Vital signs (3 sitting BP and PR measurements)	X		X	X	X	X	X	X	X		X		X	X	X

	Study Period I Screening/ Lead-in		Study Period II Treatment												Study Period III Post-Treatment Safety Follow-Up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**
Week Relative to Randomization	**-3**	**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**-**	**4 Wks post end of TXP**
Allowable Interval Tolerance (days)	**±5**	**±5**	**-**	**±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**
	Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing (See Section 10.9).														
Supine and standing BP (orthostatic vital signs)			X						X		X		X		
	Referral to Section 10.9 for description of the orthostatic vital sign measurements.														
Physical examination	X										X		X	X	X
	Visit 1 should be a complete physical while other visits should be "targeted" exams based on the physician's judgment.														
CCI															
12-Lead electrocardiogram	X		X			X	X	X	X		X		X	X	X
	Singlet-electrocardiograms should be obtained prior to collection of blood samples for laboratory testing, including PK samples (see Section 10.9 Appendix 9).														
Participant Education and Supplies															
Blood glucose (BG) meter instructions		X	X												
Dispense BG meter/supplies (if needed)		X				X	X	X	X	X	X	X			
Diabetes education		X													
	Diabetes education to be performed by personnel who are qualified 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.														

	Study Period I Screening/ Lead-in		Study Period II Treatment												Study Period III Post-Treatment Safety Follow-Up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**
Week Relative to Randomization	**-3**	**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**-**	**4 Wks post end of TXP**
Allowable Interval Tolerance (days)	**±5**	**±5**	**-**	**±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**
Blood Glucose Monitoring															
Remind participants about 7-point SMBG		X						X		X		X			
7-point SMBG			X						X		X		X		
Review SMBG and hypoglycemic events in the diary for diabetes management			X	X	X	X	X	X	X	X	X	X	X	X	X
Participant Diary (paper)															
Participant diary dispensed		X	X										X		
Diary compliance check			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
Patient-Reported Outcomes (paper)															
SF-36v2 acute form			X								X		X	X	
Eating Inventory			X								X		X	X	
Appetite Visual Analog Scale			X			X	X	X	X		X		X	X	
	If a translation is not available in the native language of a participant at baseline, the PRO questionnaire(s) will not be administered for that participant for the duration of the trial (Appendix 10.10).														
Laboratory Tests and Sample Collections															
Hematology	X					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	X
Glucose	X		X		X	X	X	X	X		X		X	X	X
Lipid panel	X		X			X	X	X	X		X		X	X	
Urinalysis	X					X		X			X		X	X	

	Study Period I Screening/ Lead-in		Study Period II Treatment												Study Period III Post-Treatment Safety Follow-Up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**
Week Relative to Randomization	**-3**	**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**-**	**4 Wks post end of TXP**
Allowable Interval Tolerance (days)	**±5**	**±5**	**-**	**±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**
Serum pregnancy	X														
	For women of childbearing potential only														
Urine pregnancy (local)			X												
	A urine pregnancy test must be performed at Visit 3 with the result available prior to first injection of study intervention(s) for women of childbearing potential only. Additional pregnancy tests (beyond those required per the SoA) should be performed at any time during the trial if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation. If the urine pregnancy test is inconclusive at Visit 3, the recommendation would be to collect an additional serum pregnancy test.														
Follicle stimulating hormone (FSH)	X														
	Only for postmenopausal women at least 40 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 1 year without an alternative medical cause.														
Insulin			X			X	X	X	X		X		X	X	
Glucagon			X				X		X		X		X	X	
C-peptide			X			X	X	X	X		X		X	X	
Intact proinsulin			X			X	X	X	X		X		X	X	
Calcitonin	X		X								X		X	X	X
Pancreatic amylase, lipase	X		X					X			X		X	X	X
Longitudinal biomarkers			X			X	X	X	X		X		X	X	
	See Section 10.11 for list of biomarkers														
Endpoint biomarkers			X						X		X		X	X	
	See Section 10.11 for list of biomarkers														
eGFR (CKD-EPI)	X		X					X	X		X		X	X	
Urinary albumin/creatinine ratio (UACR)	X		X						X		X		X	X	

		Study Period I Screening/ Lead-in		Study Period II Treatment											Study Period III Post-Treatment Safety Follow-Up
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**
Week Relative to Randomization		**-3**	**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**-**	**4 Wks post end of TXP**
Allowable Interval Tolerance (days)		**±5**	**±5**	**-**	**±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**
Pharmacokinetic (PK) sample	Predose			X	X		X		X			X	X			
	Postdose					X		X		X	X			X	X	X
		Efforts should be taken to align clinical visit scheduling with PK sampling windows specified in the Pharmacokinetic Schedule of Events table below; otherwise, participants may need to return to the clinical site for additional PK-specific visits to provide PK samples.														
Immunogenicity (ADA) samples				X			X		X			X		X	X	X
Stored Samples																
Genetic sample (pharmacogenetic stored sample)				X												
Exploratory stored samples (nonpharmacogenetic stored samples)				X		X	X	X	X	X		X		X	X	
Randomization and Dosing																
IWRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization				X												
Observe participant administer study intervention				X												
		Participants should administer their first dose of study drug at the end of Visit 3, after other study procedures and randomization have been completed. Further observation and information on self-injection can be reviewed as necessary throughout the study.														
Dispense study intervention and injection supplies				X			X	X	X	X	X	X	X			
Review injection technique					X	X	X	X	X							
Drug accountability					X	X	X	X	X	X	X	X	X	X	X	
Participant returns unused study intervention and injection supplies						X	X	X	X	X	X	X	X	X	X	

	Study Period I Screening/ Lead-in		Study Period II Treatment												Study Period III Post-Treatment Safety Follow-Up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**	**801**
Week Relative to Randomization	**-3**	**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**-**	**4 Wks post end of TXP**
Allowable Interval Tolerance (days)	**±5**	**±5**	**-**	**±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**
Assess drug compliance				X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: ADA = anti-drug antibody; BG = blood glucose; BP = blood pressure; CKD-EPI = chronic kidney disease-epidemiology; ECG = electrocardiogram; ED = early discontinuation; eGFR=estimated glomerular filtration rate; HbA1c = hemoglobin A1c; IWRS = Interactive Web Response Systems; PK = pharmacokinetics; PR = pulse rate; SF-36v2 acute form = Short Form-36 Version 2 Health Survey acute form; SMBG = self-monitoring of blood glucose; TXP = treatment period; wks = weeks.

***Notes*:**

- Visit 3 baseline assessments must be completed before processing the randomization in the IWRS.
- The visit date is determined in relation to the date of Visit 3 (randomization).
- Participants who are unable or unwilling to continue the study treatment for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as an ED visit.
- Visit 801 (safety follow-up visit) should be performed 4 weeks after the last treatment period visit.
- For fasting office visits, remind participants to report to the site before taking study drug(s) in a fasting condition, after a period of at least 8 hours without eating, drinking (except water), or any significant physical activity. Since some screening procedures need to be completed in the fasting state, Visit 1 may be conducted over more than 1 day to ensure necessary conditions are met. The participant should not take any antihyperglycemic medications prior to the fasting visit.

Pharmacokinetic Schedule of Events

Sample #	Week Relative to Randomization	Collection Timepoint Relative to LY3437943 Weekly Dose
1	0	Predose (up to -8 hours)*
2	1	Predose (up to -8 hours)
3	2	1 to 24 hours postdose
4	4	Predose (up to -8 hours)*
5	8	24 to 72 hours postdose
6	12	Predose (up to -8 hours)*
7	16	72 to 168 hours postdose
8	20	Any time during this week
9	24	Predose (up to -8 hours)*
10	30	Predose (up to -8 hours)
11	36	Postdose (approximately 1 week)*
12	Safety follow-up	5 weeks post last dose*
13	Early discontinuation	Any time*

* Immunogenicity (ADA) samples collected with PK at these visits.

2. Introduction

2.1. Study Rationale

Epidemiological studies have shown that T2D and obesity are tightly associated (Marrero 2009; Verma and Hussain 2017). The ongoing global obesity epidemic increases the incidence of T2D and other comorbidities, including hyperlipidemia and hypertension resulting in an increased incidence of chronic micro- and macrovascular complications (Garber 2012; Neeland et al. 2019; Dwivedi et al. 2020). In addition, obesity complicates treatment of T2D by worsening insulin resistance, preventing many patients from achieving their treatment goals (Kahn et al. 2006; Scheen and Van Gaal 2014; Barazzoni et al. 2018). Glucose-lowering therapeutic interventions that encompass weight loss may have a potential to slow the progression of T2D and reduce the risk of chronic complications (Lau and Teoh 2015; Aroda 2018; Pereira and Eriksson 2019; Chun and Butts 2020). Treatments that simultaneously target T2D and obesity are considered an important unmet medical need.

Glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1, and glucagon (Gcg) have a role in the regulation of carbohydrate, protein and lipid metabolism, and energy balance. While some of their actions are similar, each hormone also has unique metabolic regulatory actions, providing an opportunity to combine their respective actions in a single molecule to develop a pharmacological agent with improved efficacy and safety profile for the treatment of a range of metabolic conditions compared with existing therapies.

LY3437943 is a novel synthetic single peptide with triple receptor activity in GIP, GLP-1, and Gcg receptors (GIPR, GLP-1R, and GcgR, respectively).

In Phase 1 studies, LY3437943 was found to be safe and well tolerated, thereby justifying further investigation in Phase 2 study. Pharmacokinetic data support once-weekly administration of LY3437943.

Study GZBD is a 36-week Phase 2 study, with the primary outcome at 24 weeks, designed to examine the safety and efficacy of 4 dose levels of QW, subcutaneously administered LY3437943 compared with QW, subcutaneously administered placebo and QW dulaglutide 1.5 mg. The study objectives will be evaluated in participants with T2D who have inadequate glycemic control with diet and exercise with or without a stable dose of metformin. The primary objective at Week 24 will be to assess superiority of QW LY3437943 (0.5, 4, 8, or 12 mg) in change from baseline for HbA1c (%) relative to placebo. Participants will be studied for a total of 36 weeks of treatment to provide sufficient follow-up time to obtain additional weight loss information. This trial is designed to support dose selection for Phase 3 development.

2.2. Background

Type 2 diabetes is characterized by impaired glycemic control due to resistance in the peripheral tissues to insulin actions and inadequate insulin secretion caused by β-cell failure (Zheng et al. 2018). Type 2 diabetes is commonly associated with comorbidities such as obesity, hypertension, and dyslipidemia resulting in increased risk of chronic diabetic complications.

Structure of LY3437943

LY3437943 is a novel long-acting synthetic peptide containing 39 amino acids and a fatty acyl side chain to allow QW dosing, which shows potent agonist action at GIP, GLP-1, and Gcg receptors (GIPR, GLP-1R, and GcgR, respectively).

Nonclinical data with efficacy and toxicology

In nonclinical pharmacology models, LY3437943 demonstrated equal or greater effect on glucose-dependent insulin secretion compared with an existing GLP-1 RA, as demonstrated by intravenous glucose tolerance test in lean rats and with greater weight loss in DIO mice. The body weight reduction in DIO mice was primarily due to loss of fat mass.

Summary of clinical studies

S**tudy J1I-MC-GZBA (GZBA)** was a first-in-human, single-ascending dose (SAD) study investigating the safety, tolerability, and PK/PD of LY3437943 (dose ranging from 0.1 to 6 mg) administered as a SC injection in 45 healthy participants.

The most common treatment emergent adverse events (TEAEs) were gastrointestinal (GI) events, including vomiting, abdominal distention, and nausea, which were dose dependent, mostly mild in severity, occurred within 4 days of dosing, and resolved within a week of onset. Dose-dependent increases in heart rate (HR) and decreases in systolic blood pressure were observed, which returned to near baseline by Day 29.

