Title Page

Protocol Title: Efficacy and Safety of Tirzepatide Once Weekly versus Placebo for Maintenance of Weight Loss in Participants without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-4)

Protocol Number: I8F-MC-GPHN

Amendment Number: This is the initial protocol.

Compound: LY3298176

Study Phase: 3

Short Title: Effect of Tirzepatide versus Placebo for Maintenance of Weight Loss (SURMOUNT-4)

Acronym: SURMOUNT-4

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 139721

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

Approval Date: 17-Nov-2020 GMT

Medical Monitor Name and Contact Information will be provided separately.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: Efficacy and Safety of Tirzepatide Once Weekly versus Placebo for Maintenance of Weight Loss in Participants without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-4)

Short Title: Effect of Tirzepatide versus Placebo for Maintenance of Weight Loss (SURMOUNT-4)

Rationale:

Obesity is a chronic disease and its increasing prevalence is a public health concern associated with rising incidence of Type 2 diabetes mellitus (T2DM), increased risk for premature death, and increased risk for some cancers (American Medical Association [AMA] 2013; Council on Science and Public Health 2013; Lauby-Secretan et al. 2016). Although loss of 5% to 10% body weight through lifestyle approaches, based on caloric restriction, physical activity, and behavioral therapy, has been shown to reduce obesity-related cardiovascular risk factors, and in some cases improve health-related quality of life (Mertens and Van Gaal 2000; Knowler et al. 2002; Jensen et al. 2014; Kolotkin and Andersen 2017), lifestyle therapies alone fail to achieve sustainable weight loss in the majority of patients with obesity (Dombrowski et al. 2014). Caloric restriction, for example, has been shown to lead to metabolic adaptive responses, including increases in hunger hormones, decreases in satiety factors (including gastrointestinal [GI] peptides), increased appetitive drive and food intake, and lower energy expenditure (Leibel et al. 1995; Sumithran et al. 2011). These adaptations are thought to work in concert to cause regain and poor durability of treatment.

The gut incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are secreted after meal ingestion and mediate the incretin effect. Both hormones have effects on endocrine cells in the pancreas, increasing insulin biosynthesis and secretion, and modifying glucagon secretion (Skow et al. 2016). Based on these properties, several GLP-1 receptor (GLP-1R) agonists have been approved for pharmacological treatment of T2DM (Tomlinson et al. 2016).

In addition to its pancreatic effects, GLP-1R activation decreases gut motility, slows gastric emptying, and promotes satiety (presumably through a combination of GLP-1R activation in the central and peripheral nervous systems), thereby regulating food intake and body weight (Baggio and Drucker 2007). The US Food and Drug Administration and the European Medicines Agency approved the GLP-1R agonist liraglutide for the treatment of overweight and obesity (SAXENDA® package insert, 2014; SAXENDA summary of product characteristics, 2015).

Preclinical data indicate that GIP also exerts effects on appetite regulation and food intake, adipose tissue, and peripheral energy metabolism. Although studies evaluating effects of GIP on body weight have yielded equivocal results, GIP receptor (GIPR) activation may play a role in body weight regulation, and targeting both the GLP-1R and the GIPR simultaneously could

potentially result in additive or synergistic effects of the 2 incretins on body weight (Coskun et al. 2018).

Tirzepatide is a 39-amino acid synthetic peptide dual GIPR and GLP-1R agonist. Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety (Coskun et al. 2018). It is administered once weekly (QW) by subcutaneous injection.

As a dual GIP/GLP-1R agonist, tirzepatide could exceed the efficacy of selective GLP-1R agonists by recruiting metabolically active tissues not targeted by selective GLP-1R agonists (for example, adipose tissue as indicated by the observation of increased energy utilization) (Müller et al. 2018) and has the potential to reach higher efficacy in target tissues that express both GIPR and GLP-1R. Therefore, tirzepatide has the potential to impact several aspects of energy regulation and to be a treatment for overweight and obesity.

In a 26-week Phase 2 study in patients with T2DM, tirzepatide 10-mg and 15-mg doses produced statistically significant and clinically relevant weight loss compared to placebo and compared to the GLP-1R agonist, dulaglutide. While tirzepatide is subsequently being evaluated in Phase 3 studies in patients with obesity for its effects on weight loss, this study aims to evaluate the effect of tirzepatide on weight maintenance. Because obesity is a chronic relapsing progressive disease (Bray et al. 2017), the impact of a therapy on weight maintenance in addition to weight loss enables a more complete understanding of its benefit and helps to inform decisions on duration of therapy.

