J1I-MC-GZBF (b) Clinical Protocol

A Phase 2 Study of Once-Weekly LY3437943 Compared with Placebo in Participants Who Have Obesity or Are Overweight with Weight-Related Comorbidities

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Approval Date: 29-Aug-2022

Title Page

Protocol Title: A Phase 2 Study of Once-Weekly LY3437943 Compared with Placebo in Participants Who Have Obesity or Are Overweight with Weight-Related Comorbidities

Protocol Number: J1I-MC-GZBF

Amendment Number: b

Compound: LY3437943

Study Phase: Phase 2

Short Title: Effect of LY3437943 versus Placebo in Participants Who Have Obesity or Are Overweight

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 154659

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

Document ID: VV-CLIN-072320

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment a	*21-May-2021*
Original Protocol	*26-Feb-2021*

Amendment [b]

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 17 from Predose to Postdose	Dosing does not occur at Visit 17 (Week 48); therefore, time point is now described as approximately 1 week post the last dose (Week 47).
	Pharmacokinetic Schedule of Events table Sample #10 row: Updated collection time point from "Predose (up to -8 hours)" to "Postdose (approximately 1 week)"	Dosing does not occur on Week 48. This sample collection time point is approximately 1 week following the last dose.
	Pharmacokinetic Schedule of Events table Sample #11 row: Updated Week Relative to Randomization from "End of Treatment" to "Safety follow-up"	Treatment period ends at Week 48 visit. Updated wording to accurately describe visit.
	Pharmacokinetic Schedule of Events table Sample #11 row: Updated collection time point from "4 weeks post last dose" to "5 weeks post last dose"	Since the last dose is on Week 47, the Sample #11 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 # and Name	Description of Change	Brief Rationale
Section 7.2.1 Discontinuation of Inadvertently Enrolled Participants	This section has been removed.	Deleted as internal process will be followed for inadvertent enrollment.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2 Study of Once-Weekly LY3437943 Compared with Placebo in Participants Who Have Obesity or Are Overweight with Weight-Related Comorbidities

Short Title: Effect of LY3437943 versus Placebo in Participants Who Have Obesity or Are Overweight

Rationale:

Obesity is a chronic disease and its increasing prevalence is a public health concern associated with rising incidence of type 2 diabetes (T2D), increased risk for premature death, and increased risk for some cancers (AMA 2013; Council on Science and Public Health 2013; Lauby-Secretan et al. 2016). There remains an unmet need in the pharmacologic treatment of obesity for drugs that are safe, efficacious, and well tolerated.

LY3437943 is a novel synthetic 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 greater weight loss in diet-induced obese (DIO) mice compared with an existing GLP-1 receptor agonist (GLP-1RA). 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. In addition, LY3437943 demonstrated a greater effect on glucose-dependent insulin secretion compared with an existing GLP-1RA, as demonstrated by intravenous glucose tolerance test in lean rats. Data from the Phase 1 program in patients with T2D demonstrated that LY3437943 has the potential to induce clinically meaningful weight loss (that is, 5%-10% or more) with a safety profile consistent with other GLP-1 and GIP/GLP-1RAs. Study J1I-MC-GZBF (Study GZBF) will investigate the safety and efficacy of 48 weeks of treatment with LY3437943, administered subcutaneously once weekly (QW), in participants who have obesity (BMI $\geq$ 30 kg/m^2) or are overweight (BMI $\geq$ 27 kg/m^2 and $<$ 30 kg/m^2) with weight-related comorbidities but without T2D. The primary objective will be the effect on percent change in body weight at 24 weeks. These data will support dose selection for Phase 3 studies in participants who have obesity or are overweight with weight-related comorbidities.

Objectives and Endpoints

Objectives	Estimands/Endpoints
Primary	
To demonstrate that LY3437943 1, 4, 8, or 12 mg is superior to placebo at 24 weeks from randomization for percent change in body weight	Mean percent change in body weight
Secondary	
To demonstrate that LY3437943 1, 4, 8, or 12 mg is superior to placebo at 48 weeks from randomization for percent change in body weight	Mean percent change in body weight
To demonstrate that LY3437943 1, 4, 8, or 12 mg is superior to placebo at 24 or 48 weeks from randomization for • Body weight	• Percentage of study participants who achieve o ≥5% body weight reduction o ≥10% body weight reduction o ≥15% body weight reduction • Mean change in body weight (kg) • Mean change in BMI (kg/m^2)
• Waist circumference	• Mean change in waist circumference (cm)
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

Abbreviation: BMI = body mass index.

Overall Design

Study GZBF is a 48-week, Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to examine the safety and efficacy of 4 dose levels of QW subcutaneously administered LY3437943 compared with QW subcutaneously administered placebo in participants who have obesity (BMI ≥ 30 kg/m^2) or are overweight (BMI ≥ 27 kg/m^2 and < 30 kg/m^2) with weight-related comorbidities but without T2D.

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

Number of Participants:
Approximately 300 participants will be randomly assigned to study intervention such that approximately 240 evaluable participants will complete the study. An upper limit of 60% enrollment of women will be used to ensure a sufficiently large sample of men.

Intervention Groups and Duration:

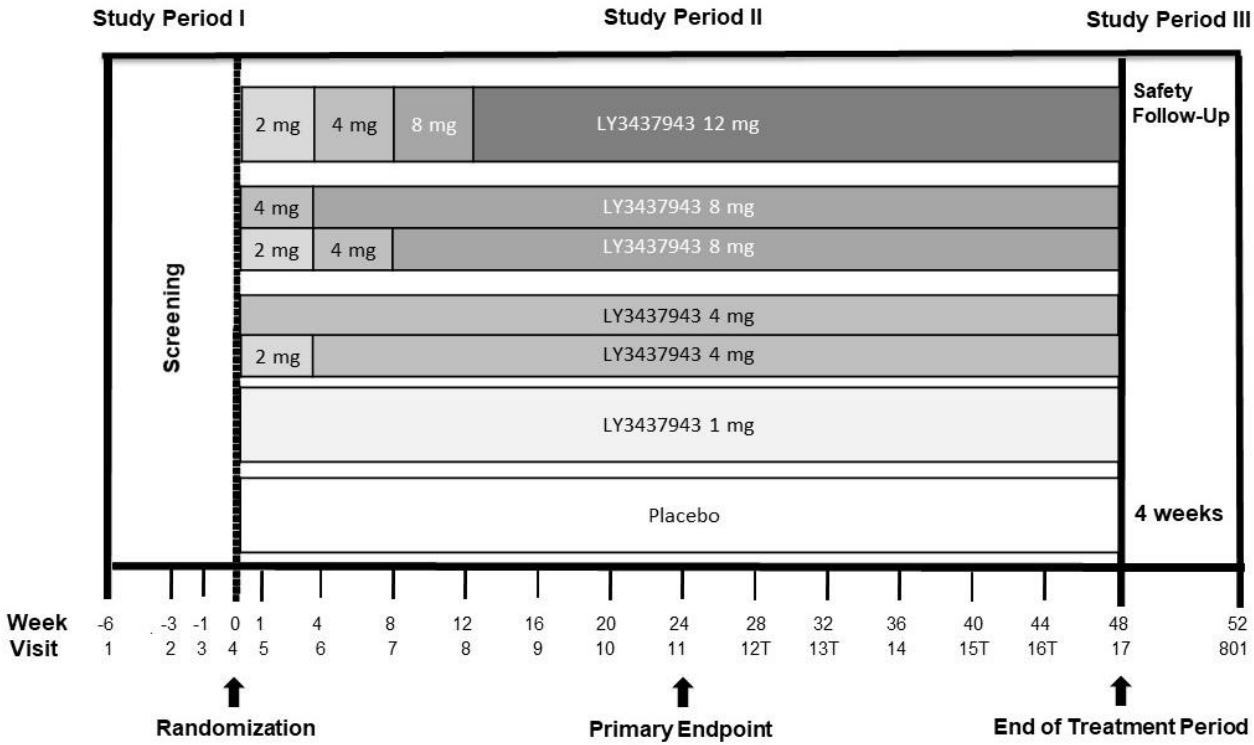
Study participants will be randomly assigned in a 2:1:1:1:1:2:2 ratio (LY3437943 1 mg QW, LY3437943 4 mg QW [with starting dose at 2 mg], LY3437943 4 mg QW [with starting dose at 4 mg], LY3437943 8 mg QW [with starting dose at 2 mg], LY3437943 8 mg QW [with starting dose at 4 mg], LY3437943 12 mg QW [with starting dose at 2 mg], placebo QW) and stratified by sex and BMI $\geq$ 36 kg/m^2.

All participants will receive diet and physical activity counseling using a standardized approach throughout the study.

Study GZBF will consist of 3 periods: a 6-week screening period, a 48-week double-blind, placebo-controlled treatment period (consisting of an up to 12-week dose-escalation period and a 36-week maintenance period), and a 4-week safety follow-up period.

Data Monitoring Committee: No

1.2. Schema



Abbreviation: T = telephone visit

1.3. Schedule of Activities (SoA)

The Schedule of Activities described below should be followed for all participants enrolled in Study GZBF. 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			Study Period II Treatment																Study Period III Post-Treatment Safety Follow-Up
Visit (see Notes below)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**99**	**ED**	**801**
Week of Treatment	**-6**	**-3**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**48**		**4 Wks post end of TXP**
					Titration period															
Allowable Interval Tolerance (days)	**±7**	**±7**	**±7**	**-**	**±2**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**
Fasting Visit	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit												**X**	**X**		**X**	**X**				
Informed consent	X																			
Inclusion and exclusion criteria review	X		X																	
Demographics	X																			
Preexisting conditions and medical history, including relevant surgical history	X																			
	Medical history includes assessment of preexisting conditions (for example, history of gallbladder disease, cardiovascular disease, and medullary thyroid carcinoma).																			
Concomitant medications	X		X	X	X	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	X	X	X	X
Physical Evaluation or Clinical Assessments																				
Height	X																			
Weight	X			X	X	X	X	X	X	X	X			X			X	X	X	X
	Weight measurements should be obtained per the detailed protocol guidance in Section 10.8. 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	X			X			X	X	X	X

	Study Period I Screening			Study Period II Treatment																Study Period III Post-Treatment Safety Follow-Up
Visit (see Notes below)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**99**	**ED**	**801**
Week of Treatment	**-6**	**-3**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**48**		**4 Wks post end of TXP**
					Titration period															
Allowable Interval Tolerance (days)	**±7**	**±7**	**±7**	**-**	**±2**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**
Fasting Visit	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit												**X**	**X**		**X**	**X**				
Sitting vital signs (3 measures of BP and PR)	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, per the instruction in Section 10.8.																			
Orthostatic vital signs				X					X		X			X			X			
	1 measurement of BP and PR in supine and standing position. See Section 10.8.																			
Physical examination	X																			
12-Lead electrocardiogram				X		X	X	X	X		X			X			X		X	X
	ECG measurements should be obtained per the instructions in Section 10.8. Electrocardiograms should be obtained prior to collection of blood samples for laboratory testing, including PK samples.																			
Participant Education and Assessment																				
Diet, physical activity counseling			X	X	X	X	X	X	X	X	X	X	X	X	X	X				
	Three-day diet and exercise diary should be reviewed as part of the counseling.																			
Patient-Reported Outcomes (PROs)																				
Patient Global Impression of Status for Physical Activity				X							X						X		X	
SF-36v2 acute form				X							X						X		X	
Eating Inventory				X							X						X		X	
	If a PRO questionnaire is not available in the native language of a participant at baseline, that questionnaire will not be administered for that participant for the duration of the trial (Appendix 10.11)																			

	Study Period I Screening			Study Period II Treatment																Study Period III Post-Treatment Safety Follow-Up
Visit (see Notes below)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**99**	**ED**	**801**
Week of Treatment	**-6**	**-3**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**48**		**4 Wks post end of TXP**
					Titration period															
Allowable Interval Tolerance (days)	**±7**	**±7**	**±7**	**-**	**±2**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**
Fasting Visit	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit												**X**	**X**		**X**	**X**				
Mental Health Questionnaires																				
Patient Health Questionnaire-9 (PHQ-9)	X			X				X			X			X			X	X	X	X
	PHQ-9 is self-administered and should be completed ***after*** assessment of adverse events.																			
Columbia-Suicide Severity Rating Scale (C-SSRS) (Baseline/Screening Version)	X																			
	The C-SSRS, Self-Harm Supplement Form should be administered ***after*** assessment of adverse events. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.																			
Columbia-Suicide Severity Rating Scale (C-SSRS) (Since Last Visit Version)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Self-Harm Follow-up Form is only required if triggered by the Self-Harm Supplement Form, per instructions in the form.																			
Laboratory Tests and Sample Collections																				
Hematology	X			X			X	X			X			X			X		X	X
HbA1c	X			X				X			X			X			X		X	X
Urinalysis	X																			
Chemistry panel (includes creatinine for eGFR	X			X			X	X			X			X			X		X	X

	Study Period I Screening			Study Period II Treatment																Study Period III Post-Treatment Safety Follow-Up
Visit (see Notes below)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**99**	**ED**	**801**
Week of Treatment	**-6**	**-3**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**48**		**4 Wks post end of TXP**
					Titration period															
Allowable Interval Tolerance (days)	**±7**	**±7**	**±7**	**-**	**±2**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**
Fasting Visit	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit												**X**	**X**		**X**	**X**				
calculation and glucose)	The CKD-EPI equation will be used by the central lab to estimate and report eGFR.																			
Lipid panel	X			X			X	X			X						X		X	X
Longitudinal biomarkers				X			X	X			X						X		X	
	See Section 10.10 (Appendix 10) for list of biomarkers																			
Endpoint biomarkers				X							X						X		X	
	See Section 10.10 (Appendix 10) for list of biomarkers.																			
Serum pregnancy	X																			
	For women of childbearing potential only.																			
Urine pregnancy (local)				X				X			X			X			X		X	
	A urine pregnancy test must be performed at Visit 4 with the result available prior to first injection of study drug(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 any visit, an additional serum pregnancy test should be collected.																			
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.																			
Calcitonin	X			X							X						X		X	X
Pancreatic amylase	X			X			X	X			X						X		X	X
Lipase	X			X			X	X			X						X		X	X