Across dose levels, the maximum observed drug concentration (C_{max}) occurred between ~1 and 3 days postdose, while the mean terminal half-life was ~5 to 7 days, thus supporting a QW dosing regimen.

Study J1I-MC-GZBB (GZBB) is an ongoing Phase 1, randomized, investigator- and participant-blind 12-week study that assesses the safety, tolerability, and PK/PD effects of multiple doses of LY3437943 when administered QW in participants with T2D. Trulicity® (dulaglutide) 1.5 mg is used as an active comparator. Participants in Cohorts 1 to 3 are receiving fixed doses of LY3437943 (0.5, 1.5, or 3 mg QW) or placebo for 12 weeks. Participants in Cohorts 4 and 5 are receiving escalated doses starting from 3 mg to 12 mg, respectively, over the 12-week treatment period.

Based on preliminary data from this study, 72 participants in all treatment arms received study treatment, and 43 completed the study to date. Gastrointestinal AEs (nausea, abdominal distention, and diarrhea) and decreased appetite were the most frequently reported events, mostly mild in severity and dose dependent. A dose-dependent increase in HR was noted. The HR effects were consistent with those of the GLP-1 or GIP/GLP-1RA class, as was seen in Phase 1 clinical development. There were no reports of severe hypoglycemia or AEs related to the site injection. Overall, data from early phase clinical trials support further development of LY3437943 in Phase 2 studies.

2.3. Benefit/Risk Assessment

This section summarizes the key observations from the completed or ongoing Phase 1 trials with LY3437943. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3437943 may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the investigational product may be found in Section 6.2 (Developmental Core Safety Information) of the IB. Information on SAEs that are expected in the study population independent of drug exposure will be assessed by the sponsor in aggregate, periodically during the course of the study, and may be found in Section 7 (Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions) of the IB.

More detailed information about the known and expected benefits and risks of dulaglutide may be found in the USPI or SmPC (Trulicity® USPI, 2020; Trulicity® SmPC, 2020).

2.3.1. Risk Assessment

Most common AEs seen in clinical trials of LY3437943 have been those related to the GI organ system. The GI AEs, as well as those related to pancreatic safety, hypoglycemia, vital signs, allergic and hypersensitivity reactions, and thyroid C-cell effects are safety topics of special interest in incretin development programs and will, therefore, be assessed in this study, too. Most of these AEs have not been observed with LY3437943 in the completed or ongoing phase trials. Please refer to the IB Section 6 for more details.

2.3.2. Benefit Assessment

LY3437943 is a tri-agonist of the GIP, GLP-1, and glucagon receptors that is currently in early clinical development. Full assessment of its potential benefits has not been completed. The purpose of this Phase 2 trial is to provide initial efficacy assessment in participants with T2D, in addition to safety and PK/PD assessments.

2.3.3. Overall Benefit: Risk Conclusion

The data from Phase 1 studies indicate that the safety profile of LY3437943 is consistent with the safety profile of other GLP-1 and GIP/GLP-1 RAs. No additional risks are anticipated. Considering the measures to minimize risk to participants included in the study protocol, potential risks identified in association with LY3437943 are considered acceptable in this study. No benefits can be assumed since LY3437943 is in the early phase of clinical development. All participants taking part in this study will receive diet and physical activity counseling according to site programs.

3. Objectives and Endpoints

Objectives	Estimands/Endpoints
Primary	
To demonstrate superiority of QW LY3437943 (0.5, 4.0, 8.0, or 12.0 mg) in change from baseline for HbA1c relative to placebo, in participants with T2D inadequately controlled with diet and exercise with or without a stable dose of metformin	Change in HbA1c (%) from baseline to 24 weeks
Secondary	
To compare the effect of QW LY3437943 versus placebo and versus dulaglutide on: • Glucose control • Body weight control	 • Change in HbA1c (%) from baseline to 24 (for dulaglutide comparison only) and 36 weeks • Percentage of participants reaching HbA1c of <7.0% at 24 and/or 36 weeks • Change in FBG from baseline to 24 and 36 weeks (mg/dL, mmol/L) • Change in body weight (kg) from baseline to 24 and 36 weeks
To assess safety and tolerability of study intervention	• Adverse events overall • Adverse events of special interest • Laboratory parameters • Electrocardiogram • Vital signs • Number of participants testing positive for anti-LY3437943 antibodies
To assess the PK of LY3437943 and potential participant factors that may influence its PK	• LY3437943 plasma concentrations
Tertiary/Exploratory	
To assess the relationship between LY3437943 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

Objectives	Estimands/Endpoints
To compare the effect of QW LY3437943 versus placebo and versus dulaglutide on:	
• Glucose control	• Change in SMBG profile from baseline to 24 and 36 weeks • Percentage of participants reaching HbA1c of <5.7%, <6.5%, and <7.0% at 24 and/or 36 weeks Dose–response including placebo
• Body weight control	• Percentage of participants with 5%, 10%, 15%, or greater body weight loss from baseline to 24 and 36 weeks • Dose–response including placebo
• Appetite VAS	• Change from baseline to 4, 8, 12, 16, 24, and 36 weeks
• Lipids	• Change from baseline to 16, 24, and 36 weeks for total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and VLDL cholesterol
• Biomarkers	• Change from baseline to Week 16, 24, and 36 weeks for mechanistic biomarkers (see detailed list of parameters in Section 10.11)
• Patient-reported outcomes	• Mean change from baseline to Weeks 16, 24, and 36 for: SF-36v2 acute form domain scores Eating Inventory domain scores

Abbreviations: FBG = fasting blood glucose; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PK = pharmacokinetics; QW = once-weekly; SF-36v2 = Short Form-36 version 2 Health Survey; SMBG = self-monitoring of blood glucose; T2D = type 2 diabetes; VAS = Visual Analog Scale; VLDL = very low-density lipoprotein.

4. Study Design

4.1. Overall Design

Study GZBD is a Phase 2, multicenter, randomized, double-blinded, parallel, placebo- and active comparator-controlled 36-week study, with the primary outcome at 24 weeks, to investigate the safety and efficacy of LY3437943 in participants with T2D who failed to achieve adequate glycemic control on diet and exercise alone or on a stable dose of metformin (≥1000 mg/day for at least 3 months prior to Visit 1) (see Section 1.2).

Four maintenance doses of LY3437943 will be evaluated in the trial, 0.5, 4, 8, and 12 mg. Dose escalation to reduce the risk of tolerability issues will occur in certain treatment groups up to Week 12 by increasing the volume of administered study drug (or placebo). For maintenance doses equal to or greater than 4 mg, the initial dose will be 2 or 4 mg followed by additional escalation steps as appropriate and as described in Section 4.1.1. Study participants will be randomized in a 2:2:2:1:1:1:1:2 ratio to either placebo, dulaglutide 1.5 mg, LY3437943 0.5 mg, LY3437943 4 mg (with starting dose at 2 mg; slow escalation), LY3437943 4 mg (with starting dose at 4 mg; no escalation), LY3437943 8 mg (with starting dose at 2 mg; slow escalation), LY3437943 8 mg (with starting dose at 4 mg; rapid escalation), or LY3437943 12 mg (with starting dose at 2 mg; slow escalation).

All participants will undergo a 3-week screening period, a 36-week treatment period, followed by a 4-week safety follow-up period.

During the 36-week treatment period, each participant will receive one injection of LY3437943 or placebo (PBO) administered with a syringe and one injection of dulaglutide or PBO administered with an SDP (see Section 6 for more details). The table below specifies the number of injections per treatment arm.

Number of Injections Per Treatment Arm

Randomization	LY3437943	PBO LY3437943	Dulaglutide 1.5 mg SDP	PBO Dulaglutide SDP	Total
LY 0.5 mg	1	0	0	1	2
LY 4 mg	1	0	0	1	2
LY 8 mg	1	0	0	1	2
LY 12 mg	1	0	0	1	2
Dulaglutide 1.5 mg	0	1	1	0	2
PBO	0	1	0	1	2

Abbreviations: LY = LY3437943; PBO = placebo; SDP = single-dose pen.

During the trial, an unblinded internal assessment committee (AC) will review safety, tolerability, and efficacy data in study participants according to a prespecified schedule in order to assure the safety of randomized participants (see Section 9.5).

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.

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Participants will be provided paper diaries and will be trained 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. See Section 10.9 for details about glucose self-monitoring.

Diabetes education will be performed by the personnel qualified to educate participants on symptoms and management of hyperglycemia and hypoglycemia, self-monitored BG, 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 10.9).

Visit 3 Randomization

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.

When collected, patient-reported outcomes questionnaires should be administered as early as possible during the visit. Preferred administration order of these questionnaires throughout the trial is

1. SF-36v2 acute form
2. Eating Inventory, and
3. Appetite Visual Analog Scale.

Following randomization, study site personnel will train participants on how to use the syringe and vial, and single-dose pen and observe the study participant inject the first dose of study drugs. The date, time, and location 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 36-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 administering their study drugs.

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 6.6.1). Study participants will be permitted to use concomitant medications that they require during the study, except certain excluded medications (see Section 6.5) that may interfere with the assessment of efficacy and safety characteristics of the study treatments.

Dose-Escalation Period (Visits 4-8)

For maintenance doses of LY3437943 equal to or greater than 4 mg, the initial dose will be 2 or 4 mg followed by additional escalation steps as appropriate and described below. Study site personnel will continue to train participants on how to use the syringe and vial at each dose titration visit during dose escalation and as needed during the trial. The dose will be increased at 4-week increments until the maintenance dose is achieved (see Section 6.1 for dosing details), as follows:

- Maintenance dose of 0.5 mg: no dose escalation
- Maintenance dose of 4 mg will be randomized 1:1 into 2 subsets:
  - 2 mg → 4 mg (slow escalation)
  - 4 mg (no dose escalation)
- Maintenance dose of 8 mg will be randomized 1:1 into 2 subsets:
  - 2 mg → 4 mg → 8 mg (slow escalation)
  - 4 mg → 8 mg (rapid escalation)
- Maintenance dose of 12 mg:
  - 2 mg → 4 mg → 8 mg → 12 mg (slow escalation).

The maintenance doses of LY3437943 or dulaglutide 1.5 mg will be continued for the remainder of the study. In participants who experience intolerable GI symptoms or may need dose adjustment for other reasons, the dose can be changed as described in Section 6.5.1.

Maintenance Period (Visits 9-13)

During the maintenance period, visits will occur every 4 weeks until 24 weeks and then every 6 weeks from Weeks 24 to 36. Visit procedures should be conducted according to the SoA (Section 1.3). At Visits 10 and 12, when collected, patient-reported outcomes questionnaires should be administered as early as possible in the visit and in the preferred administration order (Section 1.3).

Early Discontinuation Visit

Participants unable or unwilling to continue the study for any reason will perform an early discontinuation (ED) 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 ED visit. Procedures should be completed according to the SoA (Section 1.3). Participants who discontinue from the

study early and perform ED visit should also perform Visit 801 (see below) approximately 4 weeks after ED visit.

Safety Follow-up Period

Visit 801

A safety follow-up visit will occur approximately 4 weeks following the last treatment period visit. All participants are required to complete a safety follow-up visit (Visit 801), according to the SoA (Section 1.3). Participants discontinuing the study early and performing an ED visit will also be asked to perform the safety follow-up visit.

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 GZBD is a Phase 2 study designed to examine the glucose and body weight-lowering efficacy and safety of LY3437943 QW (dose ranging from 0.5 to 12 mg) compared with placebo and dulaglutide 1.5 mg during the 36-week treatment period in participants with T2D who have inadequate glycemic control with diet and exercise alone or in combination with a stable dose of metformin.