Although there is increasing recognition that adjunctive therapies to lifestyle modification, including pharmacotherapy, may be required to improve outcomes in patients with obesity (AMA 2013; Apovian et al. 2015), determining the duration of therapy has not been approached consistently across all health systems. Obesity management guidelines recommend that pharmacologic interventions be continued if patients achieve at least 3% to 5% body weight loss during an initial period, yet there is little consensus as to the total duration of therapy or whether there may be a rationale for continuation of therapy to prevent weight regain, even after weight loss goals are achieved (Garvey et al. 2016).

Study I8F-MC-GPHN (GPHN; SURMOUNT-4) is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled, 88-week study that will investigate the impact of maximum tolerated dose (MTD) of tirzepatide (10 mg or 15 mg QW), compared with placebo, on the maintenance of weight loss after an initial 36-week open-label tirzepatide lead-in treatment period, in study participants who do not have T2DM, and have obesity (body mass index [BMI] $\geq$30 kg/m^2) or are overweight (BMI $\geq$27 kg/m^2) with at least 1 weight-related comorbid condition.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate that tirzepatide MTD is superior to placebo for percent change in body weight at Week 88	• Mean percent change in body weight from randomization (Week 36) to 88 weeks
Key Secondary (controlled for type I error)	
To demonstrate that tirzepatide MTD is superior to placebo in change from randomization (Week 36) for the following (measured at 88 weeks):	
• Body weight	• Mean change in body weight (kg)
• Waist circumference	• Mean change in waist circumference (cm)
• Maintaining body weight reduction achieved during the 36-week open-label period	• Percentage of participants who maintain ≥80% of the body weight lost during the 36 weeks of open-label period
To demonstrate that tirzepatide MTD is superior to placebo in change from Visit 2 (Week 0) for the following:	
• Body weight	• Percentage of study participants who achieve ≥5% body weight reduction at 88 weeks • Percentage of study participants who achieve ≥10% body weight reduction at 88 weeks
• Prevention of weight regain following the 36 weeks of open-label period	• Time (in weeks), during the 52-week double-blind treatment period, to first occurrence of participants returning to >95% baseline weight for those who have already lost ≥5% since Week 0
To demonstrate that tirzepatide MTD is superior to placebo in change from randomization (Week 36) for percent change in body weight at Week 64	• Mean percent change in body weight from randomization (Week 36) to 64 weeks

Objectives	Endpoints
Additional Secondary	
To demonstrate that tirzepatide MTD is superior to placebo in change from randomization (Week 36) for the following (measured at 88 weeks):	
• BMI	• Mean change in BMI (kg/m^2)
• Glycemic control	• Mean change in: o Fasting glucose (mg/dL) o HbA1c (%)
• Insulin	• Mean change in fasting insulin (pmol/L)
• Lipid parameters	• Mean change in: o Total cholesterol (mg/dL) o LDL-cholesterol (mg/dL) o HDL-cholesterol (mg/dL) o VLDL-cholesterol (mg/dL) o Triglycerides (mg/dL) o Free Fatty acids (mg/dL)
• Blood pressure	• Mean change in o systolic blood pressure (mmHg) o diastolic blood pressure (mmHg)
• Patient-Reported Outcomes	• Mean change in SF-36 v2 acute form Physical Functioning domain score • Mean change in IWQOL-Lite-CT Physical Function composite score
To demonstrate that tirzepatide MTD is superior to placebo in change from Visit 2 (Week 0) for the following (measured at 88 weeks) for:	
• Body weight	• Mean change in body weight (kg) • Mean percent change in body weight (%) • Mean change in BMI (kg/m^2) • Percentage of study participants who achieve ≥15% body weight reduction
• Waist circumference	• Mean change in waist circumference (cm)