		Study Period I Screening			Study Period II Treatment																Study Period III Post-Treatment Safety Follow-Up
Visit (see Notes below)		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**99**	**ED**	**801**
Week of Treatment		**-6**	**-3**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**48**		**4 Wks post end of TXP**
						Titration period															
Allowable Interval Tolerance (days)		**±7**	**±7**	**±7**	**-**	**±2**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**
Fasting Visit		**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit													**X**	**X**		**X**	**X**				
Urinary albumin/creatinine ratio		X			X							X						X		X	X
Cystatin-c		X										X						X		X	X
Thyroid-stimulating hormone		X																			
Liver fat algorithm		X																			
Immunogenicity (ADA samples)					X		X		X			X						X		X	X
Pharmacokinetic (PK) sample	Predose				X		X		X			X									
	Postdose					X		X		X	X				X			X		X	X
		Efforts should be taken to align clinical visits 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.																			
Stored Samples																					
Genetic sample (pharmacogenetic stored sample)					X																
Exploratory samples (nonpharmacogenetic stored samples)					X			X	X			X						X		X	X
Randomization and Dosing																					
Register Visit in IWRS		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization					X																

	Study Period I Screening			Study Period II Treatment																Study Period III Post-Treatment Safety Follow-Up
Visit (see Notes below)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**99**	**ED**	**801**
Week of Treatment	**-6**	**-3**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**48**		**4 Wks post end of TXP**
					Titration period															
Allowable Interval Tolerance (days)	**±7**	**±7**	**±7**	**-**	**±2**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**
Fasting Visit	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit												**X**	**X**		**X**	**X**				
Injection training				X	X															
Dispense study drug and injection supplies				X	X	X	X	X	X	X	X			X						
Dispense study drug administration log, instruct in use				X	X	X	X	X	X	X	X			X						
	All training should be repeated as needed to encourage participant compliance. If a participant develops incident diabetes, please dispense additional log for diabetes management information.																			
Observe participant administer study drug				X	X															
	Participants should administer their first dose of study drug at the end of Visit 4, after other study procedures and randomization have been completed.																			
Review preparation of injection and injection technique				X	X	X	X	X	X	X	X			X						
Study drug administration log return and review					X	X	X	X	X	X	X			X			X		X	
Participant returns study drug and injection supplies						X	X	X	X	X	X			X			X		X	
Assess study intervention(s) compliance					X	X	X	X	X	X	X			X			X		X	

	Study Period I Screening			Study Period II Treatment																Study Period III Post-Treatment Safety Follow-Up
Visit (see Notes below)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**99**	**ED**	**801**
Week of Treatment	**-6**	**-3**	**-1**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**48**		**4 Wks post end of TXP**
					Titration period															
Allowable Interval Tolerance (days)	**±7**	**±7**	**±7**	**-**	**±2**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**
Fasting Visit	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit												**X**	**X**		**X**	**X**				
Additional Clinical Assessments																				
MRI for liver fat and body composition		X																		
	• Only for people identified with increased probability of liver fat ≥10% by liver fat algorithm from Visit 1. • MRI will be performed after a fast of at least 6 hours. Participants can take necessary medications and small quantities of water during the fast. • People who qualify for MRI based on the liver fat algorithm but have MRI contraindications may be enrolled in the main study but will not count towards the NAFLD subgroup population. • Exceeding the window of assessment for MRI is not a protocol violation, but MRI results need to be available prior to Visit 3 (for more details, see Section 4.1.2.2).																			
ABPM training			X																	
Initiate ABPM device			X								X			X						
	• Participants are not allowed to perform strenuous activity on the day of the ABPM measurements. • Participants should not be excluded from the study if arm circumference at Visit 3 does not allow for ABPM measurement. In those participants ABPM measurements should not be performed in the study.																			
Return ABPM device and check validity of results			X								X			X						
	Participants should return the ABPM device at the conclusion of the 24- to 27-hour monitoring period.																			
Record ABPM measurements			X								X			X						
	At the time participant visit data is uploaded by the site, the ABPM Data Validity Report will be generated and should be reviewed to ensure ≥70% of the readings are valid. If <70% of the readings are valid, the 24-hour monitoring session should be repeated within the visit window (for more details, see Section 4.1.2.3).																			

Abbreviations: ABPM = ambulatory blood pressure monitoring; ADA = anti-drug antibody; BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; ECG = electrocardiogram; ED = early discontinuation of treatment; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; IWRS= Interactive Web Response Systems; MRI = magnetic resonance imaging; NAFLD = non-alcoholic fatty liver disease; PK = pharmacokinetics; PR = pulse rate; SF-36v2 acute form = Short Form-36 Version 2 Health Survey acute form; TXP = treatment period.

General Notes:

- Telephone visits are shaded.
- Visit 4 baseline assessments must be completed before processing the randomization in the interactive web-response system (IWRS).
- The interval between Visit 1 and Visit 4 can be accomplished in less than 6 weeks and will not be considered as a protocol deviation. If the ABPM needs to be repeated at Visit 3 (per criteria specified in Section 4.1.2.3), then the screening period may exceed 6 weeks and this will not be considered a protocol deviation.
- Participants who do not qualify for the MRI should move from Visit 1 to Visit 3.
- The visit date is determined in relation to the date of Visit 4 (randomization).
- Participants who are unable or unwilling to continue the study drug 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 99 is only applicable to participants who discontinue the double-blind study treatment prematurely and decline to complete the remaining scheduled study visits. If the participant is unwilling to complete all the study visits, then the participant should be encouraged to come back for a Visit 99, 48 weeks ± 7 days after randomization, primarily for body weight measurement and assessment of adverse events. If the participant is unwilling to attend Visit 99, it should be documented in the participant medical record that the participant has refused to attend.
- Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit during the study treatment period or Visit 99.

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	1 to 24 hours postdose
3	4	Predose (up to -8 hours)*
4	8	24 to 72 hours postdose
5	12	Predose (up to -8 hours)*
6	16	72 to 168 hours postdose
7	20	Any time during this week
8	24	Predose (up to -8 hours)*
9	36	Any time during this week
10	48	Postdose (approximately 1 week)*
11	Safety follow-up	5 weeks post last dose
12	Early discontinuation	Any time

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

2. Introduction

2.1. Study Rationale

Study GZBF is a 48-week Phase 2 study designed to examine the efficacy and safety of 4 dose levels of QW subcutaneously administered LY3437943 compared with QW subcutaneously administered placebo in participants without T2D who have obesity or are overweight with weight-related comorbidities.

The primary objective will be the effect of LY3437943 on percent change in body weight. These data will support dose selection for Phase 3 studies in participants who have obesity or are overweight with weight-related comorbidities.

2.2. Background

Obesity is a chronic disease, and its increasing prevalence is a public health concern associated with rising incidence of T2D, increased risk for premature death, and increased risk for some cancers (AMA 2013; Council on Science and Public Health 2013; Lauby-Secretan et al. 2016). There remains an unmet need in the pharmacologic treatment of obesity for drugs that are safe, efficacious, and well tolerated.

Structure of LY3437943

LY3437943 is a novel synthetic peptide, which shows potent agonist action at GIP, GLP-1, and Gcg receptors (GIPR, GLP-1R, and GcgR, respectively). It includes a linear peptide component of 39 amino acid residues conjugated to a C20 fatty acid moiety.

Nonclinical data with efficacy and toxicology

In nonclinical pharmacology models, LY3437943 demonstrated a greater effect on glucose-dependent insulin secretion compared with an existing GLP-1RA, as demonstrated by intravenous glucose tolerance test in rats and with greater weight loss in DIO mice. 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.

The nonclinical safety profile of LY3437943 was evaluated in a single-dose cardiovascular safety pharmacology study in monkeys, 13-week and 6-month repeat-dose toxicology studies in rats and monkeys, a female fertility study in rats, embryo-fetal development studies in rats and rabbits, an in vitro human Ether-a-go-go-Related Gene (hERG) assay, and an in vivo micronucleus genotoxicity study in rats. Findings in all studies were consistent with, or secondary to, LY3437943-related pharmacology, and included body weight loss and/or decreased body weight gain, and decreased food consumption. Additional findings in monkeys included changes in cardiovascular parameters attributed to on-target GIP, GLP-1, and/or Gcg pharmacology. CCI [redacted]

Summary of clinical studies

Study J1I-MC-GZBA (GZBA) was a first-in-human, single-ascending dose study investigating the safety, tolerability, and pharmacokinetic/pharmacodynamic (PK/PD) of LY3437943 administered as a SC injection in 45 healthy participants.

The most common treatment-emergent adverse events (TEAEs) were gastrointestinal (GI) events, including vomiting (with higher doses), 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 (BP) 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 a Phase 1, randomized, investigator- and participant-blind study that assessed the safety, tolerability, and PK/PD effects of multiple doses of LY3437943 when administered QW in participants with T2D. Trulicity® (dulaglutide) 1.5 mg was used as an active comparator. Participants in Cohorts 1 to 3 received fixed doses of LY3437943 (0.5, 1.5, and 3 mg QW) or placebo for 12 weeks. Participants in Cohorts 4 and 5 received placebo or LY3437943 titrated from a starting dose of 3 mg QW to maximum doses of 6 mg QW (Cohort 4) and 12 mg QW (Cohort 5) over the 12-week treatment period.

Based on preliminary data from this ongoing study, 72 participants received study treatment, and 43 completed the study to date. Gastrointestinal adverse events (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 of 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 AEs 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 serious adverse events (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.

2.3.1. Risk Assessment

The most common AEs observed in the LY3437943 clinical trials in healthy participants and participants with T2D have been GI effects. There are safety topics of special interest identified from other GLP-1 and GIP/GLP-1RA clinical programs, including pancreatic safety,

cardiovascular events, hypoglycemia, hypersensitivity reactions, and thyroid C-cell effects; refer to Section 8.3.2 for further details. Most of these AEs have not been observed with LY3437943 in the current stage of clinical development. Please refer to the IB Section 6 for more details.

2.3.2. Benefit Assessment

LY3437943 is a triple-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 an initial efficacy assessment in participants who have obesity or are overweight with weight-related comorbidities, 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-1RAs. 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 of LY3437943 can be assumed because LY3437943 is in the early phase of clinical development. All participants in this study will receive diet and physical activity counseling.

3. Objectives and Endpoints

Objectives	Estimands/Endpoints
Primary	
To demonstrate that LY3437943 1, 4, 8, or 12 mg is superior to placebo at 24 weeks from randomization for percent change in body weight	Mean percent change in body weight
Secondary	
To demonstrate that LY3437943 1, 4, 8, or 12 mg is superior to placebo at 48 weeks from randomization for percent change in body weight	Mean percent change in body weight
To demonstrate that LY3437943 1, 4, 8, or 12 mg is superior to placebo at 24 and 48 weeks from randomization for • Body weight • Waist circumference	• Percentage of study participants who achieve o ≥5% body weight reduction o ≥10% body weight reduction o ≥15% body weight reduction • Mean change in body weight (kg) • Mean change in BMI (kg/m^2) • Mean change in waist circumference (cm)
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
Exploratory	
To investigate the effect QW LY3437943 1, 4, 8, or 12 mg versus placebo at various time points for • Body weight • Blood pressure • Heart rate	• Percentage of study participants who achieve o ≥20% body weight reduction o ≥25% body weight reduction • Mean change in o systolic BP (mmHg) measured by ABPM o diastolic BP (mmHg) measured by ABPM • Mean change in heart rate measured by ABPM

Objectives	Estimands/Endpoints
• Lipid parameters	• Mean change in fasting o total cholesterol o HDL cholesterol o LDL cholesterol o VLDL cholesterol o triglycerides
• Glycemic control	• Mean change in o fasting glucose o HbA1c • Proportion of participants with incident T2D
• Mechanistic biomarkers	• Mean change in mechanistic biomarkers (see detailed list of parameters in Section 10.10)
• Patient-reported outcomes	• Proportion of participants with change in PGIS-Physical Function • Mean change in o SF-36v2 acute form domain scores o Eating Inventory domain scores
• To assess the PK of LY3437943 and potential participant factors that may influence its PK	• LY3437943 plasma concentrations
• 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

Abbreviations: ABPM = ambulatory blood pressure modeling; BMI = body mass index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PGIS = Patient Global Impression of Status; SF-36v2 acute form = Short Form-36 Version 2 Health Survey acute form; VLDL = very low-density lipoprotein.

4. Study Design

4.1. Overall Design

Study GZBF is a 48-week, Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to examine the safety and efficacy of 4 dose levels of QW subcutaneously administered LY3437943 compared with QW subcutaneously administered placebo in participants who have obesity (BMI ≥ 30 kg/m^2) or are overweight (BMI ≥ 27 kg/m^2 and < 30 kg/m^2) with weight-related comorbidities but without T2D. The primary objective will be the effect of LY3437943 on percent change in body weight at 24 weeks. These data will support dose selection for Phase 3 studies in participants who have obesity or are overweight with weight-related comorbidities.

All participants will receive diet and physical activity counseling using a standardized approach throughout the study (Section 5.3.1).