LY3437943 was well tolerated up to a 3-mg dose in the single ascending dose study (Study GZBA) and up to a 12-mg dose with gradual dose escalation in the multiple ascending dose study (Study GZBB). Therefore, the highest dose in this study will be 12 mg. In addition, 2 dose escalation schemes are designed to provide information on optimal dose escalation schemes for Phase 3 clinical development.

The placebo comparison will provide efficacy and safety data to characterize the effects attributable to LY3437943. Inclusion of an active comparator (dulaglutide 1.5 mg) will allow for a direct comparison of QW LY3437943 to an injectable GLP-1 RA for preliminary assessment of potential additional benefits of LY3437943 on glucose control and body weight versus a selective GLP-1 RA commonly used in treatment of T2D patients in the clinical setting.

The primary efficacy measure, HbA1c, is a generally accepted surrogate of chronic glycemic exposure and has been shown to predict long-term outcome of diabetes. In addition, the protocol includes other parameters relevant to the assessment of the effects on treatment interventions of glucose control, body weight control, safety, and mechanism of action.

The primary objective will be tested at 24 weeks since this period is considered as adequate for evaluation of glucose-lowering efficacy in a Phase 2 trial. The full planned duration of 36 weeks will allow for an initial comparison of the body weight effects of the study drugs. The putative mechanism of action of LY3437943 suggests that treatment with LY3437943 may result in continued weight loss over this treatment period. The data from this trial will form the primary basis to assess dose–response/exposure–response of LY3437943 efficacy for selection of doses to be included in Phase 3 testing. In addition, safety and tolerability over a wide dose range of LY3437943 versus placebo and dulaglutide 1.5 mg will be assessed to enable robust benefit–risk characterizations in treatment of T2D.

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 T2D and partially preserved pancreatic β cell function, the key prerequisite for glucose-lowering efficacy of incretins. Stable metformin treatment for at least 3 months is required to minimize glucose variability prior to study entry.

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

LY3437943 maintenance doses of 0.5, 4, 8, and 12 mg, administered subcutaneously QW, were selected based on

- Safety and tolerability of LY3437943 in healthy subjects and T2D patients in the Phase 1 studies GZBA (0.1 to 6 mg) and GZBB (0.5 to 12 mg), respectively.
- PK/PD modeling based on preliminary data from Study GZBB.
- Acceptable margin of safety for the 12-mg maximum dose in this study relative to the no-observed-adverse-effect level in rats and monkeys in the 6-month toxicology studies.
- A maintenance dose of 0.5 mg is being investigated in this study to enable full characterization of the exposure–response relationships. This dose is predicted to achieve LY3437943 concentration levels that will demonstrate greater HbA1c lowering compared with placebo, but less than that of 1.5 mg dulaglutide.
- Maintenance doses of 4, 8, and 12 mg are expected to provide clinically relevant HbA1c reductions relative to placebo with increasing HbA1c lowering with increasing dose. For these doses, a starting dose of 2 or 4 mg prior to dose escalation will be investigated to evaluate the impact on tolerability and safety findings.
- The selected dose levels and dose range will support a robust dose–exposure–response analysis of multiple safety and efficacy measures to support selection of dose(s) of LY3437943 with optimal benefit/risk ratio for further clinical development.

4.4. End of Study Definition

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

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

5. Study Population

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 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 10.7) or other locally applicable diagnostic standards
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 (either immediate release or extended release, ≥1000 mg/day and not more than the locally approved dose) for at least 3 months prior to screening/Visit 1
4. Have had a stable body weight for the 3 months prior to randomization (5 kg body weight gain and/or loss)
5. Have not modified diet or adopted any nutritional lifestyle modification within 3 months prior to randomization
6. Have a body mass index (BMI) of 25-50 kg/m^2 at Visit 1

Sex

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

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

   - males agree to refrain from sperm donation and to use contraceptive methods as described in Section 10.4 throughout the study and for 5 half-lives of study drugs plus 90 days, corresponding to 4 months after the last injection.
   - women of childbearing potential agree to use contraceptive methods as described in Section 10.4 throughout the study and for 5 half-lives of study drugs plus 30 days, corresponding to 2 months after the last injection. Female participants should not be breastfeeding.

Note: Hormone replacement therapy in post-menopausal women and contraceptives containing an estrogen and a progestin (oral or transdermal system) in pre-menopausal women are allowed but women must be on stable therapy for 3 months prior to screening/Visit 1.

8. In the investigator's opinion, are well motivated, capable, and willing to
    - perform finger-stick BG monitoring, including scheduled BG profiles with up to 7 measurements in 1 day
    - learn how to self-inject study drugs (LY3437943/placebo and dulaglutide/placebo), as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study drugs; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drugs)
    - inject study intervention QW, and
    - maintain study diaries, as required for this protocol.

Informed Consent

9. Capable of giving signed informed consent as described in Section 10.1.2, 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 applies:

Medical Conditions

10. Have type 1 diabetes mellitus (T1DM)
11. Have history of ketoacidosis or hyperosmolar state/coma
12. Have a history of proliferative diabetic retinopathy, diabetic maculopathy, or severe nonproliferative diabetic retinopathy that requires immediate treatment intervention
13. Have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1
14. Have a history of acute or chronic pancreatitis or have signs and symptoms of acute pancreatitis at screening
15. 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
16. Have obesity induced by other endocrine disorders (such as Cushing's syndrome or Prader-Willi syndrome)

17. Have uncontrolled hypertension (systolic blood pressure above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg). For participants with uncontrolled hypertension at the screening visit, antihypertensive medication may be started. Blood pressure must meet the protocol criterion for hypertension control by Visit 3
18. Have an elevated resting pulse rate (>100 bpm) at baseline
19. Have any of the following cardiovascular conditions within 3 months prior to Screening:
    - acute myocardial infarction
    - cerebrovascular accident (stroke)
    - unstable angina, or
    - hospitalization due to congestive heart failure (CHF).
20. Have an ECG considered by the investigator indicative of active cardiac disease or with abnormalities that may have interfered with the interpretation of changes in ECG intervals at screening
21. Have a history of New York Heart Association Functional Classification III or IV CHF (see Section 10.8)
22. Have acute or chronic hepatitis, signs, and symptoms of any liver disease other than nonalcoholic fatty liver disease (NAFLD), or alanine aminotransferase (ALT) level >3.0 times the upper limit of normal (ULN) for the reference range, as determined by the central laboratory at study entry. Participants with NAFLD are eligible to participate in this trial if their ALT level is ≤3.0 times the ULN for the reference range
23. Have an estimated glomerular filtration rate <45 mL/min/1.73 m^2 (or lower than the country-specific threshold for discontinuing metformin therapy per local label), calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory at Visit 1)
24. Have family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2)
25. Have evidence of a significant, uncontrolled endocrine abnormality (for example, hypothyroidism, thyrotoxicosis, or adrenal crises), in the opinion of the investigator
26. 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
27. 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

28. 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 12 months
29. Have had a transplanted organ (only corneal transplants [keratoplasty] allowed) or awaiting an organ transplant
30. Have a history of an active or untreated malignancy or are 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
31. 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
32. Have a history of any other condition (such as known drug, alcohol abuse, or psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol

Prior/Concomitant Therapy

33. Any glucose-lowering medications other than metformin within 3 months prior to screening
34. Have been treated or plan to be treated with prescription or over-the-counter (OTC) medications that promote weight loss within 3 months prior to screening

    For example

    - Saxenda® [liraglutide 3.0 mg]
    - Xenical® [orlistat]
    - Meridia® [sibutramine]
    - Acutrim® [phenylpropanolamine]
    - Sanorex® [mazindol]
    - Adipex® [phentermine]
    - BELVIQ® [lorcaserin]
    - Qsymia™ [phentermine/topiramate combination]
    - Contrave® [naltrexone/bupropion], or
    - other similar body weight loss medication, including OTC medications, for example, allī®.

35. Have received chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) within 1 month prior to screening

Prior/Concurrent Clinical Study Experience

36. 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

37. Have participated, within the past 30 days of screening, in a clinical study involving an IP; at least 5 half-lives or 30 days (whichever is longer) should have passed
38. Have previously completed or withdrawn from this study or any other study investigating LY3437943

Other Exclusions

39. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
40. Are Eli Lilly and Company employees or are employees of any third party involved in study who require exclusion of their employees
41. Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), qualified medical staff will provide diabetes management counseling, which will include instructions on diet and exercise and education about the signs, symptoms, and treatment of hypoglycemia and hyperglycemia, should it occur. Throughout the study, participants may undergo medical assessments and review of compliance with requirements before continuing in the study.
Study participants should be instructed not to donate blood or blood products during the study.

5.3.1. Meals and Dietary Restrictions

Participants should continue their usual meal plan (with consistent meal size and time of day) throughout the course of the study, as agreed with the investigator or his or her designee. Per Inclusion Criterion 5 (Section 5.1), 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).

5.3.2. Activity and Physical Exercise

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.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened only once at the discretion of the investigator. Before rescreening is performed, the participant must sign a new ICF and receive a new identification number. If, in the opinion of the investigator, an ineligible lab test result is the result of an error or exceptional circumstance, then that parameter can be retested once without the participant having to be rescreened as outlined in Section 10.12.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

The following study interventions will be administered:

- LY3437943 vial containing 12 mg/2 mL of solution or
- Placebo to match LY3437943 vial containing 2 mL of solution and
- Dulaglutide 1.5 mg/0.5 mL single-dose pen or
- Placebo to match Dulaglutide in a 0.5 mL single-dose pen

Treatment Arm	Escalation Period Dose				Maintenance Period Dose
	LY weekly dose/ Administered as	12-Week Escalation Period			24-Week Dosing
		Week 0 to Week 3	Week 4 to Week 7	Week 8 to Week 11	Week 12 through Week 35
0.5 mg LY3437943[a]/1.5 mg dulaglutide (dula) PBO	LY weekly dose (no escalation)	0.5 mg LY QW	0.5 mg LY QW	0.5 mg LY QW	0.5 mg LY QW
	Administered as	1 dose 0.5 mg LY 1 dose 1.5 mg dula PBO	1 dose 0.5 mg LY 1 dose 1.5 mg dula PBO	1 dose 0.5 mg LY 1 dose 1.5 mg dula PBO	1 dose 0.5 mg LY 1 dose 1.5 mg dula PBO
4 mg LY3437943/1.5 mg dulaglutide (dula) PBO	LY weekly dose (slow escalation)	2 mg LY QW	4 mg LY QW	4 mg LY QW	4 mg LY QW
	Administered as	1 dose 2 mg LY 1 dose 1.5 mg dula PBO	1 dose 4 mg LY 1 dose 1.5 mg dula PBO	1 dose 4 mg LY 1 dose 1.5 mg dula PBO	1 dose 4 mg LY 1 dose 1.5 mg dula PBO