Objectives	Endpoints
• Glycemic control	• Mean change in: o Fasting glucose (mg/dL) o HbA1c (%)
• Insulin	• Mean change in fasting insulin (pmol/L)
• Lipid parameters	• Mean change in: o Total cholesterol (mg/dL) o LDL-cholesterol (mg/dL) o HDL-cholesterol (mg/dL) o VLDL-cholesterol (mg/dL) o Triglycerides (mg/dL) o Free fatty acids (mg/dL)
• Blood pressure	• Mean change in o systolic blood pressure (mmHg) o diastolic blood pressure (mmHg)
• Patient-Reported Outcomes	• Mean change in SF-36 v2 acute form Physical Functioning domain score • Mean change in IWQOL-Lite-CT Physical Function composite score

Abbreviations: BMI = body mass index; HbA1c = hemoglobin A1c, HDL = high-density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite-Clinical Trials Version; LDL = low-density lipoprotein; MTD = maximum tolerated dose; SF-36 v2 acute form = Short Form-36 Version 2 Health Survey acute form; VLDL = very low-density lipoprotein.

Overall Design

Study GPHN is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled, 88-week study that will investigate the impact of MTD of tirzepatide (10 mg or 15 mg QW), compared with placebo, on the maintenance of weight loss after an initial 36-week open-label tirzepatide lead-in treatment period, in study participants who do not have T2DM, and have obesity (BMI ≥30 kg/m^2) or are overweight (BMI ≥27 kg/m^2) with at least 1 weight-related comorbid condition.

Randomization at the end of the open-label lead-in treatment period will be stratified by country, tirzepatide MTD (10 mg versus 15 mg), percent weight loss at 36 weeks (<10% versus ≥10%), and sex.

Disclosure Statement: This is a study including 2 parallel treatment arms (tirzepatide MTD versus placebo) that is participant- and investigator-blinded.

Number of Participants:

Approximately 1000 participants will be screened and 750 participants enrolled into the 36-week open-label tirzepatide lead-in treatment period (including a 20-week dose-escalation period) in order to get approximately 600 participants to be randomized in a 1:1 ratio to tirzepatide MTD

(300 participants) or placebo (300 participants). An upper limit of 70% enrollment of women will be used to ensure a sufficiently large sample of men.

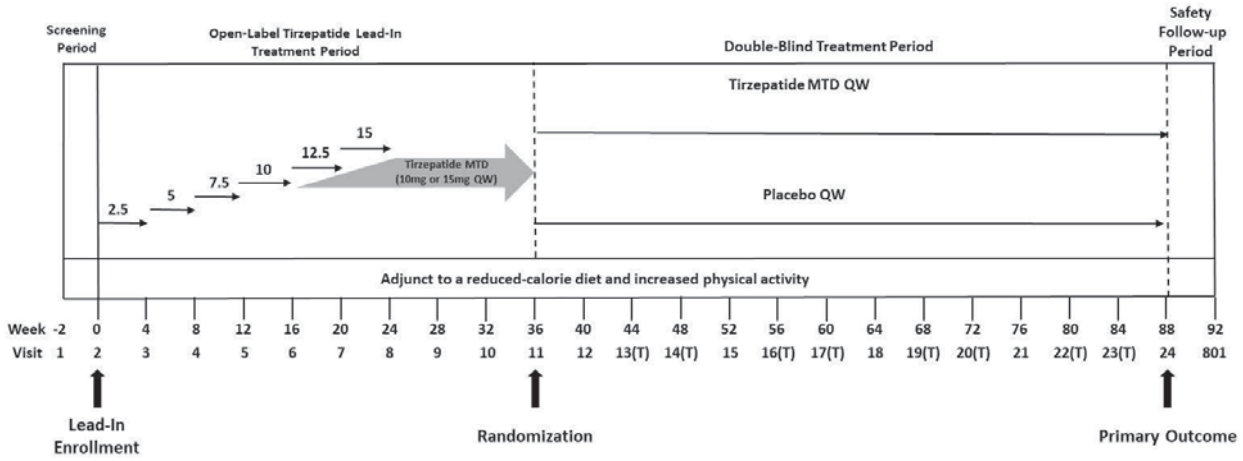
Intervention Groups and Duration:

Study participants will be randomized in a 1:1 ratio (tirzepatide MTD QW and placebo QW), stratified by country, tirzepatide MTD (10 mg versus 15 mg), percent weight loss at 36 weeks (<10% versus ≥10%), and sex.

Study GPHN will consist of 4 periods: a 2-week screening period; a 36-week open-label tirzepatide lead-in treatment period (including a 20-week dose-escalation period); a 52-week double-blind, placebo-controlled treatment period; and a 4-week safety follow-up period.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: MTD = maximum tolerated dose, QW = once weekly; (T) = telephone visit.