Participants with high probability of non-alcoholic fatty liver disease (NAFLD) and for liver fat ≥10% as determined by the screening liver fat algorithm (see Section 4.1.2.1) will undergo liver fat assessment by magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF). Participants with baseline liver fat equal to or higher than 10% as assessed by MRI-PDFF will be invited to participate in an addendum study in which the effect of LY3437943 on liver fat and serum biomarkers of nonalcoholic steatohepatitis will be evaluated. Approximately 100-125 participants will be included in this addendum study.

Four maintenance doses of LY3437943 will be evaluated in the trial: 1, 4, 8, and 12 mg. Dose escalation to improve GI tolerability 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. For 2 of the maintenance dose arms (4 and 8 mg), participants will be randomly assigned into 2 subgroups, designated by (a) and (b), with different dose escalation schemes. This is described in detail in Section 4.1.1.

Study participants will be randomly assigned in a 2:1:1:1:1:2:2 ratio (LY3437943 1 mg QW, LY3437943 4 mg QW [a], LY3437943 4 mg QW [b], LY3437943 8 mg QW [a], LY3437943 8 mg QW [b], LY3437943 12 mg QW, placebo QW) and stratified by sex and BMI ≥ 36 kg/m^2. An upper limit of 60% enrollment of women will be used to ensure a sufficiently large sample of men.

Study GZBF will consist of 3 periods: a 6-week screening period, a 48-week double-blind, placebo-controlled treatment period (consisting of an up to 12-week dose-escalation period and a 36-week maintenance period), and a 4-week safety follow-up period.

4.1.1. Overview of Study Periods

4.1.1.1. Main Study Period

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. Since some screening procedures need to be completed in the fasting state (approximately 8 hours without eating, drinking [except water], or performing any significant physical activity), Visit 1 may be conducted over more than 1 day to ensure necessary conditions are met. Participants who meet all applicable inclusion criteria and none of the applicable exclusion criteria (Sections 5.1 and 5.2) at Visit 1 will continue in the study. Participants who do not qualify for the magnetic resonance imaging (MRI) should move directly from Visit 1 to Visit 3.

Visit 2

Participants identified with a high probability for liver fat ≥10% as determined by the screening algorithm at Visit 1 will undergo liver fat and body composition assessment by MRI. Liver fat and body composition assessment will be performed after a fast of at least 6 hours. Participants can take necessary medications and small quantities of water during the fast.

Visit 3

Eligible participants (individuals who meet all applicable inclusion criteria and none of the applicable exclusion criteria) will receive education about ambulatory blood pressure monitoring (ABPM) and will be trained in its use at Visit 3. Ambulatory monitoring of HR and BP should be performed prior to Visit 4. Details on ABPM are described in Section 4.1.2.3. Diet and physical activity counseling will begin at Visit 3 so that participants will be familiar with the program prior to randomization (Section 5.3.1). This counseling will be provided at all subsequent visits until Week 44 (Visit 16).

Treatment Period

Randomization (Visit 4)

At Visit 4, ABPM results will be analyzed to ensure that at least 70% of the readings are valid as described in Section 4.1.2.3. Eligible participants with acceptable ABPM data (as described Section 4.1.2.3) will perform all required procedures prior to randomization and prior to taking the first dose of study drug. If the ABPM results are not acceptable, randomization (Visit 4) should be rescheduled, and ABPM needs to be performed again within 1 week and prior to the rescheduled Visit 4. At Visit 4, study participants are required to report after approximately 8 hours without eating, drinking (except water), or performing any significant physical activity. When collected, patient-reported outcomes questionnaires should be administered as early as possible in the visit, prior to randomization. Preferred administration order is

1. Patient Global Impression of Status for Physical Activity
2. SF-36v2 acute form, and

3. Eating Inventory.

The mental health questionnaires (PHQ-9, C-SSRS, and Self-Harm Form) should be completed after the assessment for AEs.

Following randomization, study site personnel will demonstrate study drug preparation and injection technique using a vial and syringe and observe the study participant inject the first dose of LY3437943 or placebo. The date, time, and location of the first dose of study drug will be recorded on the electronic case report form (eCRF). Beginning at randomization, all participants will receive study drug according to the randomized treatment arm for the duration of the 48-week treatment period.

Visit 5

Visit 5 needs to take place 5-9 days after Visit 4. Study participants are required to report after approximately 8 hours without eating, drinking (except water), or performing any significant physical activity. The mental health questionnaires (PHQ-9, C-SSRS, and Self-Harm Form) should be completed after the assessment for AEs during visits as indicated in the SoA, Section 1.3. Study site personnel will review the study drug preparation and injection technique using a vial and syringe and then observe the study participant inject the second dose of LY3437943 or placebo. The date, time, and location of the second dose of study drug will be recorded on the eCRF.

Dose-Escalation Period (Visits 6-8)

Dose escalation will occur in certain treatment groups up to Week 12 of treatment. On Visit 6 through Visit 8, study participants are required to report after approximately 8 hours without eating, drinking (except water), or performing any significant physical activity. The mental health questionnaires (PHQ-9, C-SSRS, and Self-Harm Form) should be completed after the assessment for AEs during visits as indicated in the SoA, Section 1.3. 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 described below. The dose will be increased at 4-week increments until the maintenance dose is achieved (Section 6.1 for details), as follows:

- Maintenance dose of 1 mg: no dose escalation
- Maintenance dose of 4 mg will be randomized 1:1 into 2 subgroups:
  - Subgroup (a): 2 mg (Visit 4) → 4 mg (Visit 6)
  - Subgroup (b): 4 mg (no dose escalation)
- Maintenance dose of 8 mg will be randomized 1:1 into 2 subgroups:
  - Subgroup (a): 2 mg (Visit 4) → 4 mg (Visit 6) → 8 mg (Visit 7)
  - Subgroup (b): 4 mg (Visit 4) → 8 mg (Visit 6)
- Maintenance dose of 12 mg:
  - 2 mg (Visit 4) → 4 mg (Visit 6) → 8 mg (Visit 7) → 12 mg (Visit 8).

Maintenance dose will be continued for the remainder of the study. Study site personnel will review the study drug preparation and injection technique using a vial and syringe at each visit. Refer to Section 6.5.1 and 6.6 for guidance on management of participants who experience GI symptoms.

Maintenance Period (Visits 9-17)

During the maintenance period, visits will occur monthly through 48 weeks. Telephone visits will occur at Weeks 28, 32, 40, and 44. For office visits, study participants are required to report after approximately 8 hours without eating, drinking (except water), or performing any significant physical activity. Office and telephone visit procedures should be conducted according to the SoA (Section 1.3). At Visit 11 and Visit 17, when collected, patient-reported outcomes questionnaires should be administered as early as possible in the visit. Preferred administration order is

1. Patient Global Impression of Status for Physical Activity
2. SF-36v2 acute form, and
3. Eating Inventory.

The mental health questionnaires (PHQ-9, C-SSRS, and Self-Harm Form) should be completed after the assessment for AEs during visits as indicated in the SoA, Section 1.3.

ABPM will be repeated at Week 24 (Visit 11) and Week 36 (Visit 14) as described in Section 4.1.2.3. Study drug and injection supplies will be returned per the SoA (Section 1.3) and according to local requirements. New supplies will be dispensed as needed. Study site personnel will review the study drug preparation and injection technique using a vial and syringe at each office visit. Participants should be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties administering their study drug. Additional unscheduled visits may be scheduled if the participant needs additional support for the study drug injection technique.

Participants should also be advised about the appropriate course of action if study drug is not taken at the required time (for details on late/missing doses, see Sections 6.1 and 6.6). 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.

Early Discontinuation of Treatment Visit

Participants unable or unwilling to continue the study treatment for any reason will perform an early discontinuation of treatment (ED) visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as an ED visit. A study participant who discontinues study drug permanently should be encouraged to continue in the study and to complete all study visits, including Visit 801 (See Participant Disposition and Timing of Safety Follow-Up figure below). Procedures should be completed according to the SoA (Section 1.3). When collected, patient-reported outcomes questionnaires should be administered as early as possible in the visit. Preferred administration order is

1. Patient Global Impression of Status for Physical Activity
2. SF-36v2 acute form, and
3. Eating Inventory.

Mental health questionnaires (PHQ-9, C-SSRS, and Self-Harm Form) should be completed after the assessment for AEs.

Visit 99

A study participant who discontinues study drug permanently should be encouraged to continue in the study and to complete all study visits. If the participant is unwilling to complete all the study visits, then the participant should be encouraged to come back for a study visit 48 weeks (± 7 days) after randomization, which is designated as Visit 99 in the SoA (See Participant Disposition and Timing of Safety Follow-Up figure below). This visit is critical to ensure complete data collection for the Week 48 secondary endpoints. Refer to the SoA, Section 1.3, for procedures to be completed.

For participants unwilling to attend this visit, their refusal to attend should be documented in the participant medical record.

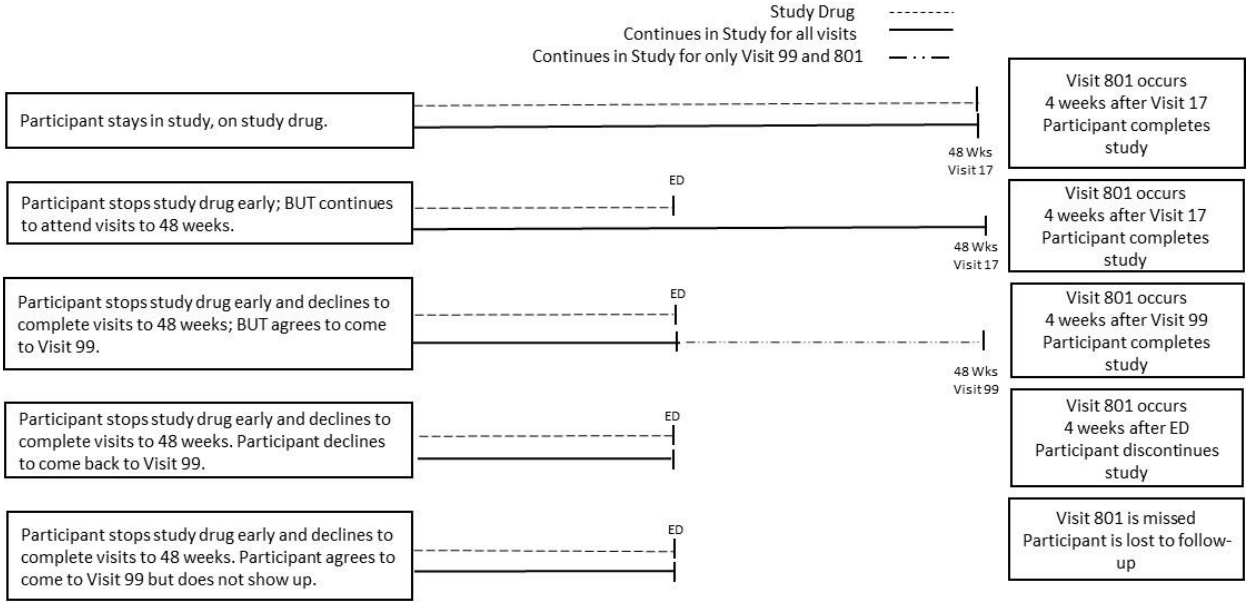
Safety Follow-Up Period (Visit 801)

Participants who complete the study treatment period should perform a Visit 801 (safety follow-up visit) 4 weeks after the last treatment visit (Visit 17). Participants who complete a Visit 99 should perform a Visit 801 four weeks after Visit 99. Participants who stop study drug early, and decline to complete visits to 48 weeks (including Visit 99), should perform a Visit 801 (safety follow-up visit) 4 weeks after the last visit of the treatment period and then discontinue the study (See Participant Disposition and Timing of Safety Follow-Up figure below). During the safety follow-up period, participants will not receive study drug.

Mental health questionnaires (PHQ-9, C-SSRS, and Self-Harm Form) should be completed after the assessment for AEs.

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

Participant Disposition and Timing of Safety Follow-Up



Abbreviations: ED = early discontinuation of treatment; Wks = weeks

4.1.2. Study Procedures

Participants will perform study procedures listed in the SoA (Section 1.3).

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 characteristics of the study treatments (Section 6.5).

Study governance considerations are described in detail in Section 10.1 (Appendix 1).

4.1.2.1. Liver Fat Algorithm

CCI [redacted] The algorithm will be implemented by the central laboratory using data obtained at Visit 1. A report will be generated to indicate whether the participant qualifies to have an MRI performed at Visit 2.

4.1.2.2. Magnetic Resonance Imaging

Individuals who qualify for the study (based on eligibility criteria at screening) and have a high probability for liver fat ≥10% based on the liver fat algorithm will undergo liver fat measurement by MRI-PDFF and body composition assessment by MRI. MRI images will be transmitted to a central reader for evaluation of the MRI-based efficacy endpoints. For participant safety, images should also be over-read locally to assure there are no underlying liver pathologies other than NAFLD. MRI will be performed after a fast of at least 6 hours. Participants can take necessary medications and small quantities of water during the fast.

Participants who qualify for MRI based on the liver fat algorithm but have

- contra-indications to MRI examinations
- extreme claustrophobia
- weight or girth that exceeds the scanner capabilities, or
- any condition or circumstance that, in the opinion of the investigator, would interfere with completion of MRI examination

should not undergo MRI assessment and may continue in the study without having the MRI performed.

For participants who suffer from claustrophobia in MRI machines, investigators may offer, at their discretion, a light sedative. However, if the participant is not willing to attempt MRI with light sedation, the participant should not have the MRI performed and may continue in the study without having the MRI performed.