	LY weekly dose (no escalation)	4 mg LY QW	4 mg LY QW	4 mg LY QW	4 mg LY QW
	Administered as	1 dose 4 mg LY 1 dose 1.5 mg dula PBO	1 dose 4 mg LY 1 dose 1.5 mg dula PBO	1 dose 4 mg LY 1 dose 1.5 mg dula PBO	1 dose 4 mg LY 1 dose 1.5 mg dula PBO
8 mg LY3437943/1.5 mg dulaglutide (dula) PBO	LY weekly dose (slow escalation)	2 mg LY QW	4 mg LY QW	8 mg LY QW	8 mg LY QW
	Administered as	1 dose 2 mg LY 1 dose 1.5 mg dula PBO	1 dose 4 mg LY 1 dose 1.5 mg dula PBO	1 dose 8 mg LY 1 dose 1.5 mg dula PBO	1 dose 8 mg LY 1 dose 1.5 mg dula PBO
	LY weekly dose (rapid escalation)	4 mg LY QW	8 mg LY QW	8 mg LY QW	8 mg LY QW
	Administered as	1 dose 4 mg LY 1 dose 1.5 mg dula PBO	1 dose 8 mg LY 1 dose 1.5 mg dula PBO	1 dose 8 mg LY 1 dose 1.5 mg dula PBO	1 dose 8 mg LY 1 dose 1.5 mg dula PBO
12 mg LY3437943/1.5 mg dulaglutide (dula) PBO	LY weekly dose (slow escalation)	2 mg LY QW	4 mg LY QW	8 mg LY QW	12 mg LY QW
	Administered as	1 dose 2 mg LY 1 dose 1.5 mg dula PBO	1 dose 4 mg LY 1 dose 1.5 mg dula PBO	1 dose 8 mg LY 1 dose 1.5 mg dula PBO	1 dose 12 mg LY 1 dose 1.5 mg dula PBO
1.5 mg Dulaglutide[b]/LY3437943 PBO	Dula weekly dose	1.5 mg dula QW	1.5 mg dula QW	1.5 mg dula QW	1.5 mg dula QW
	Administered as	1 dose 1.5 mg dula 1 dose LY PBO[c]	1 dose 1.5 mg dula 1 dose LY PBO[c]	1 dose 1.5 mg dula 1 dose LY PBO[c]	1 dose 1.5 mg dula 1 dose LY PBO[c]
	PBO weekly dose	PBO	PBO	PBO	PBO

Placebo (LY3437943 PBO/1.5 mg dulaglutide PBO)	Administered as	1 dose LY PBO[c] 1 dose 1.5 mg dula PBO	1 dose LY PBO[c] 1 dose 1.5 mg dula PBO	1 dose LY PBO[c] 1 dose 1.5 mg dula PBO	1 dose LY PBO[c] 1 dose 1.5 mg dula PBO

Abbreviations: dula = dulaglutide; LY = LY3437943; PBO = placebo; QW = once-weekly.

[a] LY3437943 QW will be administered by syringe from a 12 mg/2 mL vial.
[b] Dulaglutide QW will be administered using a single-dose pen.
[c] LY3437943 PBO will be randomly assigned to follow the injection dose schedule for one active LY arm.

The first injections of study drugs should occur at Visit 3 immediately after randomization. Subsequently, administrations should be scheduled on the same day of the week and approximately the same time of the day. If a dose of study drug(s) is missed on the regularly scheduled day, the participant should administer it as soon as possible, unless less than 72 hours remains until the next scheduled dose. If less than 72 hours remains, that dose should be skipped, and the next dose should be taken at the scheduled day and time. All participants will inject study interventions SC into the abdominal wall, using 2 different abdominal quadrants each week for the 2 injections. The injection quadrant will be changed each week for each study drug injection using the clockwise rotation rule. A caregiver may administer the injection after appropriate training. A new syringe or disposable single-use pen will be used for each injection. The actual date, time, and injection-site location of all dose administrations will be recorded in the diary by the participant.

6.1.1. Medical Devices

The combination products 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/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 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-authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the study training materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

At Visit 3, participants who meet all criteria for enrollment will be randomized to 1 of the 6 study treatment groups and 2 different starting dose subgroups within the 4 and 8 mg LY3437943 treatment groups. Assignment to treatment groups and starting dose subgroups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS) with the following stratification variables: baseline HbA1c (<8.5%, ≥8.5%) and BMI (<30, ≥30). Study participants will be randomized in a 2:2:2:1:1:1:1:2 ratio to either placebo, dulaglutide 1.5 mg, LY3437943 0.5 mg, LY3437943 4 mg (with starting dose at 2 mg), LY3437943 4 mg (with starting dose at 4 mg), LY3437943 8 mg (with starting dose at 2 mg),

LY3437943 8 mg (with starting dose at 4 mg), or LY3437943 12 mg (with starting dose at 2 mg).

This is a double-blind study. All participants will administer 2 weekly injections (syringe containing LY3437943 or PBO, single-use pen containing dulaglutide 1.5 mg or PBO) matching their treatment allocation, as described in Section 6.1. Therefore, each participant will be administering one of the following study drug combinations in a blinded fashion:

- LY3437943 and dulaglutide placebo (SDP)
- Dulaglutide (SDP) and LY3437943 placebo, and
- LY3437943 placebo and dulaglutide placebo.

Where required, dose escalation of LY3437943 (or matched placebo) will be done by increasing the volume of administered study drug. To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency unblinding may be performed through the IWRS. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All unblinding events are recorded and reported by the IWRS.

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, Lilly must be notified immediately. 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 interventions will be assessed at each visit. Compliance will be assessed by direct questioning and counting of unused study interventions and/or empty cartons returned. Study intervention compliance will be determined by the following:

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

Treatment compliance will be assessed every 4 weeks, or every 6 weeks after Visit 11, since the schedule of visits after this visit would NOT allow more frequent assessments. Treatment compliance for each 4- to 6-week interval is defined as taking at least 75% of the required SC doses of study drugs.

In addition to the assessment of a participant's compliance with administration of study drugs, 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 diaries, 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.

6.5. Concomitant Therapy

Participants will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety of the study treatments. The table below provides a summary of criteria for use of concomitant medications that may interfere with planned assessments during the study.

Criteria for Use of Concomitant Medications that May Interfere with Efficacy and Safety Assessments in Study GZBD

Drug Class	Use during Screening/Lead-In	Conditions for Use after Randomization		
		Acute Therapy[a]	Rescue Therapy[b]	During Safety Follow-Up Period
Drugs with approved weight loss indication[c]	Excluded	N	N/A	Y
Systemic glucocorticoid therapy[d]	Excluded except for acute therapy[a]	Y	N/A	Y
Antihyperglycemia medications				
Other GLP-1 RAs	Excluded	N	N	N
DPP-4 inhibitors	Excluded	N	N	N
SGLT2 inhibitors	Excluded	N	Y	Y
Insulins and insulin mixtures	Excluded except for acute therapy[a]	Y	Y	Y
Meglitinides	Excluded	N	Y	Y
Alpha-glucosidase inhibitors	Excluded	N	Y	Y
Sulphonylureas	Excluded	N	Y	Y
Thiazolidinediones	Excluded	N	Y	Y
Metformin[e]	Optional	N/A	Y[f]	Y

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; N = no; N/A = not applicable; SGLT2 = sodium-glucose co-transporter 2; Y = yes.

a Acute therapy = treatment for up to 14 days.

b Rescue therapy is glucose-lowering intervention added to manage severe persistent hyperglycemia, as defined in Section 8.3.2.2

c See Section 5.2

d From 1 month prior to Visit 1 or between Visits 1 and 3; does not apply to topical, intraocular, intranasal, intra-articular, or inhaled preparations.

e Switching metformin manufacturers is allowed as long as the dosage is the same.

f For rescue therapy, metformin dose can be increased if the dose is below maximum approved dose per country-specific label.

Investigative site staff will inform participants that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the study. This may not be possible when initiated for treatment of medical emergencies, in which case, the participant will inform the investigator or a designated site staff member as soon as possible. Any additional medication initiated during the course of the study (including OTC drugs, such as paracetamol or aspirin) must be documented, and the name of the drug and the date(s) of administration must be recorded on the "Concomitant Medications" section of the eCRF.

6.5.1. Glucose-lowering Agents

The only concomitant antihyperglycemic medication permitted at baseline is metformin. Metformin dose must be stable for at least 3 months prior to screening.

- Participants who enter the study on diet and exercise alone will not be allowed to initiate metformin therapy after study entry, unless if rescue therapy is required (for more details see below).
- Participants who are being treated with metformin upon entering this study should remain on the same metformin dose throughout the course of the study. A change in dose is allowed only after randomization when needed to protect the participant's safety (see below for further details). If needed between screening and randomization, that participant will be discontinued from the trial.
- If a participant switches from the immediate-release formulation of metformin to the sustained-release formulation, the change will be on a milligram per milligram basis.

After randomization, discontinuation of metformin or change in dosage and formulation is permitted in the following situations:

In the event of a hypoglycemic episode(s) (clinical symptoms of hypoglycemia and/or BG-confirmed symptomatic BG hypoglycemia: glucose concentration <3.0 mmol/L [<54 mg/dL]: participants may reduce/discontinue the dose of metformin.
In certain situations that require short-term discontinuation in line with the product(s) labeling for each respective country (for example, severe dehydration, elective surgery, or need for radiologic examination involving IV iodinated contrast dye). Once the situation that led to temporary discontinuation of the drug is resolved, treatment should be restarted at investigator's discretion.
If a participant develops contraindications to metformin such that the use of the drug is contraindicated according to the country-specific label.
If a participant meets the criteria for severe, persistent hyperglycemia or discontinues study drugs, then metformin may be added (for participants managed by diet/exercise alone) or the metformin dose may be increased according to country-specific label as long as that is not the sole intervention (see Section 8.3.2.2).

A participant will be considered noncompliant with the protocol (protocol deviation) if he or she changes the dose or discontinues metformin for reasons other than those described here. Dose

reduction or discontinuation of metformin during the trial should be properly documented and recorded on the appropriate eCRF.

Glucose-lowering medications other than study drugs and metformin are not allowed at any time during the study except for those participants who require permanent discontinuation of study drugs, but remain in the study, rescue therapy after randomization due to severe, persistent hyperglycemia (criteria provided in Section 8.3.2.2), or during the safety follow-up period as indicated in the table above (Section 6.5). Short-term insulin use for up to 14 days is allowed for certain clinical situations (for example, elective surgery, during hospitalization, and hyperosmolar states) and must be differentiated from insulin use as rescue therapy when reported in the eCRF.

All nonstudy medications will be recorded in the eCRF at all visits.

Nonstudy medications taken by participants who are screened but not randomly assigned to treatment will not be reported to Lilly unless an SAE or AE occurs that the investigator believes may have been caused by a study procedure.

6.5.2. Other Concomitant Medications

Treatment with medications that are excluded per entry criteria (Section 5.2, Exclusion Criteria) is not permitted during the trial.

Doses of prescription medications for treatment of concurrent medical conditions should remain constant during the study unless an adjustment is medically indicated. When needed, the sponsor should be contacted to clarify if an individual medication is allowed in the study. If an additional concomitant medication is already started, the sponsor should be informed as soon as possible.

Doses of antihypertensive and lipid-lowering therapies should not be changed and remain constant during the study unless an adjustment is medically indicated. For example, doses of antihypertensive medication may be reduced if the participant's blood pressure declines significantly during the study resulting in symptoms of lightheadedness or may be increased during a hypertensive crisis.

Nonsteroidal anti-inflammatory medications (including ibuprofen and aspirin), acetaminophen, cough suppressants, antihistamines, vitamin/mineral supplements, antibiotics, and topical ointments may be used on an as-needed basis without notifying the sponsor and are not restricted by the stable dosing requirements listed earlier. Any additional medication used during the course of the study (including those not requiring sponsor notifications) must be documented on the appropriate eCRF. Specifically excluded concomitant medications are listed in Section 5.2.

6.5.3. Management of Participants with Gastrointestinal Symptoms

Consistent with other incretins, in Phase 1 studies, the most reported TEAEs for participants receiving LY3437943 or dulaglutide 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.

- If GI AEs occur, 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 drugs. The data related to temporary interruption of study treatment should be documented in source documents and entered on the eCRF (see Section 6.6.1).
- After the symptoms have resolved, restart dosing as per the guidance provided in Section 6.6.

If intolerable GI symptoms or events persist despite the above measures, see Section 6.6.1

6.6. Dose Modification

Study drug administration should follow the schedule provided in Section 1.3 (SoA) and Section 4.1.1 (Overview of Study Periods). Dose modification is not allowed, except for

- temporary dose interruption to address tolerability or other clinically important safety issues, or
- dose reductions, without dosing interruptions, when appropriate to ensure participant safety.