1.3. Schedule of Activities (SoA)

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

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**99**	**ED**	**801**
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**88**		**4 wks post end of TxP**
Allowable Interval Tolerance (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**		**±3**
Fasting Visit	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit													**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**				
Informed consent	X																										
Inclusion and exclusion criteria review	X	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) and substance usage (such as alcohol and tobacco).																										
Concomitant medications	X	X	X	X	X	X	X	X	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	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			X			X	X	X	X
	Weight measurements should be obtained per the detailed protocol guidance in Section 10.7. Body weight must be measured in the 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.																										
Waist circumference		X	X	X	X	X	X	X	X	X	X	X			X			X			X			X	X	X	X
Vital Signs (systolic and	X	X	X	X	X	X	X	X	X	X	X	X			X			X			X			X		X	X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	99	ED	801
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**88**		**4 wks post end of TxP**
Allowable Interval Tolerance (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**		**±3**
Fasting Visit	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit													**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**				
diastolic blood pressure, pulse rate)	Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, per the instructions in Section 10.7.																										
Physical examination	X																										
Electrocardiogram		X									X													X		X	X
	ECG measurements should be obtained per the instructions in Section 10.7. ECGs should be collected at least 30 minutes prior to collection of blood samples for laboratory testing, including PK samples.																										
Participant Education and Assessment																											
Lifestyle Program Instruction		X	X	X	X			X			X	X			X			X			X			X		X	
	Counseling on diet and exercise, to be performed by a dietician or equivalent qualified delegate, to include calculation of individualized energy requirement and methods to change dietary composition and amount of physical activity. The Lifestyle Program Instruction may be delivered on a separate day from the rest of that visit's study procedures but must occur within the visit window. Beginning at Week 8, the Lifestyle Program Instruction may be delivered by phone.																										
Review diet and exercise goals		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
	All training should be repeated as needed to encourage participant compliance. Study personnel to provide reinforcement and encouragement for lifestyle modifications.																										
Injection training with autoinjector demonstration device		X																									
Participant Diary (paper)																											
Dispense diary; instruct in use		X	X	X	X	X	X	X	X	X	X	X			X			X			X						
	All training should be repeated as needed to encourage participant compliance.																										

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	99	ED	801
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**88**		**4 wks post end of TxP**
Allowable Interval Tolerance (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**		**±3**
Fasting Visit	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit													**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**				
Diary review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Patient-Reported Outcomes																											
PGIs	X	X									X													X		X	
SF-36 v2, acute form	X	X									X													X		X	
IWQOL-Lite-CT	X	X									X													X		X	
EQ-5D-5L		X									X													X		X	
Mental Health Questionnaires																											
PHQ-9	X	X			X			X			X				X			X			X			X	X	X	X
	PHQ-9 is self-administered and should be completed *after* assessment of adverse events.																										
C-SSRS (Baseline/Screening Version)	X																										
	The C-SSRS 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.																										
C-SSRS (Since Last Visit Version)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	The C-SSRS should be administered *after* assessment of adverse events and capture information since most recent C-SSRS administration. 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.																										
Self-Harm Supplement Form	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	The Self-Harm supplement form should be administered *after* assessment of adverse events.																										