4.1.2.3. ABPM

The ABPM device will be attached to the nondominant arm and participants will be instructed to wear the monitor for a 24- to 27-hour period. Participants will be instructed to keep track of daily activities throughout the testing period and not to engage in strenuous activity.

Ambulatory BP measurements

- should be collected on a typical workday, not on a non-working day
- will be recorded every 30 minutes during daytime hours (0700 to 2200 hours), and
- will be recorded every 60 minutes during nighttime hours (2200 to 0700 hours).

A 24-hour session of ambulatory monitoring produces technically acceptable measurements if ≥70% of the readings are valid. Between Visit 3 and Visit 4 (Week 0) and within 7 days following Visit 11 (Week 24) and Visit 14 (Week 36), participants will undergo a 24-hour ambulatory monitoring session. Upon return of the ABPM device, the recordings must be transmitted to the Core Laboratory and reviewed for validity of the readings before the participant leaves the site. If a technically satisfactory result is not achieved (less than 70% of readings are valid), the investigator should review the device settings and placement and the participant's activity track to correct any user error or device malfunctions. Another 24-hour ambulatory monitoring session should be conducted prior to Visit 4 (Randomization) or within 14 days following Visit 11 and Visit 14, respectively. If the second session also provides technically unsatisfactory results, data will be considered missing and the participant may continue in the study.

4.2. Scientific Rationale for Study Design

Data from the Phase 1 program in patients with T2D demonstrated that LY3437943 has the potential to induce clinically meaningful weight loss (that is, 5%-10% or more) with a safety profile consistent with other GLP-1 and GIP/GLP-1RAs.

The placebo arm is included to determine whether any efficacy or safety effects of LY3437943 are different in magnitude from no treatment (that is, placebo). Although it will not be feasible to blind the participant and the investigator to the injection volume of study drug, they will not know whether the participant is receiving LY3437943 or placebo. To preserve the blind, participants randomized to placebo will be randomly assigned to follow the injection dose schedule for 1 of the LY3437943 treatment arms.

Consistent with current guidelines for weight management, all participants will receive diet and physical activity counseling throughout the study, which will be based on guidelines published by the U.S. Department of Agriculture and U.S. Department of Health and Human Services (HHS 2018; USDA and HHS 2020).

The primary efficacy measure, mean percent change in body weight, is an accepted Phase 2 endpoint for investigational drugs being developed for weight management (FDA 2007). In addition, the protocol includes other parameters relevant to assessment of the effects of LY3437943 on safety, BP, HR, lipids, glycemic control, mechanism of action, PK parameters, and patient-reported outcomes.

The primary objective will be evaluated at 24 weeks because this period is considered adequate for evaluation of weight loss efficacy in a Phase 2 trial and sufficient to assess the dose–exposure–response of LY3437943 efficacy for selection of doses to be included in Phase 3 testing. The planned 48-week treatment period should be sufficient to capture the maximal or near-maximal weight loss effects of LY3437943. The putative mechanism of action of LY3437943 suggests that treatment with LY3437943 will result in continued weight loss over

this treatment period. In addition, safety and tolerability over a wide dose range of LY3437943 versus placebo will be assessed to enable robust benefit–risk characterizations in treatment of participants who have obesity or are overweight.

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, starting with either 2 mg or 4 mg doses, are designed to provide information on optimal dose escalation schemes for Phase 3 clinical development.

To minimize the potential confounding effect of changes to 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.

The sample size is determined based on data from Study GZBB that provided preliminary PD data for LY3437943 in participants with T2D over a 12-week treatment period, and on data from the semaglutide Phase 2 obesity study (O'Neil et al. 2018).

4.3. Justification for Dose

LY3437943 doses of 1, 4, 8, and 12 mg, administered subcutaneously QW, were selected based on the following

- Safety and tolerability of LY3437943 in healthy participants and participants with T2D in the Phase 1 studies GZBA (0.1 to 6 mg dose range) and GZBB (0.5 to 12 mg dose range).
- PK/PD modeling of 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 dosage of 1 mg is predicted to achieve LY3437943 concentration levels that will demonstrate greater body weight loss compared with placebo and is being investigated in this study to enable full characterization of exposure–response relationships.
- Maintenance dosages of 4, 8, and 12 mg are expected to provide clinically relevant weight loss relative to placebo with increasing weight loss 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.

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 the following criteria apply:

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 a BMI of
   - ≥ 30 kg/m^2 and ≤ 50 kg/m^2
   - ≥ 27 kg/m^2 and <30 kg/m^2 with at least 1 of the following weight-related comorbidities
     - hypertension: on BP-lowering medication or having systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg at screening
     - dyslipidemia: on lipid-lowering medication or having low-density lipoprotein (LDL) ≥160 mg/dL (4.1 mmol/L) or triglycerides ≥150 mg/dL (1.7 mmol/L), or high-density lipoprotein (HDL) <40 mg/dL (1.0 mmol/L) for men or HDL <50 mg/dL (1.3 mmol/L) for women at screening
     - cardiovascular disease: (for example, ischemic cardiovascular disease, New York Heart Association [NYHA] Functional Classification Class I-II heart failure)
3. In the investigator's opinion, are well motivated, capable, and willing to
   - learn how to self-inject study drug, 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 drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug)
   - inject study drug (or receive an injection from a trained individual if visually impaired or with physical limitations), and
   - follow study procedures for the duration of the study, including, but not limited to, follow lifestyle advice (for example, dietary changes and physical activity plan), maintain a study drug administration log, and complete required questionnaires.

In addition, a subgroup of approximately 100-125 participants will meet the following inclusion criterion

4. Have liver fat content ≥10% by MRI-PDFF

Sex

5. Male and/or female

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

   Males, women of childbearing potential and women not of childbearing potential (for definitions, see Section 10.5 [Appendix 5]) can participate in this study considering the following:

   - males agree to refrain from sperm donation and to use contraceptive methods as described in Section 10.5 (Appendix 5) throughout the study and for 5 half-lives of study drug plus 90 days, corresponding to 4 months after the last injection.
   - women of childbearing potential must have negative pregnancy tests at Visit 1 and Visit 4 as indicated in the SoA and agree to use contraceptive methods as described in Section 10.5 (Appendix 5) throughout the study and for 5 half-lives of study drug plus 30 days, corresponding to 2 months after the last injection. Female participants should not be breastfeeding.

   Note: Hormone replacement therapy in postmenopausal women and contraceptives containing an estrogen and a progestin (oral or transdermal system) in premenopausal women are allowed but women must be on stable therapy for 3 months prior to screening.

Informed Consent

6. Capable of giving signed informed consent as described in Section 10.1 (Appendix 1), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

Diabetes Related

7. Have history of diabetes mellitus including T1D or T2D, history of ketoacidosis, or hyperosmolar state/coma

8. Have at least 1 laboratory value suggestive of diabetes during screening, including 1 or more of HbA1c ≥6.5% (48 mmol/mol), fasting serum glucose ≥126 mg/dL (7.0 mmol/L), or random glucose ≥200 mg/dL (11.1 mmol/L)

Obesity Related

9. Have a self-reported change (increase or decrease) in body weight >5 kg within 3 months prior to screening

10. Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty, if performed >1 year prior to screening)

11. Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months prior to screening including but not limited to

    - mucosal ablation
    - gastric artery embolization
    - intragastric balloon, and
    - duodenal-jejunal endoluminal liner

Other Medical

12. Have renal impairment measured as estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology (CKD-EPI) as determined by central laboratory during screening

13. Have a known clinically significant gastric emptying abnormality (for example, severe gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect GI motility

14. Have a history of acute or chronic pancreatitis. A participant with a history of acute pancreatitis caused by gallstones may be included in the study if the participant has a cholecystectomy to resolve the problem

15. Have thyroid-stimulating hormone outside of the range of 0.4 to 6.0 mIU/L at screening visit

    Note*:* Participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 6 months.

    Note: Thyroid-stimulating hormone values above the normal range can, in some participant, suggest subclinical hypothyroidism. If, in the investigator's opinion, the participant has subclinical hypothyroidism and may require initiation of thyroid hormone replacement during the study, the participant should be excluded from the study.

16. Have obesity induced by other endocrinologic disorders (for example, Cushing's syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader–Willi Syndrome)

17. Have a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years

    Note: Participants with MDD or generalized anxiety disorder whose disease state is considered stable for the past 2 years and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications

18. Have a lifetime history of suicide attempt

19. Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more at Visit 1

20. On the C-SSRS at Visits 1, 3, or 4, prior to randomization:

- a "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS

or

- a "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS

or

- a "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS

and

- the ideation or behavior occurred within the past month

21. Have uncontrolled hypertension (systolic BP above or equal to 160 mmHg and/or diastolic BP above or equal to 100 mmHg). If a participant is on anti-hypertensive therapies, doses must be stable for 30 days prior to screening. For participants with uncontrolled hypertension at the screening visit, antihypertensive medication may be started or adjusted. Blood pressure must meet the protocol criterion for hypertension control by Visit 3 with stable treatment for at least 30 days

22. Have an elevated resting pulse rate (>100 bpm) at baseline

23. 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)

24. Ongoing or history of frequent intermittent or chronic tachyarrhythmia syndromes (such as atrial fibrillation, supraventricular tachycardia, and positional orthostatic tachycardia syndrome).

Note: Participants with history of premature atrial contractions or premature ventricular contractions may be included.

25. Have NYHA Functional Classification III or IV CHF

26. Have an electrocardiogram (ECG) considered by the investigator indicative of active cardiac disease or with abnormalities that may interfere with the interpretation of changes in ECG intervals at screening

27. Have acute or chronic hepatitis, or signs and symptoms of any other liver disease other than NAFLD, or any of the following, as determined by the central laboratory during screening

- ALT level >3.0X upper limit of normal (ULN) for the reference range
- alkaline phosphatase (ALP) level >1.5X ULN for the reference range, or
- total bilirubin level (TBL) >1.5X ULN for the reference range (except for cases of known Gilbert's Syndrome)

28. Have a serum calcitonin level (at Visit 1) of

    - ≥20 ng/L, if eGFR ≥60 mL/min/1.73 m^2 or
    - ≥35 ng/L if eGFR <60 mL/min/1.73 m^2 (as determined by central laboratory at Visit 1)

29. Have a family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia (MEN) syndrome type 2

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 any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to GLP-1RA

32. Have a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder, or other psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol

33. Alcohol consumption >14 units/week for women and >21 units/week for men

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

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

35. Have had a transplanted organ (corneal transplants [keratoplasty] are allowed) or are awaiting an organ transplant

36. Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias and sickle cell disease)

37. 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, hemolytic anemia, sickle cell anemia, or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with HbA1c methodology

38. Have a history of atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis)

39. Have a fasting serum triglyceride level of >500 mg/dL at screening. If a participant is on lipid-lowering therapies, doses must be stable for 30 days prior to screening

40. Have evidence of a significant active, uncontrolled medical condition or a history of any medical problem capable of constituting a risk when taking the study medication or interfering with the interpretation of data, as judged by the screening investigator at screening

41. Have a history of symptomatic gallbladder disease within the past 2 years, defined by the presence of gallstones on an imaging study and abdominal pain attributed to the gallstones by the participant's physician; subjects who had a procedure to remove the gallstones and/or the gallbladder (cholecystectomy), with no long-term complications, are eligible for participation as long as the procedure was completed at least 3 months prior to screening

42. Have a history of documented human immunodeficiency virus (HIV) infection

Prior/Concomitant Therapy

43. Are receiving or have received within 3 months prior to screening chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, single intraarticular injection, or inhaled preparations) or have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intraarticular, or inhaled preparations) during the course of the study

44. Have current treatment with or history of treatment with (within 3 months prior to screening) medications that may cause significant weight gain including, but not limited to, tricyclic antidepressants, atypical antipsychotics, and mood stabilizers

Examples:

- imipramine
- amitriptyline
- mirtazapine
- paroxetine
- phenelzine
- chlorpromazine
- thioridazine
- clozapine
- olanzapine
- valproic acid and its derivatives, and

- lithium.

Note: Selective serotonin reuptake inhibitors other than paroxetine are permitted.

45. Have taken within 3 months prior to screening medications (prescribed or over the counter) or alternative remedies intended to promote weight loss

Examples include, but are not limited to:

- Saxenda® (liraglutide 3.0 mg) or other GLP-1RA
- Xenical®/Alli® (orlistat)
- Meridia® (sibutramine)
- Acutrim® (phenylpropanolamine)
- Sanorex® (mazindol)
- Apidex® or Lomaira™ (phentermine)
- Qsymia™ (phentermine/topiramate combination)
- Contrave® (naltrexone/bupropion)

46. Use of metformin, or any other glucose-lowering medication, whether prescribed for polycystic ovarian syndrome or diabetes prevention is not permitted

47. Have started implantable or injectable contraceptives, such as Depo Provera® and Nexplanon®, within 18 months prior to screening. Intrauterine devices, including levonorgestrel-releasing intrauterine systems, are allowed if the participant has been using the device for at least 3 months

Prior/Concurrent Clinical Study Experience

48. Have known allergies to GLP-1R agonists or LY3437943

49. Are currently enrolled in any other clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study

50. Within the last 30 days, have participated in a clinical study and received treatment, whether active or placebo. If the study involved an IP, 5 half-lives or 30 days, whichever is longer, should have passed

51. Have previously received LY3437943 as part of this study or any another study investigating LY3437943

Other Exclusions

58. 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

59. Are Lilly employees

Note: The inclusion and exclusion criteria numbered from 52 to 57 are part of J1I-MC-GZBF Addendum (1). So, in Section 5.2, the exclusion criteria continue with the next available number in the sequence from the last number in the protocol addendum (58–59).