Any changes in dosing will be documented in the participant diaries and eCRF. Dose reductions may occur at unscheduled visits.

6.6.1. Temporary Interruption of Study Drug

In certain situations, participants may need to temporarily interrupt study drug, for example due to

- occurrence of intolerable GI AEs, and
- other AEs deemed by the investigator severe enough to warrant dosing interruption.

If the reason for temporary dosing interruption is related to poor participant tolerability, for example when protracted GI events of vomiting and/or diarrhea trigger a request from the participant and/or from the investigator for temporary discontinuation of dosing, 1 weekly dose of study drug can be omitted. A longer interruption must be approved by Lilly study physician upon review of the case with the primary investigator or designee. In other situations when participant safety is compromised, for example due to an SAE, more than 1 dose may need to be skipped. The decision to interrupt dosing in any of these situations will not be considered a protocol deviation. If the participant interrupts dosing for other reasons, that are not related to the tolerability or safety of the participant, dosing interruption will be considered a protocol deviation. Every effort should be made by the investigator to restart dosing as soon as it is safe to do so. A participant may experience multiple events that require dosing interruption; each event should be addressed individually per guidance provided in this section. Any other situation of study drug interruption that is not described in this section will be discussed between the primary investigator or designee and Lilly study physician to decide on an appropriate dosing plan for any participant with such events.

The following table provides detailed guidance on additional procedures to follow temporary interruption of study drugs in a blinded fashion.

Reason for Interruptions	Number of Doses Missed	Actions at Dosing Re-Initiation
Tolerability TEAEs related to study drug	1 dose	Dosing will be restarted with the same dose that was last administered prior to interruption for 1 week and will then follow the planned dosing schedule. • If the rechallenge with LY3437943 is not tolerated, the dose will be reduced to the previously tolerated dose and the participant will be kept on that dose until the end of the treatment period. If the starting LY3437943 dose of 0.5 mg or 2 mg or maintenance dose of 4 mg or dulaglutide 1.5 mg dose is not tolerated on rechallenge, the participant will discontinue study drug. If the starting LY3437943 dose of 4 mg is not tolerated upon rechallenge, the participant will be switched to the 2 mg starting dose, per the alternate dose escalation scheme.
	2 or more consecutive doses	For participants on LY3437943, dosing will be restarted on the previously tolerated, lower dose (that is, one dose level lower for that treatment arm than the dose that was not tolerated) for 2 weeks and then resume dosing per the planned dosing schedule. Participants in the dulaglutide group will be restarted on 1.5 mg dose. If the rechallenge with LY3437943 is not tolerated for a second time, the dose will be reduced to the previously tolerated dose and the participant will be kept on that dose until the end of the treatment period. If the starting LY3437943 dose of 0.5 mg or 2 mg, or maintenance dose of 4 mg or

Reason for Interruptions	Number of Doses Missed	Actions at Dosing Re-Initiation
		dulaglutide 1.5 mg is not tolerated upon rechallenge, the participant will discontinue study drug. If the starting LY3437943 dose of 4 mg is not tolerated upon rechallenge, the participant should be switched to the 2 mg starting dose, per the alternate dose escalation scheme.
Other TEAEs or reasons not related to TEAEs (that is, due to a protocol deviation)	1 dose	Dosing will be restarted with the same dose that was last administered prior to interruption for 1 week and then follow the planned dosing schedule.
	2 or more consecutive doses	For participants on LY3437943, dosing will be restarted at one dose lower (for that treatment arm) than the last dose administered prior to interruption; continue this dose for 2 weeks and then resume the planned dosing schedule. If the dose prior to interruption is the lowest dose level, restart dosing on that dose. Participants in the dulaglutide group will be restarted on 1.5 mg dose.

Investigators should inform the sponsor that study drug has been temporarily interrupted. The data related to temporary interruption of study treatment will be documented in source documents and entered on the eCRF.

6.6.2. Dose Reductions Indicated to Ensure Participant Safety

In addition to the dose modifications described in Section 6.6, there may be situations when dose interruptions occur, where only dose reduction (without interrupting dosing) would be appropriate (for example, clinically significant changes in vital signs accompanied by AEs or similar events when it is reasonable to assume causal relationship with active treatments [LY3437943, dulaglutide] in the trial).

If a participant is experiencing any such safety issue, dose reduction to the next lower maintenance dose level or discontinuation of study drug, if the participant is already on the lowest dose level, should be considered. The decision to lower the dose or discontinue study drug in such situation should be approved by Lilly CRP.

All dosing modifications described in this section and in Section 6.6 will be conducted in a blinded fashion, by modifying administration of both LY3437943 and dulaglutide as appropriate.

Participants will be blinded during dose modification. LY3437943 dose modification should occur together with temporary interruption of the dulaglutide SDP as described in Section 6.6.1.

6.7. Intervention after the End of the Study

LY3437943 will not be made available to participants after conclusion of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study interventions. If study interventions are definitively 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 interventions and follow-up and for any further evaluations that need to be completed. The participants will receive additional glucose-lowering agents if needed based on the investigator's judgment (see Section 6.5.1. for detailed guidance).

Possible reasons leading to permanent discontinuation of study drug:

participant decision

the participant requests to discontinue study drug

clinical considerations

BMI ≤ 19 kg/m^2

initiation of prohibited concomitant medications (see Section 6.5) if participants will not or cannot discontinue them

intolerable GI symptoms despite management as described in Section 6.5.3

> ***Note:*** The investigator should contact the Lilly CRP/Clinical research scientist (CRS) to discuss whether it is medically appropriate for the participant to continue study treatment.

diagnosis of T1DM

diagnosis of MTC or MEN2 after randomization

significant elevation of calcitonin (serum calcitonin value ≥20 ng/L and <35 ng/L and ≥50% increase from the screening value; or serum calcitonin value ≥35 ng/L and ≥50% over the screening value) or diagnosis of C-cell hyperplasia

diagnosis of acute or chronic pancreatitis

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

If the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction has occurred related to study drug administration, the participant should be permanently discontinued from the investigational drug

onset of pregnancy in a female participant

occurrence of any other TEAE, SAE, or clinically significant finding for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken

- **discontinuation due to a hepatic event or liver test abnormality**
    - participants who are discontinued from study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF
    - discontinuation of the study drug for abnormal liver tests **should be** considered by the investigator when a participant meets one of the following conditions after consultation with the Lilly-designated medical monitor:
        - ALT or aspartate aminotransferase (AST) >8X ULN
        - ALT >2X baseline value (for participants with elevated ALT levels at baseline) OR ≥300 U/N, whichever occurs first, if baseline ALT ≥2X ULN
        - ALT or AST >5X ULN for more than 2 weeks
        - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio (INR) >1.5
        - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
        - alkaline phosphatase (ALP) >3X ULN
        - ALP >2.5X ULN and TBL >2X ULN
        - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

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

At the time of discontinuing from the study, if possible, an ED visit should be conducted. See 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 both from the study intervention and from 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 or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee 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.

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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.

- HbA1c as determined by the central laboratory
- Fasting blood glucose (FBG) as determined by the central laboratory, and
- Body weight (see Section 10.9 for measurement procedure).

Exploratory:

- Seven-point SMBG (see Section 10.9)
  Lipid profile, consisting of total cholesterol, low-density lipoprotein (LDL)-cholesterol, very low-density lipoprotein (VLDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides
  Mechanistic biomarkers: to explore potential mechanism of action modifying glucose, lipid, or nutrient metabolism, markers will be assessed (see Section 10.11 for detailed list of biomarkers) related to

insulin sensitivity
pancreatic beta or alpha cell function
glucagon receptor target engagement
fatty acid oxidation
lipolysis
purine metabolism, and
cardiovascular risk.

Patient-reported outcomes (see Section 10.10)
Short Form-36 version 2 Health Survey acute form, 1-week recall version
Eating Inventory, and

Appetite Visual Analog Scale.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

For each participant, measurements including height, weight, and waist circumference should be conducted according to SoA, and following the study-specific recommendations included in Section 10.9.

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

skin, including feet
cardiovascular (CV)
respiratory
GI
neurological systems CCI and
thyroid exam.

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

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to SoA, and following the study-specific recommendations included in Section 10.9.

Any clinically significant findings from vital sign 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, a single 12-lead ECG should be collected according to Section 1.3 (for details, please see Section 10.9. In addition, tracings collected at the baseline, 24 and 36 weeks will be assessed qualitatively by a blinded cardiologist.

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, 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 via the eCRF.

8.2.4. Clinical Safety Laboratory Assessments

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

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

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 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 or 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, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.5. 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 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, cardiovascular, thyroid c-cell function, and renal safety data. The hepatic safety monitoring plan is provided below; for additional information, please see also Section 8.3.2.

8.2.5.1. Hepatic Safety Monitoring

Close hepatic monitoring

If any of the following abnormalities occurred, laboratory tests (Section 10.5), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyltransferase, and creatine kinase, should be

repeated within 48 to 72 hours to confirm the abnormality and to determine if the values are increasing or decreasing:

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 reduced to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

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

If a participant with baseline results of…	develops the following elevations:
ALT or AST <1.5X ULN	ALT or AST ≥3X ULN with hepatic signs or 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 or 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 or symptoms are severe fatigue, nausea, vomiting, jaundice, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

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

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

Additional hepatic safety data collection in hepatic safety 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 an SAE

5. Discontinuation of study drug due to a hepatic event.

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

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

The definitions of the following events can be found in Section 10.3 Appendix 3.

- AEs
- SAEs, and
- Product complaints (PCs).

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest, 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 10.3.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Adverse Event					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE eCRF	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE 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
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	35 days after the last dose	Within 24 hours of learning of the pregnancy	SAE eCRF	SAE paper form
PCs					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A

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

Abbreviations: AE = adverse event; eCRF = electronic case report form; N/A = not applicable; PC = product complaint; SAE = serious adverse events.

*Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

8.3.2. Adverse Events of Special Interest

The following are adverse events that will be adjudicated by an external adjudication committee:

- pancreatitis (see Section 8.3.2.3)
- major adverse cardiovascular events (see Section 8.3.2.5), and
- deaths.

The following are additional adverse events of special interest :

- hypoglycemia (Level 2 and 3)
- severe persistent hyperglycemia
- thyroid malignancies and C-cell hyperplasia
- CV safety
- hypersensitivity events
- injection site reactions
- hepatobiliary disorders
- severe GI AEs
- antidrug antibodies, and
- acute renal events.

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

8.3.2.1. 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 blood glucose confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence of absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

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

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

- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE 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.

8.3.2.2. Severe Persistent Hyperglycemia

An additional glucose-lowering intervention should be considered by the investigator for participants with any persistent severe hyperglycemia, defined as meeting any of the following criteria during the treatment period:

During the first 8 weeks postrandomization (between Visits 3 and 7): An average fasting blood glucose (FBG) above 255 mg/dL (14.1 mmol/L) over at least a 2-week period (at least 4 values/week must be available)

OR

Between Weeks 8 and 16 (between Visits 7 and 9): An average FBG above 240 mg/dL (13.3 mmol/L) over at least a 2-week period (at least 4 values/week must be available)

OR

Between Weeks 16 and 24 (between Visits 9 and 11): An average FBG above 200 mg/dL (11.1 mmol/L) over at least a 2-week period (at least 4 values/week must be available

OR

Beginning at Week 24 (Visits 11 through 13): HbA1c above 8.0% (64.0 mmol/mol) which is not at least 0.3% lower than the HbA1c at the previous scheduled measurement.