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	99	ED	801
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**88**		**4 wks post end of TxP**
Allowable Interval Tolerance (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**		**±3**
Fasting Visit	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit													**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	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
HbA1c	X	X			X			X			X				X			X			X			X		X	X
Chemistry panel (includes Cr for eGFR calculation and glucose)	X	X			X			X			X				X			X			X			X		X	X
	The CKD-EPI equation will be used by the central lab to estimate and report eGFR.																										
Insulin		X			X			X			X				X			X			X			X		X	X
C-peptide		X			X			X			X				X			X			X			X		X	X
Lipid panel	X	X						X			X													X		X	X
Free fatty acids	X	X						X			X													X		X	X
Serum pregnancy	X																										
	For women of childbearing potential only																										
Urine pregnancy (local)		X			X			X			X				X			X			X			X		X	
	A urine pregnancy test must be performed at Visit 2 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.																										
Follicle-stimulating Hormone (FSH)	X																										
	Follicle-stimulating hormone test is to be performed at Visit 1 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	X
Pancreatic amylase	X				X			X			X													X		X	X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	99	ED	801
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**88**		**4 wks post end of TxP**
Allowable Interval Tolerance (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**		**±3**
Fasting Visit	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit													**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**				
Lipase	X				X			X			X													X		X	X
Urinary albumin/ creatinine ratio	X										X													X		X	X
Cystatin-c	X										X													X		X	X
Thyroid-stimulating hormone (TSH)	X																										
Immunogenicity (includes PK sample)		X	X		X			X			X				X						X			X		X	X
	In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional unscheduled samples should be collected as detailed in Section 8.3.2.7 (Hypersensitivity Reactions). Immunogenicity samples and PK samples for immunogenicity must be taken prior to drug administration.																										
Stored Samples																											
Pharmacogenetic sample		X																									
Nonpharmacogenetic sample		X			X			X			X													X		X	X
Randomization and Dosing																											
Randomization											X																
Dispense study intervention(s)		X	X	X	X	X	X	X	X	X	X	X			X			X			X						
Observe participant administer study intervention(s)		X																									
	Patients should administer their first dose of study drug at the end of Visit 2, after other study procedures are completed.																										

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	99	ED	801
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**88**		**4 wks post end of TxP**
Allowable Interval Tolerance (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**		**±3**
Fasting Visit	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**			**X**			**X**	**X**	**X**	**X**
Telephone Visit													**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**				
Participant returns study interventions and injection supplies			X	X	X	X	X	X	X	X	X	X			X			X			X			X		X	
Assess study intervention(s) compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; C-SSRS = Columbia-Suicide Severity Rating Scale; Cr = creatinine; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite-Clinical Trials Version; PGIs = Patient Global Impression of status for physical activity; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetics; SF-36 v2 acute = Short Form-36 Version 2 Health Survey acute form; TxP = treatment period; wks = weeks.

Note:

- Visit 2 baseline assessments must be completed before processing in the interactive web-response system (IWRS).
- The visit date is determined in relation to the date of Visit 2 (± the visit interval tolerance).
- Visit 99 is only applicable to participants who discontinue the double-blind study treatment prematurely (after Week 36 and before Week 88) and decline to complete the remaining scheduled study visits. Participants wanting to discontinue the study treatment after randomization and before Week 88 will be asked to return for Visit 99 (88 weeks ± 7 days after Visit 2) 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.
- Participants who are unable or unwilling to continue the study treatment for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as an ED visit.
- For all office visits, remind participants to report to the site in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or any significant physical activity. Since some screening procedures need to be completed in the fasting state, Visit 1 may be conducted over more than 1 day to ensure necessary conditions are met.
- Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit of the participant's treatment period.

2. Introduction

Obesity is a chronic disease and its increasing prevalence is a public health concern associated with rising incidence of Type 2 diabetes mellitus (T2DM), increased risk for premature death, and increased risk for some cancers (American Medical Association [AMA] 2013; Council on Science and Public Health 2013; Lauby-Secretan et al. 2016). Although loss of 5% to 10% body weight through lifestyle approaches, based on caloric restriction, physical activity, and behavioral therapy, has been shown to reduce obesity-related cardiovascular risk factors, and in some cases, improve health-related quality of life (HRQoL) (Mertens and Van Gaal 2000; Knowler et al. 2002; Jensen et al. 2014; Kolotkin and Andersen 2017), lifestyle therapies alone fail to achieve sustainable weight loss in the majority of patients with obesity (Dombrowski et al. 2014).

Caloric restriction, for example, has been shown to lead to metabolic adaptive responses, including increases in hunger hormones, decreases in satiety factors (including gastrointestinal [GI] peptides), increased appetitive drive and food intake, and lower energy expenditure (Leibel et al. 1995; Sumithran et al. 2011). These adaptations are thought to work in concert to cause regain and poor durability of treatment. The addition of physical activity is essential and can help maintain weight loss, but generally, maintaining lifestyle-induced weight loss is recognized as being more challenging than losing weight for individuals with obesity (Swift et al. 2018).

Pharmacologic agents, in contrast to voluntary caloric restriction, can directly impact the physiology of energy balance, including the regulation of food intake and/or energy expenditure, to drive towards a lower fat mass and body weight (Heymsfield et al. 2018). Some current or previously marketed weight-management medications have had a demonstrable effect on maintaining initial weight loss over time while on treatment (James et al. 2000; Smith et al. 2010; Wadden et al. 2013). There is increasing recognition that adjunctive pharmacotherapy may be required to improve weight loss, weight maintenance, and health outcomes in individuals with obesity (AMA 2013; Apovian et al. 2015).