5.3. Lifestyle Considerations

Throughout the study, participants may undergo medical assessments and review of compliance with requirements before continuing in the study. Participants will report to the clinical research site for safety assessments and will remain in the clinic until all procedures for that visit are complete and the investigator has deemed it safe to release the participant from the clinic. There will be no inpatient stays. In addition, participants will report to the clinical research site for pharmacokinetic (PK)-specific visits.

Meals/Diet – Participants will fast for at least 8 hours overnight prior to each in-person site visit where fasting samples are drawn and when weight measurements are taken.

Physical Activity – Participants will be advised to avoid strenuous exercise within 24 hours prior to each study site visit. When certain study procedures are in progress at the site, participants may be required to remain supine or seated.

Alcohol – Alcohol will not be permitted 8 hours prior to the study site visits, until the participant has been discharged from the clinical research site.

Blood Donation – Study participants should be instructed not to donate blood or blood products during the study and for 8 weeks following the study.

5.3.1. Diet and Physical Activity Counseling

Study participants will receive diet and physical activity counseling, using a standardized approach, by a dietician/nutritionist or a similar qualified healthcare professional, as specified in the SoA (Section 1.3). Based on the counseling provided, participants should follow a healthy lifestyle plan throughout the course of the study (HHS 2018; USDA and HHS 2020). Refer to Section 10.7 (Appendix 7) for details of the diet and physical activity recommendations.

To encourage adherence, it is recommended that a 3-day diet and exercise diary be completed prior to each counseling visit. During each visit, the participant's diet is reviewed and advice to maximize adherence is provided if needed.

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 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.

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. In addition to administration of study drug, this protocol includes diet and physical activity counseling using a standardized approach, which may also be considered a study intervention.

6.1. Study Interventions Administered

ARM Name	LY 3437943 X mg	LY3437943 Placebo
Unit Dose Strength(s)	12 mg/2 mL vial (6 mg/mL)	Placebo
Doses Administered [mg, QW]	1 mg 2 mg 4 mg 8 mg 12 mg	Participants randomized to placebo will be randomly assigned to follow the injection dose schedule for 1 of the LY3437943 treatment arms. Equivalent volumes will be specified in the participant dosing instructions
Route of Administration	SC QW	
Use	Experimental	Placebo
Sourcing	Provided centrally by the Sponsor	
Packaging and Labeling	LY3437943 will be provided in single-use vials. Clinical study materials will be labeled according to country regulatory requirements	LY3437943 placebo to match will be provided in single-use vials. Clinical study materials will be labeled according to country regulatory requirements

Abbreviations: SC = subcutaneous, QW = once-weekly.

The first injection of study drug should occur at Visit 4 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 is missed, the participant should take it as soon as possible, unless it is within 72 hours of the next 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. The day of weekly administration can be changed if necessary, as long as the last dose was administered 72 or more hours before.

All participants will inject study drug SC into the abdominal wall, alternating between 4 sites weekly, that is right and left upper quadrants and right and left lower quadrants, using the injection supplies provided. A caregiver may administer the injection after appropriate training. A new syringe will be used for each injection. The actual date, time, and injection-site location of all dose administrations will be recorded in the study drug administration log by the participant.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Only participants enrolled in the study may receive study drug. Only study personnel may supply, prepare, or administer study drug. All study drugs 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 drug accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study drug interventions are provided in the study training materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study.

Participants who meet all criteria for enrollment will be randomly assigned to 1 of the study treatment arms at Visit 4. Assignment to treatment arms will be determined by a computer-generated random sequence using an IWRS. Participants will be randomly assigned in a 2:1:1:1:1:2:2 ratio (LY3437943 1 mg QW, LY3437943 4 mg QW (a), LY3437943 4 mg QW (b), LY3437943 8 mg QW (a), LY3437943 8 mg QW (b), LY3437943 12 mg QW, placebo QW).

Although the participant and the investigator will know the injection volume of study drug, they will not know whether the participant is receiving LY3437943 or placebo. To preserve the blind, participants randomized to placebo will be randomly assigned to follow the injection dose schedule for 1 of the LY3437943 treatment arms.

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) or clinical research scientist (CRS) 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 drug will be assessed at each visit. Compliance will be assessed by direct questioning and counting of unused study drug and/or empty vials returned. Study drug compliance will be determined by the following:

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

Treatment compliance will be assessed every 4 weeks, or every 12 weeks after Visit 11, at the time of visits to the study site. Treatment compliance for each 4- to 12-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 the study drug administration, other aspects of compliance with the study treatments will be assessed at each visit based on the participant's adherence to the visit schedule, completion of study, study drug administration logs, and any other parameters the investigator considers necessary.

Participants considered to be poorly compliant with their medication, and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol. Additional unscheduled visits may be scheduled if study site personnel determine that a participant requires additional training for the study drug preparation and injection techniques.

6.5. Concomitant Therapy

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.

Participants will be permitted to use concomitant medications that they require during the study, except certain medications (for example, other medications for weight management) that may interfere with the assessment of efficacy and safety characteristics of the study treatments. Treatment with, or initiation of, medications that are excluded in the entry criteria (Section 5.2) is not permitted during the study, except for medications required for the management of incident diabetes (see Section 6.5.2). Hormone replacement therapy in postmenopausal women

and contraceptives containing an estrogen and a progestin (oral or transdermal system) in premenopausal women should not be started after entering the study. The sponsor should be contacted if a participant starts treatment with a medication that is prohibited by the protocol.

Doses of other prescription medications for treatment of concurrent medical conditions should remain constant during the study unless an adjustment is medically indicated. For example, doses of anti-hypertensive medication may be reduced if the participant's BP declines significantly during the study resulting in symptoms of lightheadedness.

Any medication or vaccine (including over-the-counter or prescription medicines and acetaminophen/paracetamol), vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF.

Nonsteroidal anti-inflammatory medications (including ibuprofen and aspirin), acetaminophen, cough suppressants, antihistamines, 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. Apart from these medications, the sponsor should be contacted to clarify if an individual medication is allowed in the study. If the need for additional concomitant medication arises, the participant may be continued in the study-on-study drug if, in the investigator's opinion, the addition of the new medication does not pose a safety risk. If an additional concomitant medication is started, the sponsor should be informed as soon as possible.

6.5.1. Management of Participants with Gastrointestinal Symptoms

In the Phase 1 program, the most reported TEAEs for participants receiving LY3437943 were nausea, vomiting, and diarrhea. To mitigate GI symptoms and manage participants with intolerable GI AEs, the investigator should

- Advise participants to eat smaller meals, for example, splitting 3 daily meals into 4, or more smaller meals, and to stop eating when they feel full. Also, participants may be informed that lower-fat meals could be better tolerated.
- Prescribe symptomatic medication (for example, anti-emetic or antidiarrheal medication) per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the eCRF.
- Temporarily interrupt study drug (omit 1 dose). Refer to Section 6.6.1 for further guidance on restarting study drug after temporary discontinuation of study drug. The data related to temporary interruption of study treatment should be documented in source documents and entered on the eCRF.

If intolerable GI symptoms or events persist despite the above measures, see Section 6.6.

6.5.2. Definition and Management of Incident Diabetes

Definition of Incident Diabetes

Incident diabetes is defined when any 1 of the following occurs after randomization (ADA 2020):

- In a participant with classic symptoms of hyperglycemia or hyperglycemic crisis, a random serum glucose ≥200 mg/dL (11.1 mmol/L)

- Within a 4-week period, any 2 of the following criteria are observed or 1 abnormal value is observed and confirmed
    - HbA1c ≥6.5% (48 mmol/mol)
    - Fasting serum glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h, and
    - Initiation of any medication for the treatment of diabetes.

Management of Incident Type 2 Diabetes

Participants who develop T2D during the study will be

- provided and trained to use a glucometer (the frequency of self-monitoring of BG will be at the discretion of the investigator)
- educated on the signs and symptoms of hypoglycemia and its treatment, and
- provided a diary to record hypoglycemic episodes per Section 8.3.2.1.

Participants will be referred to their usual care provider and provided with a letter showing the study results indicative of diabetes. The decision to initiate glucose-lowering medication and the choice of glucose-lowering medication will be at the discretion of the participant's usual care provider, except for the following medications that are not allowed in the study:

- GLP-1RA, and
- Dipeptidyl peptidase-4 (DPP-4) inhibitors.

GLP-1RA and DPP-4 inhibitors should not be used in combination with LY3437943 due to overlapping pharmacology and the potential for increased GI side effects. Although metformin is not allowed upon study entry, it is allowed for treatment of incident T2D and is recommended for initial glucose-lowering therapy in this circumstance. Metformin should not be initiated during the study for the treatment of other metabolic conditions (for example, polycystic ovary syndrome and diabetes prevention). If additional glucose-lowering therapy beyond metformin is needed to treat incident T2D, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, sulfonylureas, or long-acting basal insulin may be considered.

Monitoring for hypoglycemia includes capture of events as defined in Section 8.3.2.1. Date of diagnosis of diabetes will be captured in the eCRF. If participants are diagnosed with incident T1D, discontinuation of study drug should be considered as noted in Section 7.1.

6.6. Dose Modification

Study drug administration should follow the schedule provided in Section 1.3 (Schedule of Activities) and Section 4.1.1. 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 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 of study drug, 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 as deemed necessary by the investigator. 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 safety of the participant, dosing interruption will be considered a protocol deviation. Every effort should be made by the investigator to maintain participants on study drug and 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 (for example, interruption of treatment for more than 3-4 weeks) will be discussed between the primary investigator or designee and Lilly study physician to decide on an appropriate dosing plan for any participants with such events.

The following table provides detailed guidance on procedures related to temporary interruption of study drug.

Reason for interruption	Number of doses missed	Actions at dosing reinitiation
Tolerability TEAEs related to study drug	1 dose	Restart dosing with the same dose that was last administered prior to interruption for 1 week and then follow the planned dosing schedule. • If the rechallenge is not tolerated, reduce the dose to the previously

Reason for interruption	Number of doses missed	Actions at dosing reinitiation
		tolerated dose and keep the participant on that dose until the end of the treatment period. • If the starting dose of 1 or 2 mg is not tolerated, the participant will discontinue study drug. • If the starting dose of 4 mg is not tolerated upon rechallenge, the participant may be switched to the 2 mg starting dose, per the alternate dose escalation regimen.
	2 or more consecutive doses	Restart dosing on the previously tolerated, lower dose for 2 weeks (that is, 1 dose level lower than the dose that was not tolerated) and then resume dose escalation per the planned dosing schedule. • If dose escalation is not tolerated for a second time, reduce the dose to the previously tolerated dose and keep the participant on that dose until the end of the treatment period. • If the starting dose of 1 or 2 mg is not tolerated, the participant will discontinue study drug. • If the starting dose of 4 mg is not tolerated upon rechallenge, the participant may be switched to the 2 mg starting dose, per the alternate dose escalation regimen.
Other TEAEs	1 dose	Restart dosing 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	Restart dosing at 1 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

Reason for interruption	Number of doses missed	Actions at dosing reinitiation
		the dose prior to interruption is the lowest dose level, restart dosing on that dose.
Not related to TEAEs (i.e., due to a protocol deviation)	1 dose	Restart dosing with the same dose that was last administered prior to interruption for 1 weeks and then follow the planned dosing schedule.
	2 or more consecutive doses	Restart dosing at 1 dose level 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.

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 6.6.1, there may be situations where only a dose reduction (without interrupting dosing) would be appropriate. Phase 1 clinical data with LY3437943 demonstrated that increases in HR and decreases in body weight are anticipated. Whereas increases in HR with other incretin therapies (for example, GLP-1 RA) have been well tolerated, it is possible that a participant may experience undesirable symptoms in association with larger increases in HR. Although weight loss is desired in the population of participants included in this trial, it is possible that a participant may achieve a level of weight loss that is sufficient for health benefits with further weight loss being considered undesirable. Therefore, the dose of study drug should be decreased to 1 dose level lower (for a given treatment arm) in the following circumstances:

- any clinically significant changes in the vital signs accompanied by AEs, as deemed necessary by the investigator, and
- if BMI decreases to less than or equal to 22 kg/m^2.

If the participant is already on the lowest dose for their assigned dosing schedule, the participant will discontinue study drug. The decision to lower the dose or discontinue study drug in such situations should be approved by the Lilly CRP. The investigator should contact the sponsor with any questions regarding dose reductions.

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 drug. If study drug is definitively discontinued, the participant will remain in the study to be evaluated for all planned efficacy and safety measures. In addition, the participant may continue to receive diet and physical activity counseling. Participants who are unwilling to attend all scheduled visits after stopping study drug will be asked to return for a final visit 48 weeks after randomization, primarily for weight measurement and assessment of AEs (Visit 99). If participants are unwilling to attend Visit 99, their refusal to attend should be documented in the participant medical record. See the SoA for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

Possible reasons leading to permanent discontinuation of study drug:

- **participant decision**
  - the participant requests to discontinue study drug
- **clinical considerations**
  - 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 6.5.1 and Section 6.6.1

    Note: The investigator should contact the Sponsor CRP/CRS to discuss whether it is medically appropriate for the participant to continue study treatment.
  - 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
  - BMI $\leq$19 kg/m^2 is reached at any time during the treatment period
  - diagnosis of T1D
  - diagnosis of MTC or MEN2 after randomization
  - significant elevation of calcitonin (Section 8.3.2.3.1)
  - 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
  - onset of pregnancy in a female participant

- occurrence of any other treatment-emergent AE (TEAE), SAE, or clinically significant finding for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
- PHQ-9 score ≥15
  - Participants should be referred to a Mental Health Professional (MHP) to assist in deciding whether the participant should be discontinued from study drug. If a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the participant, at the discretion of the Investigator (in agreement with the MHP), may be continued in the trial on randomized therapy.
- in addition, study drug may be discontinued if participants
  - answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS

    or
  - answered "yes" to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS

    or
  - answered "yes" to any of the suicide-related behaviors (Actual attempt, Interrupted attempt, Aborted attempt, Preparatory act or behavior) on the "Suicidal Behavior" portion of the C-SSRS.