In considering whether initiation of rescue therapy is warranted, investigators should first confirm that the participant is fully compliant with the assigned therapeutic regimen and that he or she does not have an acute condition causing severe hyperglycemia. If these other reasons are excluded, the investigator will initiate an appropriate glucose-lowering intervention (rescue intervention) according to the guidance outlined in Section 6.5, and it will be recorded on the eCRF specified for collecting antihyperglycemic medications. Other GLP-1 RAs or DPP-4 inhibitors must not be used as the rescue intervention. Participants who receive rescue intervention for hyperglycemia management should also continue administering study drug for the remaining period in the trial.

8.3.2.3. Pancreatitis

Diagnosis of acute pancreatitis

Acute pancreatitis is an AE of interest in all studies with LY3437943, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 2006; Kouzumi 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, and
- 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 6.6 (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.

8.3.2.4. 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 LY3437943 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.

8.3.2.5. Major Adverse Cardiovascular Events

Nonfatal cardiovascular 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 cardiovascular 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.

8.3.2.6. 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 must be reported as SAEs.

8.3.2.7. Deaths

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

8.3.2.8. Hypersensitivity Reactions

Many drugs, particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

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

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Section 10.2. Laboratory results are provided to the sponsor via the central laboratory.

8.3.2.9. Injection Site Reactions

Symptoms of a local injection site reaction (ISR) may include erythema, induration, pain, pruritus, and edema. If an injection site event is reported, the AE will be recorded, and additional data will be provided to the sponsor in the eCRF. At the time of occurrence of severe or serious ISRs, samples will be collected for measurement of LY3437943 antidrug antibodies (ADAs) and LY3437943 concentration.

8.3.2.10. Hepatobiliary Disorders

All events of TE biliary colic, cholecystitis, or other suspected events related to 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 8.2.5.1.

8.3.2.11. Severe Gastrointestinal Adverse Events

LY3437943 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 6.5.3.

8.3.2.12. 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 LY3437943, 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. Treatment of Overdose

For this study, any total dose of study intervention within a 48-hour time period greater than the dose assigned by IWRS for that participant will be considered an overdose and should be reported as per criteria described in Section 10.3.

In the event of an overdose, the investigator should

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 30 days). Refer to Section 8.3 for reporting details.
3. Obtain a plasma sample for PK analysis within 5 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).

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

In the event of overdose, refer to the IB for the study drug and/or product label for Trulicity (dulaglutide), as applicable.

8.5. Pharmacokinetics

Blood samples for PK analyses will be collected from all randomized participants in accordance with schedule provided in Section 1.3 and at ED. Efforts should be taken to align clinical visits with PK sampling windows specified in the Pharmacokinetic Schedule of Events table (Section 1.3). Otherwise, participants may need to return to the clinical site for additional PK-specific visits to provide PK samples. Only samples from participants assigned to treatment with LY3437943 will be analyzed for drug concentration.
Date and time of each sample and the most recent LY3437943 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.

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

8.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3437943 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.

8.6. Pharmacodynamics

Pharmacodynamic assessments for LY3437943 are included as part of the efficacy and safety measures listed in Section 8.1 and will be collected according to the SoA (Section 1.3).

8.7. Genetics

A blood sample will be collected to enable exploratory pharmacogenetic analyses as specified in the SoA (Section 1.3), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples may be used to investigate variable exposure or response to LY3437943 and to investigate genetic variants thought to play a role in diabetes mellitus and related clinical traits or complications, including nonalcoholic steatohepatitis or obesity. Assessment of variable response may include evaluation of AEs or differences in pharmacodynamic, mechanistic, safety, or efficacy measures.

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

Samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and/or the Ethical Review Board (ERB) impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3437943 or after LY3437943 is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole-genome or exome sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

8.8. Biomarkers

In addition to the planned biomarker research as indicated in the SoA and Section 10.11, biomarker research on stored nonpharmacogenetic samples may be performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules, including DNA, RNA, proteins, lipids, and other cellular elements.

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

CCI [redacted]

CCI [redacted]

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 of 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 LY3437943 or after LY3437943 becomes commercially available.

8.9. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), blood samples will be collected to determine antibody production against LY3437943. Antibodies may be further characterized for cross-reactive binding to endogenous counterparts (native GIP, GLP-1, and glucagon), and their ability to neutralize the activity of LY3437943 and endogenous counterparts. To interpret the results of immunogenicity, a blood sample will be collected at the same time points to determine the concentrations of LY3437943. All samples for immunogenicity should be taken predose when applicable and possible.

Treatment-emergent ADAs are defined in Section 9.4.6. If the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE-ADA positive, additional samples may be taken until the signal returns to baseline (in other words, no longer indicates TE-ADA) or for up to 1 year after last dose. A PK sample may be collected at each time point at the investigator's discretion.

Samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and Ethical Review Boards allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the LY3437943. Any samples remaining after 15 years will be destroyed.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary hypothesis that is being tested in this study is that LY3437943 0.5, 4, 8, or 12 mg administered SC QW is superior to placebo with regards to change in HbA1c from baseline to Week 24, in participants with T2D inadequately controlled with diet and exercise with or without a stable dose of metformin

Secondary hypotheses are that at least one of LY3437943 doses is superior to placebo and dulaglutide 1.5 mg with regards to

- change in HbA1c from baseline to 24 and 36 weeks except comparison with placebo at 24 weeks (primary objective)
- percentage of participants reaching HbA1c of <7.0% at 24 and/or 36 weeks
- change in FBG from baseline to 24 and 36 weeks, and
- change in body weight (kg) from baseline to 24 and 36 weeks.

9.2. Sample Size Determination

Approximately 300 participants will be randomized in a 2:2:2:1:1:1:1:2 ratio to either placebo, dulaglutide 1.5 mg, LY3437943 0.5 mg, LY3437943 4 mg (with starting dose at 2 mg), LY3437943 4 mg (with starting dose at 4 mg), LY3437943 8 mg (with starting dose at 2 mg), LY3437943 8 mg (with starting dose at 4 mg), or LY3437943 12 mg (with starting dose at 2 mg). Assuming a 20% dropout rate, this results in approximately 40 completers per arm. Sample size selection is guided by the objective of establishing superiority of each LY3437943 maintenance dose to placebo relative to the change in HbA1c from baseline to 24 weeks. The evaluation of superiority to placebo will be conducted for each of the 4 LY3437943 maintenance doses at 2-sided significance level of 0.05 using 2-sample t-test. The LY3437943 group mean reduction in HbA1c at Week 24 from baseline compared to placebo is assumed to be -2.1% assuming a common standard deviation (SD) of 1.1%. The chosen sample size provides at least 99% power to establish superiority of LY3437943 0.5 mg, LY3437943 4 mg, LY3437943 8 mg, or LY3437943 12 mg compared to placebo. No adjustment for multiplicity will be performed.

9.3. Populations for Analyses

The following populations are defined for the purpose of analysis:

Population	Description
Screened	All participants who have signed informed consent.
Randomized	All participants who are randomly assigned to a treatment arm.
Efficacy analysis set (EAS)	All randomized participants who take at least 1 dose of double-blinded study treatment from randomization. Excludes data after discontinuation of study drug or initiation of rescue medication. Participants will be included in the treatment group to which they were randomized.
Full analysis set (FAS)	All randomized participants who take at least 1 dose of double-blinded study treatment, regardless of adherence to study drug or initiation of rescue medication. Participants will be included in the treatment group to which they were randomized.

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analyses of this study will be the responsibility of Lilly or its designee.

Any change to the data analyses methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to data analyses 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 the 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 the confidence interval (CI) will be calculated at 95%, 2-sided. In statistical summaries and analyses, participants will be analyzed as randomized.

The baseline value used for the analyses will be the last scheduled baseline value obtained for each participant prior to randomization.

The primary estimand of interest in comparing efficacy of LY3437943 doses with placebo for this study is the "efficacy estimand," which represents the efficacy prior to discontinuation of study drug without confounding effects of antihyperglycemic rescue therapy. The primary efficacy assessment, guided by the "efficacy estimand," will be conducted using the EAS. The "treatment-regimen estimand," using the FAS, which represents the efficacy irrespective of adherence to study drug or initiation of rescue antidiabetic drug, and the "principle-stratification estimand" that shows efficacy for those who would comply with the study treatment LY3437943 (as defined in Section 9.4.2.4) will be estimated in the exploratory analyses.

The summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum, and for categorical measures will include sample size, frequency, and percentage. The analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time (in addition to the baseline and end of treatment measurements) will be a mixed model for repeated measures (MMRM) with terms:

treatment
visit
treatment-by-visit interaction
baseline HbA1c category [<8.5% or ≥8.5%]
baseline BMI category [<30 or ≥30], and
baseline measurement as a covariate.

Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Fisher's exact test will be used to examine the treatment difference in categorical outcomes. Logistic regression may be used to examine the treatment difference in binary efficacy outcomes. The negative binomial regression model will be used for the treatment comparison of discrete count measures if deemed appropriate.

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

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

Frequency counts and percentages of all participants screened, randomized, and receiving at least 1 dose of study drug will be presented by treatment groups. A listing of randomized participants not receiving study drug will be provided. All participants who discontinue the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized by treatment. The percentage of participants discontinuing from each treatment will be compared using the Fisher's exact test. A Kaplan-Meier analyses of time from randomization to premature discontinuation from study and premature discontinuation from study drug by treatment group will be provided.

9.4.2.2. Participant Characteristics

Demographics, medical history, and concomitant illness will be summarized by treatment group using the full FAS.

9.4.2.3. Concomitant Therapy

Concomitant medications, including previous therapy for diabetes, will be summarized by drug class and treatment group using the FAS. In particular, the incidence of rescue therapy for severe, persistent hyperglycemia will be analyzed as an exploratory safety endpoint.

9.4.2.4. Treatment Compliance

Treatment compliance for each 4- to 6-week interval is defined as taking at least 75% of the required SC doses of study drug. Frequency counts and percentages of participants compliant to study drug will be summarized by treatment arm using the FAS.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

The primary efficacy analyses will be conducted to establish superiority of LY3437943 0.5 mg, LY3437943 4 mg, LY3437943 8 mg, or LY3437943 12 mg to placebo with regards to change in HbA1c from baseline to 24 weeks. The primary analyses will be performed on EAS using MMRM with treatment, visit, and treatment-by-visit interaction as fixed effects, baseline HbA1c and stratification factors as covariates, and participant as a random effect. An unstructured variance-covariance matrix will be used to model the within-participant effects. Additional covariates may be added, and this MMRM analysis will be detailed in the SAP.

9.4.3.2. Secondary Analyses

In addition to the primary efficacy analysis of change in HbA1c in study population, the following secondary study objectives will be analyzed on the EAS:

- change in HbA1c from baseline to 24 and 36 weeks
- percentage of participants reaching HbA1c of <7.0% at 24 and/or 36 weeks
- change in FBG from baseline to 24 and 36 weeks, and
- change in body weight (kg) from baseline to 24 and 36 weeks.

Continuous endpoints, including change in HbA1c from baseline to 24 and 36 weeks, change in FBG from baseline to 24 and 36 weeks, change in body weight (kg) from baseline to 24 and 36 weeks, will be conducted in a manner similar to the primary efficacy analyses discussed in Section 9.4.3.1. The details will be provided in SAP.

9.4.3.3. Tertiary/Exploratory Analyses

A Bayesian approach will be used as the dose–response model for change in HbA1c and body weight from baseline to the 24-week endpoint. The placebo group will be modeled with LY3437943 doses. Details of the prior distribution specifications along with other analyses with regards to the exploratory objectives will be provided in the SAP.

9.4.4. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3437943 doses with placebo irrespective of adherence to study drug or initiation of rescue therapy. Thus, safety analyses will be conducted using the FAS. Selected safety analyses may be conducted after excluding data on rescue therapy or data after starting another antihyperglycemic medication.

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.

9.4.4.1. 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.