2.1. Study Rationale

The gut incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are secreted after meal ingestion and mediate the incretin effect.

Both hormones have effects on endocrine cells in the pancreas, increasing insulin biosynthesis and secretion, stimulating beta-cell neogenesis and proliferation, and protecting beta cells from apoptosis. They also exert actions on alpha cells, modifying glucagon secretion (Skow et al. 2016). Based on these properties, several GLP-1 receptor (GLP-1R) agonists have been approved for pharmacological treatment of T2DM (Tomlinson et al. 2016).

In addition to its pancreatic effects, GLP-1R activation decreases gut motility, slows gastric emptying, and promotes satiety (presumably through a combination of GLP-1R activation in the central and peripheral nervous systems), thereby regulating food intake and body weight (Baggio and Drucker 2007). The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the GLP-1R agonist liraglutide for the treatment of overweight and obesity (SAXENDA package insert, 2014; SAXENDA summary of product, 2015).

Preclinical data indicate that GIP also exerts effects on appetite regulation and food intake as well as on adipose tissue and peripheral energy metabolism. Although studies evaluating effects of GIP on body weight have yielded equivocal results, GIP receptor (GIPR) activation may play a role in body weight regulation and targeting both the GLP-1R and the GIPR simultaneously could potentially result in additive or synergistic effects of the 2 incretins on body weight (Coskun et al. 2018).

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the GIPR and GLP-1R. Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety (Coskun et al. 2018). It is administered once weekly (QW) by subcutaneous (SC) injection. As a dual GIP/GLP-1R agonist, tirzepatide could exceed the efficacy of selective GLP-1R agonists by recruiting metabolically active tissues not targeted by selective GLP-1R agonists (for example, adipose tissue as indicated by the observation of increased energy utilization) (Müller et al. 2018) and has the potential to reach higher efficacy in target tissues that express both GIPR and GLP-1R. Therefore, tirzepatide has the potential to impact several aspects of energy regulation and be a treatment for overweight and obesity.

Obesity management guidelines recommend that pharmacologic interventions be continued if patients achieve at least 5% body weight loss during an initial treatment period (Apovian et al. 2015). Prior studies with anti-obesity medications have demonstrated durability of initial weight loss while on treatment and regain after withdrawal of treatment, indicating a need to continue therapy to maintain its benefits (James et al. 2000; Smith et al. 2010). Despite this, there is poor adoption of obesity management guidelines by health care providers, low adherence to most anti-obesity medications among patients, and little consensus as to the total duration of pharmacotherapy across health care systems (Garvey et al. 2016; Ganguly et al. 2018; Turner et al. 2018).

Study I8F-MC-GPHN (GPHN; SURMOUNT-4) is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled, 88-week study that will investigate the impact of maximum tolerated dose (MTD) of tirzepatide (10 mg or 15 mg QW), compared with placebo, on the maintenance of weight loss, in study participants who do not have T2DM, and have obesity (body mass index [BMI] ≥30 kg/m^2) or are overweight (BMI ≥27 kg/m^2) with at least 1 weight-related comorbid condition.

2.2. Background

There remains an unmet need in the pharmacologic treatment of obesity for drugs that are safe, efficacious, and well-tolerated. There are currently only a few medications FDA-approved for long-term use for the treatment of obesity that yield a placebo-adjusted average weight loss between 3% and 7% (Srivastava and Apovian 2018, FDA 2020). Although moderate weight loss of 5% to 10% in individuals with obesity/overweight has long been shown to yield significant metabolic benefits, including improvements in cholesterol, blood pressure, and glucose parameters (Goldstein 1992; Wing et al. 2011), greater weight loss can maximize these benefits and may be required to realize clinically meaningful improvements in other obesity-related comorbidities such as sleep apnea, nonalcoholic steatohepatitis, and cardiovascular disease (Ryan et al. 2017). In addition to moderate efficacy, some centrally-acting weight loss agents to date have had adverse neurocognitive, psychiatric, or cardiovascular effects, further limiting their application in clinical practice (Srivastava and Apovian 2018).