Note: A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

- **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 1 of the following conditions after consultation with the Lilly-designated medical monitor:
    - ALT or AST >8X ULN
    - ALT >2X baseline value OR ≥300 U/L, whichever occurs first, if baseline ALT ≥2X ULN
    - ALT or AST >5X ULN for more than 2 weeks
    - ALT or AST >3X ULN and 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%)

- 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%).

Refer to Section 10.1.8 for discontinuation of specific sites or of the study as a whole.

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, and
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

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

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.

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 body weight. Body weight measurements will be collected at specific clinic visits as summarized in the SoA. Methods for measuring body weight are described in Section 10.8.

Secondary:

The following secondary efficacy measures will be collected at the times shown in the SoA.

- BMI (derived using body weight in kilograms divided by the square of height in meters), and
- waist circumference (see Section 10.8).

Exploratory:

The following exploratory efficacy measures will be collected at the times shown in the SoA:

- blood pressure (see Section 4.1.2.3)
- heart rate measured by ABPM (see Section 4.1.2.3)
- lipid parameters
- glycemic control
- mechanistic biomarkers related to insulin sensitivity, pancreatic beta cell function, glucagon receptor target engagement, fatty acid oxidation, lipolysis, purine metabolism, cardiovascular risk, and inflammation (see table in Appendix 10 [Section 10.10]), and
- patient-reported outcomes (see Section 10.11 [Appendix 11]).

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 10.8 (Appendix 8).

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

- skin, including feet
- cardiovascular
- respiratory
- GI
- neurological systems, 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 the SoA and following the study-specific recommendations included in Section 10.8 (Appendix 8).

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 12-lead ECG should be collected according to Section 1.3 (for details, please see Section 10.8). 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. In addition, tracings collected at the baseline, 24, and 48 weeks will be assessed qualitatively by a blinded cardiologist.

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2 (Appendix 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 1 month after the last dose of study drug (Visit 801) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2 (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 therapeutic area physician or clinical scientist.

8.2.5.1. Hepatic Safety Monitoring

Close Hepatic Monitoring

Laboratory tests (Section 10.9), including ALT, AST, ALP, total bilirubin, direct bilirubin, gamma-glutamyltransferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of…	**develops the following elevations**
ALT or AST <1.5X 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 over-the-counter), herbal and dietary supplements, and history of alcohol drinking and other substance abuse.

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

Comprehensive Hepatic Evaluation

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

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

* Hepatic signs/symptoms are severe fatigue, nausea, vomiting, 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.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Participants who have obesity or are overweight are at increased risk for depression (Luppino et al. 2010). Depression can increase the risk for suicidal ideation and behavior. Therefore, study participants will be screened at trial entry and monitored during the study for depression, suicidal ideation, and behavior.

Participants should be monitored appropriately for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study medication in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

Columbia Suicide-Severity Rating Scale (C-SSRS) is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health (NIMH) trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events.

Baseline and treatment-emergent assessment of depression, suicidal ideation, and behavior will be monitored during the study using the C-SSRS and PHQ-9 (Section 8.3.2.13).

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

The definitions of the following events can be found in Section 10.4 (Appendix 4):

- 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 drug or study procedures, or that caused the participant to discontinue the study drug (see Section 7).

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.2) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.4 (Appendix 4).

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	2 months after last injection for female participants and 4 months after last injection for female partners of male participants	Within 24 hours of learning of the pregnancy	SAE eCRF	SAE paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed product complaint form with all changes signed and dated by the investigator	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
PC (after participant's study participation has ended **and** the investigator becomes aware)	After participant's study participation has ended	N/A	Promptly	Product complaint form	N/A

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.

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading AE collection should occur prior to the collection of the C-SSRS.

If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form.

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

8.3.2. Adverse Events of Special Interest

The following are adverse events of special interest and will be adjudicated by an independent clinical endpoint committee (CEC):

- pancreatitis
- major adverse cardiovascular events, and
- deaths.

The following are additional adverse events of special interest for this program that will not be adjudicated by an external committee:

- hypoglycemia (Level 2 and 3)
- thyroid malignancies and C-cell hyperplasia
- supraventricular arrhythmias and cardiac conductive disorders
- hypersensitivity events
- injection site reactions

- hepatobiliary disorders
- severe GI AEs
- antidrug antibodies
- acute renal events, and
- depression, suicidal ideation or behavior monitoring.

Sites should collect additional details and data regarding these safety topics, 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 and how to treat hypoglycemia. Participants will be asked to contact site personnel if they experience any of these symptoms.

Hypoglycemia may be identified by spontaneous reporting of symptoms from participants (whether confirmed or unconfirmed by simultaneous glucose values) or by blood glucose (BG) samples collected during study visits.

All participants who develop incident diabetes during the study will be provided with glucometers. Participants without diabetes may, at the investigator's discretion, be given glucometers to assist in the evaluation of reported symptoms consistent with hypoglycemia. Participants receiving glucometers will be provided a diary to record relevant information (for example, glucose values and symptoms).

Participants who develop incident diabetes during the study may be started on allowed glucose-lowering medications (Section 6.5.2). In the event that participants subsequently develop persistent or recurrent unexplained hypoglycemia during the treatment period, participants will be asked to reduce the dose or discontinue any concomitant glucose-lowering medication commonly associated with hypoglycemia (for example, sulfonylurea or insulin).

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). **Level 2** and **Level 3** hypoglycemia events are considered as adverse events of special interest:

Level 1 hypoglycemia:

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

Level 2 hypoglycemia:

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

Level 3 hypoglycemia:

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

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

Nocturnal hypoglycemia:

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

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

8.3.2.2. 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, Koizumi 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 MRI.

If acute pancreatitis is suspected, the investigator should ensure that the following steps are taken:

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase, and
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal MRI.

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

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

Discontinuation for Acute Pancreatitis

If acute pancreatitis is suspected by the investigator, the participant must temporarily discontinue use of the study drug. Afterwards, if the case is confirmed as acute pancreatitis by the adjudication committee, study drug must be permanently discontinued; the participant may continue in the study. If the case is not confirmed, then the participant can restart study drug, if the investigator deems as clinically appropriate, as described in the Section 6.6.

Case Adjudication and Data Entry

An independent 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 p-amylase ≥3X ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

8.3.2.3. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or MEN-2 will be excluded from the study. Participants who are diagnosed with MTC and/or MEN-2 during the study will have study drug stopped and should continue follow-up with an endocrinologist.

The assessment of thyroid safety during the trial will include reporting of any case of thyroid malignancy (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.

8.3.2.3.1. Calcitonin Measurements

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 asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the study drug should be stopped, and the participants encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude any serious adverse effects on the thyroid.
- *Serum calcitonin value ≥35 ng/L AND ≥50% over the screening value*. In these participants, study drug should be stopped, and the participants 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, study drug should be discontinued (after first confirming the value) and the participants recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist to exclude any serious adverse effect on the thyroid.

8.3.2.4. 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.

8.3.2.5. Deaths

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

8.3.2.6. 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 10.4 (Appendix 4) must be reported as SAEs.

8.3.2.7. Hypersensitivity Reactions

Many drugs, but 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 10.3 (Appendix 3). Laboratory results are provided to the sponsor via the central laboratory.

8.3.2.8. Injection Site Reactions

Symptoms of a local injection site reaction 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 AE occurrence of severe or serious types, samples will be collected for measurement of LY3437943 antidrug antibodies (ADAs) and LY3437943 concentration.

8.3.2.9. Antidrug Antibodies

The occurrence of ADA formation will be assessed as outlined in Section 8.9.

8.3.2.10. Hepatobiliary Disorders

All events of treatment-emergent (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 laboratory tests, hepatic monitoring should be initiated as outlined in Section 8.2.5.1.

8.3.2.11. Severe Gastrointestinal Adverse Events

LY3437943 may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the eCRF/AE

and Concomitant Medications forms, respectively. For detailed information concerning the management of GI AEs, please refer to Section 6.5.1.

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). These events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Participants should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

8.3.2.13. Depression, Suicidal Ideation, or Behavior Monitoring

Participants will be monitored for depression and suicidal ideation or behavior through AE collection and by using the C-SSRS and the PHQ-9 questionnaires. Scores of the questionnaires must be reviewed by the investigator at the time of each visit and appropriate actions as described below should be taken.

Columbia Suicide-Severity Rating Scale (C-SSRS) is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health (NIMH) trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

The PHQ9 questionnaire is a validated, participant-completed 9-item depression module of the Patient Health Questionnaire, which is used as a diagnostic instrument for common mental disorders. The PHQ-9 consists of 9 items each scored on a scale of 0 = “not at all” to 3 = “nearly every day” with a recall period of “the last 2 weeks.” Major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least “more than half the days” in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia. As a severity measure, a higher score indicates greater severity.

Participants will be referred to a MHP if in the opinion of the investigator it is necessary for the safety of the participant or if the participant had any of the following:

- a PHQ-9 score ≥15
- C-SSRS responses of
  - A “yes” answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the “Suicidal Ideation” portion of the C-SSRS
    or
  - A “yes” answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the “Suicidal Ideation” portion of the C-SSRS
    or

- A "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS

8.4. Treatment of Overdose

For this study, any total dose of study drug within a 48-hour time period greater than the dose prescribed by IWRS for that participant will be considered an overdose and should be reported as per criteria described in Section 10.4 (Appendix 4).

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 drug can no longer be detected systemically (at least 30 days). Refer to Section 8.3 for reporting details, and
3. obtain a plasma sample for PK analysis within 5 days from the date of the last dose of study drug 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 Medical Monitor based on the clinical evaluation of the participant. In the event of overdose, refer to the LY3437943 IB.

8.5. Pharmacokinetics

Blood samples for PK analyses will be collected from all randomized participants at the specified visits in accordance with SoA. Efforts should be taken to align clinical visits with PK sampling windows specified in the Pharmacokinetic Schedule of Events (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.

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 are not planned.

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

8.6. Pharmacodynamics

Pharmacodynamics assessments for LY3437943 are included as part of the efficacy measures listed in Section 8.1 and will be collected in accordance with the SoA.

8.7. Genetics

A whole blood sample will be collected to enable exploratory pharmacogenetic analyses as specified in the SoA (Section 1.3), where local regulations allow (see Section 10.6).

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 obesity, diabetes mellitus, and related clinical traits or complications, including nonalcoholic steatohepatitis. 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 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

Biomarker research is performed on stored samples to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules, including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements (see Section 10.10).

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

Samples will be used for research on the drug targets, disease process, variable response to LY3437943, pathways associated with obesity, diabetes mellitus, and related clinical traits or complications, including nonalcoholic steatohepatitis, mechanism of action of LY3437943, and/or research method, or for validating diagnostic tools or assay(s) related to obesity, diabetes mellitus, or related clinical traits or complications.

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

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

8.9. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous 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 venous 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 9.4.4.4. If the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE-ADA positive, additional samples may be taken until the ADA signal returns to baseline (that is, no longer indicates TE-ADA) or 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 ERBs 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 1, 4, 8, or 12 mg administered SC QW is superior to placebo with regard to percent change in body weight from baseline to Week 24, in participants without T2D who have obesity or are overweight with weight-related comorbidities.

9.2. Sample Size Determination

Approximately 300 participants will be randomly assigned to LY3437943 1 mg, LY3437943 4 mg (a), LY3437943 4 mg (b), LY3437943 8 mg (a), LY3437943 8 mg (b), LY3437943 12 mg or placebo with a 2:1:1:1:1:2:2 ratio. Assuming a 20% dropout rate, approximately 48 participants will complete each LY3437943 dose and placebo. An upper limit of 60% enrollment of women will be used to ensure a sufficiently large sample of men.

Sample size selection is guided by the objective of establishing superiority of each LY3437943 dose to placebo relative to the percent change in body weight from baseline to Week 24. The evaluation of superiority to placebo will be conducted for each of the 4 LY3437943 doses at 2-sided significance level of 0.05 using 2-sample t-test. Assuming a standard deviation (SD) of 10%, the LY3437943 group mean percent change in body weight at Week 24 from baseline compared to placebo is assumed to be -8%. The chosen sample size provides at least 97% power to establish superiority of LY3437943 1 mg, LY3437943 4 mg, LY3437943 8 mg, or LY3437943 12 mg compared to placebo. No adjustment for multiplicity will be performed.

In addition, this sample size provides approximately 83% power to show that at least 1 LY3437943 dose has superior effects of reducing waist circumference compared with placebo at Week 24. This assumes a reduction of 5.8 cm in waist circumference compared with placebo at Week 24 and a SD of 9.6 cm.

9.3. Populations for Analyses

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

Analysis Set	Description
Entered	All participants who sign the ICF.
Randomized	All participants who are randomly assigned to a treatment arm.
Efficacy analysis set	Data obtained during treatment period from all randomly assigned participants who take at least 1 dose of double-blind study treatment. Excludes data after discontinuation of study drug. Participants will be analyzed according to the treatment group to which they were randomly assigned.
Full analysis set	Data obtained during treatment period from all randomly assigned participants who take at least 1 dose of double-blind study treatment, regardless of adherence to study drug.