9.4.4.2. Gastrointestinal Events

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

9.4.4.3. Central Laboratory Measures, Vital Signs, and Electrocardiograms

Values and change from baseline to postbaseline values of central laboratory measures, vital signs, and selected ECG parameters will be summarized at each scheduled visit. The analysis model to make comparisons among treatment groups relative to continuous change from baseline values assessed over time will be an MMRM similar to the primary efficacy analysis and with baseline measurement as a covariate. An unstructured covariance structure will model relationship of within-participant errors.

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.

The analysis details will be provided in the SAP.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

LY3437943 concentration data will be summarized and analyzed using a population PK approach via nonlinear mixed-effects modeling. The relationships between LY3437943 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. If antidrug antibody titers are detected from immunogenicity testing, then the impact of immunogenicity titers on LY3437943 PK or any relevant PD parameters may also be examined. Additional analyses may be conducted if they are deemed appropriate. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan.

9.4.6. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with treatment-emergent ADA+ to LY3437943 may be tabulated. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the treatment-emergent ADA+ participants, the distribution of maximum titers may be described. The frequency of neutralizing antibodies against LY3437943, if performed, may be tabulated in treatment-emergent ADA+ participants. If cross-reactivity to native GIP, GLP-1, and glucagon or neutralizing antibodies against native GIP, GLP-1, and glucagon assays are performed, the frequency of each may be reported.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to LY3437943 may be assessed.

9.4.7. Subgroup Analyses

Subgroup analyses of important factors, including baseline BMI, baseline HbA1c, and other factors to be specified in the SAP, are planned for the key outcomes. The models used for these analyses will vary depending on the subgroups and the outcome. More details of the modeling will be provided in the SAP. Other exploratory subgroup analyses may be performed as deemed appropriate.

9.5. Interim Analyses

An interim efficacy and safety assessment after all participants complete Visit 9 (Week 16) of the treatment period will be conducted to provide initial guidance for the design of future clinical studies of LY3437943. An internal 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 to monitor safety of study participants. 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. Study team members who have potential contact with the sites will remain blinded throughout the study. 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 until 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 LY3437943 versus placebo and 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 primary database lock and primary data analysis for Study GZBD will occur when all participants have completed 24 weeks of treatment. The final analyses for this study will be performed after all randomized participants have completed 36 weeks of treatment and the 4-week follow-up period. 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.

9.6. Data Monitoring Committee (DMC)

Not applicable.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - applicable ICH Good Clinical Practice (GCP) Guidelines, and
  - applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an Institutional Review Boards (IRB)/Independent Ethics Committees (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, and
  - 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 (CTA).

10.1.2. Informed Consent Process

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

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his or 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 or her data to be used as described in the informed consent.
- The participant must be informed that his or 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. Committees Structure

An independent CEC will be formed to adjudicate major adverse cardiovascular events, deaths, and pancreatitis AEs. Sections 8.3.2.3 and 8.3.2.5 outline additional information on pancreatic and cardiovascular adjudication committees, respectively.

An internal AC will be formed compromising individuals with expertise needed for the evaluation and interpretation of the results from the interim analyses. The AC for this study is comprised of 3 members: one clinical physician, one GPS physician, and one statistician, including a designated chairperson. The AC will include members from Lilly only.
The primary responsibility of the AC is to review the efficacy and safety reports after all participants reach 16 weeks of treatment in an unblinded manner. The details regarding number of participants and analysis plan will be provided in the AC charter (see Section 9.5).

10.1.5. Dissemination of Clinical Study Data

Required clinical trial registries (for example, ClinicalTrials.gov) will be updated with the results from registered clinical trials regardless of the research outcome in accordance with local laws and regulations.

All CSRs, amendments, and addenda will be submitted to external regulatory authorities, external partners (as applicable), and sites.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF 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 (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (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.

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

Additionally, clinical outcome assessment data (participant/clinician-focused outcome instrument) will be collected by the participant/authorized study personnel, via a paper source document and will be transcribed by the authorized study personnel into the EDC system.

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

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

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

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on 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 study training material.

10.1.8. Study and Site Start and Closure

10.1.8.1. Discontinuation of the Study

The sponsor designee reserves the right to terminate the study at any time for any reason at the sole discretion of the sponsor. 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.

Medical Oversight and Safety Review

Ongoing safety review(s) by designated sponsor personnel will occur and be documented. Such reviews will include

- monitoring and assessing the safety information collected during the trial both in real time and periodically
- reviewing safety data for trends that need action, and
- detecting adverse drug/device effects.

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

- Two 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.
- One study participant develops any TEAE or SAE regardless of attribution to study drug that has life-threatening consequences or requires urgent intervention.
- Death of any study participant at any time.
- Any other clinically significant safety signal.

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

10.1.8.2. Discontinuation of Study Sites

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

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

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

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

10.1.9. Publication Policy

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

10.1.10. Investigator Information

Physicians with experience in Phase II or Phase III diabetes clinical trials will participate as investigators in this clinical trial.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed 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. 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.
- Pregnancy testing (please refer to Section 5.1 (Inclusion Criteria) for screening pregnancy criteria).

Investigators must document their review of the laboratory safety results.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel and are denoted in the table below.

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)	
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	

Hormones (female)	
Serum pregnancy	Assayed by Lilly-designated laboratory
Urine pregnancy	Evaluated locally
Follicle stimulating hormone (FSH)	Assayed by Lilly-designated laboratory
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 – LY3437943 concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Biomarkers	Assayed by Lilly-designated laboratory
HbA1c	
Calcitonin	
Pancreatic amylase	
Lipase	
Insulin	
Glucagon	
C-peptide	
Intact proinsulin	
Longitudinal biomarkers	Assayed by Lilly-designated laboratory. Results in this group of biomarkers (see Section 10.11), which are not defined in this table, will not be provided to the sites.
Endpoint biomarkers	Assayed by Lilly-designated laboratory. Results in this group of biomarkers (see Section 10.11), which are not defined in this table, will not be provided to the sites.
Genetic sample	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)	
P800	

Whole blood (EDTA)	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3437943 antibodies	
Anti-LY3437943 antibodies neutralization	
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.
Anti-LY antibodies (immunogenicity/ADA)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3437943 concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
CCI	
CCI	

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: 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.

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
- An AE that can be attributed to a medical device or device constituent deficiency is referred to as ADE (adverse device effect). It 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, and vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug–drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an

AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.

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

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs or symptoms of the disease under study, death due to progression of disease). An SAE that can be attributed to a medical device or device constituent is referred to as SADE (serious adverse device effect). An SAE that can be attributed to a not previously identified device risk is referred to as UADE (unanticipated adverse device effect).

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

Results in death

Is life-threatening

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

Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the

physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
Results in persistent disability or incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly or birth defect
Other situations • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint
A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs: deficiencies in labeling information, and use errors for device or drug–device combination products due to ergonomic design elements of the product. Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

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

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

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

AE, SAE, and PC Recording

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

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

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the (e)CRF page for AE/SAE and the PC Form for PCs.
- 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 or symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, for marketed products, in his or her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he or 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 or 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 paper SAE data collection tool (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 paper SAE form (see next section) or to the sponsor contact for SAE reporting by telephone.
- Contacts for SAE reporting can be found in study training material.

SAE Reporting via Paper CRF

Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor contacts for SAE reporting.

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 training material.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

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

Women of childbearing potential (WOCBP) and women not of childbearing potential (WNOCBP) may participate in this trial. WOCBP need to either remain abstinent (if this is their usual preferred lifestyle) or if they are in a same-sex relationship exclusively, they do not need to use contraception. If they are in a heterosexual relationship, they need to use contraception as described below throughout the study and for 5 half-lives of study drug plus 30 days, corresponding to 2 months after the last injection.

Word/Phrase	Definition
Women of childbearing potential	Females are considered a WOCBP 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.
Women not of childbearing potential	Females are considered WNOCBP 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.
Post-menopausal state	The post-menopausal 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, 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.

Please see guidance for specific participant populations below:

- **WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle**

Must…	**Must not…**
agree to either remain abstinent, or	• use periodic abstinence methods calendar ovulation symptothermal, or post-ovulation • declare abstinence just for the duration of a trial, or
stay in a same-sex relationship without sexual relationships with males	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle:

Topic	**Condition**
Pregnancy testing	Negative serum result at screening followed by a negative urine result within 24 hours prior to treatment exposure.
Contraception	Agree to use 2 forms of effective contraception, where at least one form must be highly effective (less than 1% failure rate).

Examples of different forms of contraception:

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

	○ female condom with spermicide. ***Note:*** The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, and female condom with spermicide) to be considered effective.
Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, and symptothermal) • withdrawal • post coital douche, and • lactational amenorrhea.

- **Males**

Topic	Guidance
For all men	• should refrain from sperm donation for the duration of the study and for 5 terminal half-lives of the study drug (30 days) plus 90 days, corresponding to 4 months after the last injection.
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms plus 1 additional highly effective (less than 1% failure rate) method of contraception for the duration of the study, and for 5 terminal half-lives of the study drug (30 days) plus 90 days, corresponding to 4 months after the last injection.
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, or
	• 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 (that is, condom with spermicide, diaphragm with spermicide, and female condom with spermicide) to be considered effective.

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

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of 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 drug. If the participant is discontinued from the study drug, follow the standard discontinuation process for each study period.

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

For testing selected, analysis is required to be completed by the Lilly-designated central laboratory, except for microbiology.
Local testing may be performed in addition to central testing when required 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]
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; PT-INR=prothrombin time-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: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples may be used for research related to LY3437943 or diabetes mellitus and related clinical traits or complications, including nonalcoholic steatohepatitis or obesity and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to LY3437943, study interventions related to this drug class, or diabetes mellitus and related clinical traits or complications, including nonalcoholic steatohepatitis or obesity. Genetic research may consist of the analysis of one or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3437943 or study interventions related to this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on LY3437943 or diabetes mellitus and related clinical traits or complications, including nonalcoholic steatohepatitis or obesity continues but no longer than 15 years or other period as per local requirements.

10.7. Appendix 7: 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, and weight loss), but despite hyperglycemia and 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).

10.8. Appendix 8: New York Heart Association Functional Classification IV CHF

New York Heart Association (NYHA) classification NYHA grading MET*

Class I No limitations. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations (asymptomatic LV dysfunction). >7

Class II Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pectoris (mild CHF). 5

Class III Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF). 2–3

Class IV Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF). 1.6

*MET (metabolic equivalent) is defined as the resting VO2 for a 40-year-old, 70-kg man. 1 MET = 3.5 mL O2 /min/kg body weight.

10.9. Appendix 9: Protocol GZBD Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, Vital Signs, ECG, SMBG and MNSI

The following information has been adapted from standardized physical measurement protocols for the World Health Organization'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 must 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 and 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 kg.

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, patient gowns 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 HR, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing.
- The participant should sit quietly for 5 minutes before vital sign measurements are taken.
- For each parameter, 3 measurements will be taken using the same arm, preferably the nondominant arm.
- The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and blood pressure needs to be recorded in the eCRF.
- Blood pressure must be taken with an automated arm blood pressure equipment with full range of cuff sizes up to XL.
- 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.

Orthostatic Vital Sign Measurements

- Orthostatic vital sign measurements (blood pressure and HR, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing. They should be done after completing the triplicate measures in the sitting position.
- The participant should lie quietly for 5 minutes before vital sign measurements are taken.
- The participant should be comfortably lying flat without legs crossed, in a calm, quiet area for 5 minutes before vital sign measurements are taken.
- For measurement of vital signs in the supine position, the arm should be supported by a pillow so that it is at the level of the right atrium (approximately halfway between the bed and the level of the sternum).