Analysis Set	Description
	Participants will be analyzed according to the treatment group to which they were randomly assigned.
Safety analysis set	Data obtained during treatment period plus safety follow-up period from all randomly assigned participants who take at least 1 dose of double-blind study treatment, regardless of adherence to study drug. Participants will be analyzed according to the treatment group to which they were randomly assigned.

9.4. Statistical Analyses

9.4.1. General Considerations

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

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated, and all confidence intervals (CIs) will be given at a 2-sided 95% level. In statistical summaries and analyses, participants will be analyzed as randomized.

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. The primary efficacy assessment, guided by the “efficacy” estimand, will be conducted using the efficacy analysis set. The “treatment-regimen” estimand, which represents the efficacy irrespective of adherence to study drug, may also be used to compare the primary efficacy of LY3437943 doses with placebo. The analysis guided by the “treatment-regimen” estimand will use the full analysis set. Additional exploratory analyses for participants who can comply with treatment of LY3437943 based on principal stratification may be performed. Details will be provided in the SAP.

The summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. 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). Analysis of covariance (ANCOVA) may be used to make comparisons among treatment groups for continuous measurements with only 1 post-baseline assessment.

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 may be used for the treatment comparison of discrete count measures if deemed appropriate.

Participant-specific random effects may be added to the logistic and the negative binomial regression models if longitudinal measurements are available.

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 and dose escalation subgroups. 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. 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, baseline characteristics, medical history, and concomitant illness will be summarized by treatment group using the full analysis set.

9.4.2.3. Concomitant Therapy

Concomitant medications will be summarized by drug class and treatment group using the full analysis set.

9.4.2.4. Treatment Compliance

Treatment compliance is defined as taking at least 75% of required injections of study drug during the treatment period while on study drug. Frequency counts and percentages of participants compliant to study drug will be summarized by treatment group and dose escalation subgroup using the full analysis set.

9.4.3. Primary Endpoint(s)

The efficacy analyses for the primary endpoint will be conducted to establish superiority of LY3437943 1 mg, LY3437943 4 mg, LY3437943 8 mg, or LY3437943 12 mg to placebo with regard to mean percent change of body weight from randomization (Week 0) to Week 24.

The primary efficacy analysis will be guided by the "efficacy" estimand and conducted using the efficacy analysis set. The primary analyses model will be a MMRM with treatment, visit, and treatment-by-visit interaction as fixed effects, baseline body weight at randomization (Week 0) and sex as covariates, and participant as a random effect. Additional covariates may be added and will be detailed in the SAP.

9.4.4. Secondary Endpoint(s)

9.4.4.1. Efficacy Analyses

The following secondary endpoints will be analyzed on the efficacy analysis set:

- mean percent change of body weight from randomization (Week 0) to Week 48
- percentage of study participants who achieve the following criteria from randomization (Week 0) at Weeks 24 and 48:
  - ≥5% body weight reduction
  - ≥10% body weight reduction, and
  - ≥15% body weight reduction
- mean change in body weight (kg) from randomization (Week 0) at Weeks 24 and 48
- mean change in BMI (kg/m^2) from randomization (Week 0) at Weeks 24 and 48, and
- mean change in waist circumference (cm) from randomization (Week 0) at Weeks 24 and 48.

Analyses of continuous endpoints, including change in body weight (kg), BMI (kg/m^2), and waist circumference (cm), will be conducted in a manner similar to the primary efficacy analyses discussed in Section 9.4.2.

Analyses for percentages of participants reaching ≥5% body weight reduction, ≥10% body weight reduction, and ≥15% body weight reduction from baseline at Weeks 24 and 48 will be conducted using a longitudinal logistic regression model with treatment, visit, and treatment-by-visit interaction as fixed effects, baseline values at randomization (Week 0) and sex as covariates, and participant as a random effect. Missing body weight data at Weeks 24 and 48 may be imputed first before conducting the analyses. Additional secondary efficacy analyses may be performed, if deemed necessary. The details will be provided in the SAP.

9.4.4.2. 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. Thus, safety analyses will be conducted using the full analysis set.

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. 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 each dose escalation subgroup, and Fisher's exact test will be used to compare the LY dose groups with placebo.

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 for each treatment group at each scheduled visit. The details will be provided in the SAP.

9.4.4.4. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with treatment-emergent ADA+ to LY3437943 may be tabulated. Treatment-emergent ADA 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 GLP-1, GIP, and glucagon or neutralizing antibodies against native GLP-1, GIP, 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.

9.4.5. Exploratory Endpoints

Details will be provided in the SAP.

9.4.6. Other Safety Analyses

Other safety analyses may be conducted, if deemed necessary. Details will be provided in the SAP.

9.4.7. Other Analyses

9.4.7.1. Analysis of PHQ-9 Data

Specific diagnostic symptoms that determine the presence of a clinical depressive disorder per the Diagnosis and Statistical Manual for Mental Disorders will be summarized based on responses to the PHQ-9 questionnaire (Kroenke et al. 2001, Moriarty et al. 2015). Details will be provided in SAP.

9.4.7.2. Analysis of C-SSRS Data

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (C-SSRS WWW). Details will be provided in SAP.

9.4.8. 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 ADA 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.

9.5. Interim Analyses

No interim analyses are planned for this study. Unplanned interim analyses may be performed as necessary if a safety concern is identified from review of blinded data. In the event an interim analysis is conducted, both efficacy and safety data will be reviewed to assess the balance of benefit and risk.

If there are unplanned interim analyses, an assessment committee (AC) will be formed to review the interim analyses in an unblinded manner. The details regarding number of participants and type of analysis will be provided in the AC charter. 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. Study sites will receive information about interim results only if deemed necessary for the safety of the participants.

The primary database lock and primary data analysis for Study GZBF may occur when all participants have completed 24 weeks of treatment. The final database lock and final analyses for this study will be performed after all randomized participants have completed 48 weeks of treatment and the 4-week follow-up period. Unblinded data and results will not be shared with the study sites in order to maintain blinding at the sites while the study is still ongoing. Details will be specified in the blinding/unblinding plan and in the AC charter.

The addition of an interim analysis can be determined at any time during the study and will not result in 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 International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an 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.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2 Informed Consent Process

- The investigator or his 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 and receive a new identification number.

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, as specified in Section 8.3.2.

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.

The publication policy for Study GZBF is outlined in Section 10.1.9 and further described in the Clinical Trial Agreement (CTA).

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

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 product complaint 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, and
- 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

Health care professionals with experience in managing participants who have obesity will serve as investigators. Each site must have a physician designated either as a principal investigator or a sub-investigator to provide necessary medical oversight of participant care.

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.

Investigators must document their review of the laboratory safety results.

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

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 (HDL)	
Low-density lipoprotein (LDL-C)	This value will be calculated. If triglycerides are >400 mg/dL, the direct LDL will be assayed
Very low-density lipoprotein (VLDL-C)	
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	
Cystatin-C	
Thyroid-stimulating hormone (TSH)	
Longitudinal biomarkers	Assayed by Lilly-designated laboratory. Results in this group of biomarkers (See Section 10.10) that 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 10.10) that 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
Stored Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Exploratory samples:	
Serum	
Plasma (EDTA)	
LTS 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	

Abbreviation: EDTA = ethylenediaminetetraacetic acid

10.3. Appendix 3: Laboratory Assessments for Hypersensitivity Events

- 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.

The table below summarizes the laboratory parameters that will be evaluated. These laboratory tests are bundled in the hypersensitivity laboratory testing kit.

Clinical Lab Tests for Hypersensitivity Events

Hypersensitivity Tests	**Notes** Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.
LY3437943 ADAs (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	
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.

Abbreviations: ADA = antidrug antibody; IgE = immunoglobulin E; IL = interleukin; PK = pharmacokinetic.

10.4. Appendix 4: 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

10.4.1 Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, 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 that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy 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.

10.4.2 Definition of SAE

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

SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

e. Is a congenital anomaly/birth defect

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

f. Other situations:

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

10.4.3 Definition of Product Complaints

Product Complaint

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

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

AE, SAE, and Product Complaint Recording

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

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

10.4.5 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.

10.4.6 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.

10.5. Appendix 5: 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 who remain abstinent as their preferred lifestyle or WOCBP who are in a same-sex relationship exclusively do not need to use contraception. WOCBP who do NOT remain abstinent as their preferred lifestyle or WOCBP who are NOT in a same-sex relationship exclusively need to use contraception as described below throughout the study and for 5 half-lives of study drug (30 days) 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 1 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.
Postmenopausal state	The postmenopausal state should be defined as 1. A woman at any age at least 6 weeks postsurgical 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 o calendar o ovulation o symptothermal, or o post-ovulation • declare abstinence just for the duration of a trial, or • use the withdrawal method
stay in a same-sex relationship without sexual intercourse with males	

- **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

	○ 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, 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, 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 during intercourse 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, and • 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, 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, 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 randomized male participants who receive study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of 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 up 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. 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.

10.6. 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 obesity, diabetes mellitus, and related clinical traits or complications, including nonalcoholic steatohepatitis and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to LY3437943, study interventions related to this drug class, or obesity, diabetes mellitus, and related clinical traits or complications, including nonalcoholic steatohepatitis. Genetic research may consist of the analysis of 1 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 obesity, diabetes mellitus, and related clinical traits or complications, including nonalcoholic steatohepatitis, continues but no longer than 15 years or other period as per local requirements.

10.7. Appendix 7: Diet and Physical Activity Counseling

10.7.1 Diet

For this study, counseling on a healthy diet will be based on the *Dietary Guidelines for Americans 2020-2025* published by the U.S. Department of Agriculture and the U.S. Department of Health and Human Services (USDA and HHS 2020). The following principles form the basis of these guidelines.

- "Customize and enjoy nutrient-dense food and beverage choices to reflect personal preferences, cultural traditions, and budgetary considerations.
    - A healthy dietary pattern can benefit all individuals regardless of age, race, or ethnicity, or current health status. The *Dietary Guidelines* provides a framework intended to be customized to individual needs and preferences, as well as the foodways of the diverse cultures in the United States."
- "Focus on meeting food group needs with nutrient-dense foods and beverages, and stay within calorie limits.
    - An underlying premise of the *Dietary Guidelines* is that nutritional needs should be met primarily from foods and beverages—specifically, nutrient-dense foods and beverages. Nutrient-dense foods provide vitamins, minerals, and other health-promoting components and have no or little added sugars, saturated fat, and sodium. A healthy dietary pattern consists of nutrient-dense forms of foods and beverages across all food groups, in recommended amounts, and within calorie limits.
    - The core elements that make up a healthy dietary pattern include:
        - **Vegetables of all types**—dark green; red and orange; beans, peas, and lentils; starchy; and other vegetables
        - **Fruits**, especially whole fruit
        - **Grains**, at least half of which are whole grain
        - **Dairy**, including fat-free or low-fat milk, yogurt, and cheese, and/or lactose-free versions and fortified soy beverages and yogurt as alternatives
        - **Protein foods**, including lean meats, poultry, and eggs; seafood; beans, peas, and lentils; and nuts, seeds, and soy products
        - **Oils**, including vegetable oils and oils in food, such as seafood and nuts"
- "Limit foods and beverages higher in added sugars, saturated fat, and sodium, and limit alcoholic beverages."
    - "Meeting food group recommendations—even with nutrient-dense choices—requires most of a person's daily calorie needs and sodium limits. A healthy dietary pattern doesn't have much room for extra added sugars, saturated fat, or sodium—or for alcoholic beverages. A small amount of added sugars, saturated fat, or sodium can be added to nutrient-dense foods and beverages to help meet food group recommendations, but foods and beverages high in these components should be limited. **Limits are:**"
        - **Added sugars**—Less than 10 percent of calories per day

- **Saturated fat**—Less than 10 percent of calories per day
- **Sodium**—Less than 2,300 milligrams per day
- **"Alcoholic beverages**—Adults of legal drinking age can choose not to drink, or to drink in moderation by limiting intake to 2 drinks or less in a day for men and 1 drink or less in a day for women, when alcohol is consumed. Drinking less is better for health than drinking more. There are some adults who should not drink alcohol, such as women who are pregnant."

10.7.2 Physical Activity

To safely engage in physical activity, types of physical activity appropriate for the participant's current fitness should be chosen. Furthermore, the amount and duration of physical activity should be gradually increased over time. Participants with chronic conditions and symptoms should be under the care of a health care provider who can advise about the types and amounts of physical activity that are appropriate for the participant.

For this study, counseling on physical activity will be based on the *Physical Activity Guidelines for Americans, 2nd Edition* published by the U.S. Department of Health and Human Services (HHS 2018). The following principles form the basis of these guidelines.

- Key Guidelines for Adults (age <65 years)
  - "Adults should move more and sit less throughout the day. Some physical activity is better than none. Adults who sit less and do any amount of moderate-to-vigorous physical activity gain some health benefits.
  - For substantial health benefits, adults should do at least 150 minutes (2 hours and 30 minutes) to 300 minutes (5 hours) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Preferably, aerobic activity should be spread throughout the week.
  - Additional health benefits are gained by engaging in physical activity beyond the equivalent of 300 minutes (5 hours) of moderate-intensity physical activity a week.
  - Adults should also do muscle-strengthening activities of moderate or greater intensity and that involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits."
- Key Guidelines for Older Adults (age ≥ 65 years)
  - "The key guidelines for adults also apply to older adults. In addition, the following key guidelines are just for older adults:
    - As part of their weekly physical activity, older adults should do multicomponent physical activity that includes balance training as well as aerobic and muscle-strengthening activities.
    - Older adults should determine their level of effort for physical activity relative to their level of fitness.

        - Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely.
        - When older adults cannot do 150 minutes of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow."
- Key Guidelines for Adults With Chronic Health Conditions and Adults With Disabilities
    - "Adults with chronic conditions or disabilities, who are able, should do at least 150 minutes (2 hours and 30 minutes) to 300 minutes (5 hours) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Preferably, aerobic activity should be spread throughout the week.
    - Adults with chronic conditions or disabilities, who are able, should also do muscle-strengthening activities of moderate or greater intensity and that involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits.
    - When adults with chronic conditions or disabilities are not able to meet the above key guidelines, they should engage in regular physical activity according to their abilities and should avoid inactivity.
    - Adults with chronic conditions or symptoms should be under the care of a health care provider. People with chronic conditions can consult a health care professional or physical activity specialist about the types and amounts of activity appropriate for their abilities and chronic conditions."

10.8. Appendix 8: Protocol GZBF Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs

The following information has been adapted from standardized physical measurement protocols for the 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 that measures in kg to 1 decimal place, with a capacity to accommodate participants with overweight/obesity.
- 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, 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.

Sitting Vital Sign Measurements

- Vital sign measurements (BP and HR, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing.
- The participant should sit quietly for 5 minutes before vital 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 BP needs to be recorded in the eCRF.
- Blood pressure must be taken with an automated BP instrument with full range of cuff sizes up to extra-large.
- If BP and pulse measurements are taken separately, pulse should be taken prior to BP.

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

Orthostatic Vital Sign Measurements

- Orthostatic vital sign measurements (BP and HR, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing. 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

- 12-lead ECGs should be obtained after the participant has rested in a supine position for at least 5 minutes.
- Electrocardiograms should be collected at least 30 minutes prior to collection of blood samples for laboratory testing, including PK samples.

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 48 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).

10.9. Appendix 9: 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.

Hepatic Evaluation Labs

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs – red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs – white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
Prothrombin Time, INR (PT-INR)	Ethyl Alcohol
Serology	Haptoglobin
Hepatitis A Virus (HAV) testing:	Immunoglobulin IgA (Quantitative)
HAV total antibody	Immunoglobulin IgG (Quantitative)
HAV IgM antibody	Immunoglobulin IgM (Quantitative)
Hepatis B Virus (HBV) Testing:	Phosphatidylethanol (Peth)
Hepatitis B surface antigen (HbsAg)	**Urine Chemistry**
Hepatitis B surface antibody (Anti-HBs)	Drug Screen
Hepatitis B core total antibody (Anti-HBc)	Ethyl glucuronide (EtG)
Hepatitis B core IgM antibody	**Other Serology**
Hepatitis B core IgG antibody	Anti-nuclear antibody (ANA)

HBV DNA[a]	Anti-smooth muscle antibody (ASMA)[b]
Hepatis C Virus (HCV) Testing:	Anti-actin antibody[c]
HCV antibody	Epstein-Barr Virus (EBV) Testing:
HCV RNA[a]	EBV antibody
Hepatitis D Virus (HDV) Testing:	EBV DNA[a]
HDV antibody	Cytomegalovirus (CMV) Testing:
Hepatitis E Virus (HEV) Testing:	CMV antibody
HEV IgG antibody	CMV DNA[a]
HEV IgM antibody	Herpes Simplex Virus (HSV) Testing:
HEV RNA[a]	HSV (Type 1 and 2) antibody
Microbiology[d]	HSV (Type 1 and 2) DNA[a]
Culture:	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Blood	
Urine	

Abbreviations: EBV = Epstein-Barr Virus; Ig = immunoglobulin; INR = international normalized ratio.

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

[b] This is not required if anti-actin antibody is tested.

[c] This is not required if anti-smooth muscle antibody is tested.

[d] Assayed by investigator-designated local laboratory ONLY. No central testing available.

10.10. Appendix 10: Metabolic Mechanistic Biomarkers

Mechanistic biomarkers will be measured at frequent intervals (longitudinal biomarkers) or less frequently to correspond with the primary and secondary endpoints (endpoint biomarkers). These biomarker results will not be reported to sites during conduct of the study. To explore potential mechanisms of action of LY3437943 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, total adiponectin, CCI , and leptin
  - Calculation: homeostasis model assessment of insulin resistance ([HOMA2-IR] computed with fasting glucose and fasting insulin or fasting C-peptide)
- Biomarkers related to pancreatic beta cell function: fasting insulin, fasting C-peptide, and intact proinsulin
  - Calculation: homeostasis model assessment of beta-cell function ([HOMA2-B] computed with fasting glucose and fasting insulin or fasting C-peptide), intact proinsulin/C-peptide ratio, and intact proinsulin/insulin ratio
- CCI
- Biomarker of fatty acid oxidation: beta-hydroxybutyrate
- Biomarkers of lipolysis: free fatty acids
- Biomarker of purine metabolism: uric acid
- Biomarkers related to cardiovascular risk: apolipoprotein B (Apo B) and apolipoprotein C-III (Apo C3)
- Biomarkers related to inflammation: high sensitivity C-reactive protein (hsCRP)

The table below outlines which biomarkers will be assessed more frequently (longitudinal biomarkers) and those that will be evaluated at the timepoints for primary and secondary endpoints. Refer to the SoA (Section 1.3) for the specific visits at which these biomarkers will be assessed.

Metabolic Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
Insulin sensitivity	Fasting insulin Fasting C-peptide Calculation: HOMA2-IR (computed with fasting glucose and with fasting insulin or fasting C-peptide)	Total adiponectin CCI Leptin
Pancreatic beta cell function	Fasting insulin Fasting C-peptide Intact proinsulin Calculation:	

Metabolic Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
	HOMA2-B (computed with both fasting insulin and fasting C-peptide) intact proinsulin/C-peptide ratio intact proinsulin/insulin ratio	
CCI [redacted]	CCI [redacted]	
Fatty acid oxidation		Beta-hydroxybutyrate
Lipolysis	Free fatty acids	
Purine metabolism		Uric acid
Cardiovascular risk		Apo B Apo C3
Inflammation		hsCRP

CCI [redacted]

10.11. Appendix 11: Patient-Reported Outcomes

When feasible, the self-administered questionnaires will be translated into the native language of participants, linguistically validated and administered according to the SoA (Section 1.3). The language of the signed ICF will be considered the participant's 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 questionnaires are not collected due to a translation not being available, this will not be considered a protocol deviation.

When the PROs are collected as per the SOA, 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.

- ***Patient Global Impression of Status for Physical Activity***

  Study participants will be asked to complete a Patient Global Impression of Status (PGIs) for Physical Activity item specifically developed for this study. This is a participant-rated assessment of current limitation on physical activity due to health and is rated on a 5-point scale ranging from "1 - not at all limited" to "5 - extremely limited."

- ***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 are further aggregated into 2 health component summary scores: Physical Component Summary and Mental Component Summary. Items are answered on Likert scales of varying lengths (3-point, 5-point, or 6-point scales). Scoring of each domain and both summary scores are norm-based and presented in the form of T-scores, with a mean of 50 and 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 3 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.

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 Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

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

- participation in remote visits, as defined in Section "Remote Visits"
- dispensation of additional study drug during an extended treatment period
- alternate delivery of study drug 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

Remote visits may apply to Visits 6, 7, 8, 9, 10, and 14.

Any procedures that cannot be accomplished at a remote visit should be conducted at the next on-site visit and captured as a protocol deviation related to the exceptional circumstances. Of note, procedures from the missed visit that were not collected and are the same as ones at the next site visit do not need to be duplicated. ABPM scheduled for Visit 14 (Week 36) should be collected as close to the schedule as possible and before Visit 17 (Week 48). Electrocardiograms may be collected at alternate locations and reviewed by the investigator for participant safety; however, if collection of centralized ECGs is not feasible with a remote visit, they should be collected per the SoA at the next in-office visit.

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
- product complaints
- concomitant medications
- diet and physical activity counseling
- review of study participant diary (including study drug compliance), and
- mental health questionnaires (for example, C-SSRS, PHQ-9).

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
- brief physical assessments or general wellness check
- vital signs
- collection of blood and urine samples, and
- collection of health information.

Other alternative locations:

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

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: PK, immunogenicity, and biomarkers. The local laboratory must be qualified in accordance with applicable local regulations.

Study drug 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 drug 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 the screening visit (Visit 1) are valid for a maximum of 70 days prior to the randomization visit (Visit 4). The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening period is paused for less than 50 days from screening (Visit 1) to Visit 3 (or Visit 2 for participants identified with increased probability of liver fat ≥10% by the liver fat algorithm), the participant will proceed to the next study visit per the usual SoA, provided that the randomization visit (Visit 4) must be conducted within 70 days from first screening (Visit 1).
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.

    - 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 period is paused for more than 50 days from screening (Visit 1) to Visit 3 (or Visit 2 for participants identified with increased probability of liver fat ≥10% by the liver fat algorithm), the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen fail in the CRF. This screen fail is allowed in addition to the main protocol screen fail. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at the screening visit (Visit 1) to ensure participant eligibility by the randomization visit (Visit 4).

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 after randomization (Visit 4).

Visit Number	Tolerance
Visit 5	Within 3 days before the intended date, or up to 3 days after the intended date
Visit 6 through Visit 8	Within 7 days before the intended date, or up to 7 days after the intended date
Visit 9 through Visit 17 and Visit 99	Within 14 days from the intended date, or up to 14 days after the intended date (can be up to 28 days after the intended date for Visits 11, 17, and 99)
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 drug 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/shipment records of study drug 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
ABMP	ambulatory blood pressure monitoring
AC	assessment committee
ADAs	antidrug 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
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
blinding/masking	a double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BP	blood pressure
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CEC	clinical endpoint committee
CFR	Code of Federal Regulations
CHF	congestive heart failure
CKD-EPI	Chronic Kidney Disease Epidemiology
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, 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.

CRS	clinical research scientist
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DIO	diet-induced obese
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
ED	early discontinuation of treatment
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.
FBG	fasting blood glucose
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
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.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	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.
IWRS	interactive web-response system
LDL	low-density lipoprotein
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MEN	multiple endocrine neoplasia
MMRM	mixed-model for repeated measures
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging-derived proton density fat fraction
MTC	medullary thyroid carcinoma
NAFLD	non-alcoholic fatty liver disease
NYHA	New York Heart Association
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
PHQ-9	Patient Health Questionnaire-9

PK/PD	pharmacokinetics/pharmacodynamics
PR	pulse rate
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QW	once weekly
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
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-monitored blood glucose
SUSARs	suspected unexpected serious adverse reactions
T1D	Type 1 diabetes
T2D	Type 2 diabetes
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.
ULN	upper limit of normal
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 a: 21-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 table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Added the following note to Patient-Reported Outcomes (PROs), "If a PRO questionnaire is not available in the native language of a participant at baseline, that questionnaire will not be administered for that participant for the duration of the trial (Appendix 10.10)"	If a PRO questionnaire is not available in the native language, then there is no scientific value in collecting these data as participants would not be able to meaningfully understand and provide appropriate responses to the questions
	Removed Predose Pharmacokinetic (PK) sample collection at Visit 801	Correction in timepoint for PK sample collection at Visit 801
	Updated the general notes to include information on ambulatory blood pressure modeling (ABPM)	If the ABPM needs to be repeated at Visit 3, then the screening period may exceed 6 weeks and this will not be considered a protocol deviation
Section 4.1.1 Overview of Study Periods	Addition of "when collected" for PROs at Visit 4, during maintenance period (Visit 11 and Visit 17), and during early discontinuation of treatment visit	To be aligned with PROs in Schedule of Events
Section 5.2 Exclusion Criteria	Addition of history of symptomatic gallbladder disease	To address Food and Drug Administration (FDA) feedback
	Addition of history of documented human immunodeficiency virus infection	Medications used to treat HIV infection may affect body fat distribution
	Revised language for implantable or injectable contraceptives	Clarified that intrauterine devices are allowed if the

Section # and Name	Description of Change	Brief Rationale
		participant has been using the device for at least 3 months
	Clarified language for participants who have previously received LY3437943	Minor edit to clarify language
	Inclusion and Exclusion Criteria 1–51 and 58–59 can be referred to in the current protocol For inclusion and Exclusion Criteria 52–57, refer to J1I-MC-GZBF Addendum (1)	The inclusion and exclusion criteria numbered from 52 to 57 are part of J1I-MC-GZBF Addendum (1). So, in the current protocol, the exclusion criteria continue with the next available number in the sequence from the last number in the protocol addendum (58–59)
Section 8.3.1 Timing and Mechanism for Collecting Events	Change of "Pregnancy eCRF" to "SAE eCRF"	Correction in mechanism for reporting
Section 10.2 Appendix 2: Clinical Laboratory Tests	Removed uric acid from clinical chemistry tests	To maintain internal document consistency. It is presented in Appendix 10 as biomarker of purine metabolism
	Added LTS P800 to exploratory samples	Addition of plasma metabolic marker
Section 10.8 Appendix 8: Protocol GZBF Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs	Updated electrocardiogram tracings to be assessed qualitatively by a blinded cardiologist	To maintain consistency with Section 8.2.3 (Electrocardiograms)
Section 10.11 Appendix 11: Patient-Reported Outcomes	Added information to clarify that PRO questionnaires will be translated into the native language of participants if feasible. If a translation is not available in the native language of a participant, then that PRO questionnaire will not be administered for that participant for the duration of the trial	If a PRO questionnaire is not available in the native language, then there is no scientific value in collecting the data as participants would not be able to meaningfully understand and provide appropriate responses to the questions

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