  - Incorrect arm positioning results in erroneous BP values.
  - Upper arm below the level of the right atrium (for example, arm hanging down) results in readings that are too high.
  - Upper arm above the heart level results in readings that are too low.
- Measure BP and pulse rate once in the supine position.
- After the BP and pulse rate are determined in the supine position, the participant should immediately move to the standing position, bend the arm used for BP determination at the elbow, and rest the arm on an adjustable table or stand so that the upper arm is supported at the heart level.
- Determine the standing BP and pulse rate in the supported arm immediately after standing for 3 minutes. Only 1 measurement is needed.
- Record all symptoms (AEs) that the participant may experience, such as lightheadedness, syncope, or dizziness as AEs.

Electrocardiogram

- Electrocardiograms should be collected at least 30 minutes prior to collection of blood samples for laboratory testing, including PK samples.
- Electrocardiograms should be recorded after the participant has been supine for 5 minutes in a quiet room.

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. In addition, tracings collected at the baseline, 24 weeks, and 36 weeks will be assessed qualitatively by a blinded cardiologist. At a future time, the remaining visits may be overread by a cardiologist at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements at timepoints as per the SoA. The machine-read ECG intervals and HR may be used for data analysis and report-writing purposes, unless a cardiology overreading of the ECGs is conducted prior to completion of the final study report (in which case, the overread data would be used).

Self-Monitoring of Blood Glucose

During the trial, participants will monitor their blood glucose to assess efficacy of study interventions, using glucometers provided by the sponsor. Procedures described in this section will be initiated immediately after participant eligibility is confirmed at Visit 2.

Glucose self-monitoring will consist of daily FBG measurements and QW 4-point BG measurements consisting of fasting (before morning meal/after awakening), before mid-day meal, dinner, and bedtime. In addition, a 7-point daily glucose profile consisting of measurements obtained before each meal, approximately 2 hours after each meal, and at bedtime per schedule provided in Section 1.3 (SoA). 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. At the weeks when 7-point daily BG profile is taken,

participants will not be required to perform weekly 4-point daily BG profiles. All self-monitoring BG values will be recorded in participants' diaries and will be discussed with the site personnel at each scheduled clinic visit. All events of hypoglycemia should also be recorded in the participant diary, according to instructions.

The 7-point self-monitoring of blood glucose values and all hypoglycemic events should be entered into the eCRF.

CCI

CCI

[redacted]

10.10. Appendix 10: Patient-Reported Outcomes

When feasible, the self-administered questionnaires will be translated into the native language of the participant, linguistically validated and administered according to the SoA (Section 1.3). The language of the signed ICF will be considered the native language. If a translation is not available in the native language of a participant at baseline, the questionnaire(s) will not be administered for that participant for the duration of the trial. If PRO questionnaire(s) is not collected due to a translation not being available, this will not be considered a protocol deviation.

When the PRO questionnaire(s) is collected as per the SOA, the questionnaire(s) should be completed before the participant has discussed their medical condition or progress in the study with the investigator and/or site staff, if the participant is not adversely affected by their fasting condition.

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

The SF-36v2 acute form, 1-week recall version is a 36-item generic, participant-administered 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 is 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 SD of 10; higher scores indicate better levels of function and/or better health (Maruish 2011).

Eating Inventory

The Eating Inventory is a 51-item, participant-administered measure designed to assess three aspects of eating behavior (Stunkard and Messick 1985)

dietary restraint (21 items)
disinhibition (16 items), and
perceived hunger (14 items).

Thirty-six items are rated in true/false format, 14 items are rated on a 4-point scale, and 1 item is rated on a 6-point scale. Dietary restraint refers to both cognitive and behavioral dietary restraint, disinhibition measures the tendency to overeat in response to external cues, and perceived hunger measures susceptibility to feelings

of hunger. Higher domain scores denote higher levels of restrained eating, disinhibited eating, and predisposition to hunger, respectively.

- ***Appetite Visual Analog Scale***

  The aim of the appetite Visual Analog Scale (VAS) is to determine the effects of study treatments on appetite sensations and desire for specific foods.

  The questionnaires should be completed before the participant has discussed their medical condition or progress in the study with the investigator and/or site staff, if the participant is not adversely affected by their fasting condition.

  The VAS scales will be analyzed as continuous variables on the 0-100 scale for individual components. Overall appetite score is calculated as the average of the 4 individual scores (satiety + fullness + [100-prospective food consumption] + [100-hunger]/4) (van Can et al. 2014; Flint et al. 2000). The higher overall appetite score indicates less appetite and the lower score indicates more appetite.

10.11. Appendix 11: Metabolic Mechanistic Biomarkers

Mechanistic biomarkers will be measured at longitudinal intervals (longitudinal biomarkers) or less frequently to correspond with interim analysis, primary and secondary endpoints (endpoint biomarkers). Results will not be provided to the investigative sites. To explore potential mechanisms of action related to changes in glucose, lipid, or nutrient metabolism, the following markers will be assessed:

- Biomarkers related to insulin sensitivity: fasting insulin, fasting C-peptide, homeostasis model assessment of insulin resistance ([HOMA2-IR] computed with fasting glucose and fasting insulin or fasting C-peptide), insulin-like growth factor binding protein 2 (IGFBP-2), total adiponectin, CCI and leptin
- Biomarkers related to pancreatic beta or alpha cell function: homeostasis model assessment of beta-cell function ([HOMA2-B] computed with fasting glucose and fasting insulin or fasting C-peptide), intact proinsulin, intact proinsulin/C-peptide ratio, intact proinsulin/insulin ratio, and fasting glucagon
- CCI
- Biomarker of fatty acid oxidation: beta-hydroxybutyrate
- Biomarkers of lipolysis: free fatty acids and glycerol
- Biomarker of purine metabolism: uric acid
- Biomarkers of bone formation or resorption: C-terminal telopeptide of Type I collagen (CTX-1) and procollagen Type I N-terminal propeptide (P1NP)
- Biomarkers related to cardiovascular risk: apolipoprotein B (ApoB) and apolipoprotein C-III (Apo C3).

Metabolic Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
Insulin sensitivity	HOMA2-IR (computed with fasting glucose and with fasting insulin or fasting C-peptide) IGFBP-2	Total adiponectin CCI Leptin
Pancreatic beta cell function	HOMA2-B (computed with fasting glucose and with fasting insulin or fasting C-peptide) Intact proinsulin/C-peptide ratio Intact proinsulin/insulin ratio	
CCI		
Fatty acid oxidation		Beta-hydroxybutyrate
Lipolysis	Free fatty acids Glycerol	
Purine metabolism		Uric acid

Metabolic Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
Bone formation or resorption		CTX-1 P1NP
Cardiovascular risk		ApoB Apo C3

CCI [redacted]

10.12. Appendix 12: 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, AEs, PCs, concomitant medications, and review of study participant diary (including study drug compliance).

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, weight and waist measurements, physical assessments, vital signs, PRO, collection of blood samples, and health information.

Other alternative locations: Laboratory draws and ECGs may be done at an alternate location in exceptional circumstances.

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. 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 paused for less than 30 days from screening: 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.
    - 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: the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen fail in the CRF. The participant can reconsent and be rescreened as a new participant as described in the protocol. This rescreen is in addition to the one allowed by the main protocol. 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 3 through Visit 6	Within 7 days from the intended date, or up to 7 days after the intended date
Visit 7 through Visit 11	Within 10 days from the intended date, or up to 10 days after the intended date
Visit 12 through Visit 13	Within 14 days from the intended date, or up to 14 days after the intended date
Visit 801	Within 14 days from the intended date, or up to 14 days after the intended date

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

Documentation

Changes to study conduct will be documented

- Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing or 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.

10.13. Appendix 13: Abbreviations

Term	Definition
AC	assessment committee
ADA	anti-drug antibodies
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
blinding/masking	A double-blind study 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
CHF	congestive heart failure
CKD-EPI	Chronic Kidney Disease-Epidemiology
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
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.
CSR	clinical study report

CT	computed tomography
CTA	Clinical Trial Agreement
DIO	diet-induced obese
DPP-4	dipeptidyl-peptidase-4
EAS	efficacy analysis set
ECG	electrocardiogram
EDC	electronic data capture system
eCRF	electronic case report form
ED	early discontinuation
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.
FAS	full analysis set
FBG	fasting blood glucose
FSH	follicle-stimulating hormone
Gcg	glucagon
GcgR	glucagon receptor
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIPR	glucose-dependent insulinotropic polypeptide receptor
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
GPS	Global Patient Safety
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein

hERG	human ether-a-go-go-related gene
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committees
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
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 or locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Boards
ISR	injection site reaction
IWRS	interactive web-response system
LDL	low-density lipoprotein
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MEN	multiple endocrine neoplasia
MEN2	multiple endocrine neoplasia syndrome type 2
MMRM	mixed-model for repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NAFLD	nonalcoholic fatty liver disease
NYHA	New York Heart Association

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	patient-reported outcomes/
QW	once weekly
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SDP	single-dose pen
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	Short Form-36 Health Survey (SF-36), version 2
SMBG	self-monitoring of blood glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TE	treatment emergent
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.
Tx	treatment
ULN	upper limit of normal
VAS	visual analog scale
VLDL	very low-density lipoprotein

WOCBP	women of childbearing potential
WNOCBP	women not of childbearing potential

10.14. Appendix 14: Protocol Amendment History

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

Amendment b: 10-May-2021

Overall Rationale for the Amendment:

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

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Events	Addition of the following note to Patient-Reported Outcomes (PROs), "If a translation is not available in the native language of a participant at baseline, the PRO questionnaire(s) will not be administered for that participant for the duration of the trial (Appendix 10.10)"	To have translation of PRO questionnaire(s) available in native language for participants
Section 4.1.1 Overview of Study Periods	Addition of "when collected" for PROs at Visit 3 and during maintenance period (Visits 9-13)	To be aligned with PROs in Schedule of Events
Section 8.3.1 Timing and Mechanism for Collecting Events	Change of Pregnancy eCRF to SAE eCRF	Editorial consistency
Section 10.10 Appendix 10 Patient-Reported Outcomes	Added information on translation of PRO questionnaire(s) not being available in the native language of a participant at baseline	To have translation of PRO questionnaire(s) available in native language for participants
Section 10.2 Appendix 2: Clinical Laboratory Tests	Removed uric acid from clinical chemistry.	To maintain internal document consistency. It is presented in Appendix 11 as biomarker of purine metabolism
	Added P800 to exploratory samples	Addition of plasma metabolic marker
Section 10.9 Appendix 9: Protocol GZBD Standardized Protocols for the Measurement of	Updated electrocardiogram tracings to be collected at baseline, 24 and 36 weeks and	To maintain consistency with Section 8.2.3 (Electrocardiograms)

Section # and Name	Description of Change	Brief Rationale
Height, Weight, Waist Circumference, Vital Signs, ECG, SMBG and MNSI	will be assessed qualitatively by a blinded cardiologist	

Amendment a: March 1, 2021

Overall Rationale for the Amendment:

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

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Events	Diary dispensation and return has been updated. An eGRF procedure was added at Visit 8 (Week 12) and removed at Visit 12 (Week 30).	The Schedule of Activities was updated to match operational changes related to diaries and to align eGFR visits with clinical chemistry visits.
Section 5.1 Inclusion Criteria	The sentence "Female participants should not be breastfeeding" was added to Inclusion criteria 7.	Text added for clarification
Section 8.3.2 Adverse Events of Special Interest	The section heading was changed from "~~Safety Topics~~ of Special Interest" to "**Adverse Events** of Special Interest". "Safety topics" was changed to "adverse events" throughout the section.	Corrected heading to match template. Section wording was corrected to match the heading.
Section 10.4 Contraceptive Guidance-Female participants who become pregnant	The greater than sign was changed to greater than or equal to in the following sentence: "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."	Corrected error

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Approval	PPD tor 25-Aug-2022 22:03:40 GMT+0000

Approval	PPD anagement 29-Aug-2022 15:14:27 GMT+0000

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