Weight loss induced by GLP-1R agonists, while appearing to be centrally-mediated through a combination of hormonal inputs to satiety centers (van Bloemendaal et al. 2014), has not been consistently associated with changes in mental health or with potential for addiction in long-term studies conducted to establish cardiovascular safety in patients with diabetes (Marso et al. 2016a, 2016b; Gerstein et al. 2019). Tirzepatide, which is both a GLP-1R and GIPR agonist, has been associated with predominantly mild-to-moderate GI adverse effects similar to currently marketed GLP-1R agonists, but has also demonstrated significant weight loss at both the 10-mg and 15-mg doses in Phase 2 studies with nearly half of the participants in both dose arms achieving ≥10% weight loss (Frias et al. 2018).

Tirzepatide dose selection for obesity treatment has been informed by 3 clinical trials: a Phase 1 study, Study I8F-MC-GPGA (GPGA), and 2 Phase 2 studies, Study I8F-MC-GPGB (GPGB) and I8F-MC-GPGF (GPGF).

Phase 1 Study GPGA was a combination of single-ascending dose (SAD) and multiple-ascending dose (MAD) study in healthy subjects followed by a multiple-dose study in patients with T2DM. A total of 142 participants (89 healthy subjects and 53 patients with T2DM) received at least 1 dose of treatment. Doses of tirzepatide ranged from:

- 0.25 mg to 8 mg in the SAD (with MTD achieved at 5 mg) in healthy subjects,
- multiple doses in the MAD from 0.5 mg to 4.5 mg QW and titrated doses up to 10 mg QW for 4 weeks in healthy subjects, and
- multiple-doses at 0.5 mg and 5 mg QW and titrated up to 15 mg QW for 4 weeks in patients with T2DM.

The safety, tolerability, and pharmacokinetic/pharmacodynamic (PK/PD) profiles of tirzepatide at doses and escalation regimens administered in this Phase 1 study supported further development of tirzepatide for QW dosing in patients with T2DM.

Phase 2 Studies GPGB and GPGF provided initial safety, tolerability, and efficacy data in the tirzepatide 1-mg to 15-mg dose-range when used in treatment of patients with T2DM. In the dose range of 5 to 15 mg, tirzepatide provided significantly greater reductions in hemoglobin A1c (HbA1c) and body weight compared with placebo. In addition, the 10-mg and 15-mg dose arms demonstrated significantly greater weight loss compared to the GLP-1R agonist dulaglutide 1.5 mg QW. The most common adverse events (AEs), which were also dose-dependent, were mild-to-moderate nausea, vomiting, and diarrhea. Study GPGF showed that adjustments in the tirzepatide dose-escalation algorithm resulted in additional reductions in the frequency of GI AEs and reduced the frequency of treatment discontinuations due to GI AEs.

2.3. Benefit/Risk Assessment

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate that tirzepatide MTD is superior to placebo for percent change in body weight at Week 88	• Mean percent change in body weight from randomization (Week 36) to 88 weeks
Key Secondary (controlled for type I error)	
To demonstrate that tirzepatide MTD is superior to placebo in change from randomization (Week 36) for the following (measured at 88 weeks):	
• Body weight	• Mean change in body weight (kg)
• Waist circumference	• Mean change in waist circumference (cm)
• Maintaining body weight reduction achieved during the 36-week open-label period	• Percentage of participants who maintain ≥80% of the body weight lost during the 36 weeks of open-label period
To demonstrate that tirzepatide MTD is superior to placebo in change from Visit 2 (Week 0) for the following:	
• Body weight	• Percentage of study participants who achieve ≥5% body weight reduction at 88 weeks • Percentage of study participants who achieve ≥10% body weight reduction at 88 weeks
• Prevention of weight regain following the 36 weeks of open-label period	• Time (in weeks), during the 52-week double-blind treatment period, to first occurrence of participants returning to >95% baseline weight for those who have already lost ≥5% since Week 0
To demonstrate that tirzepatide MTD is superior to placebo in change from randomization (Week 36) for percent change in body weight at Week 64	• Mean percent change in body weight from randomization (Week 36) to 64 weeks

Objectives	Endpoints
Additional Secondary	
To demonstrate that tirzepatide MTD is superior to placebo in change from randomization (Week 36) for the following (measured at 88 weeks):	
• BMI	• Mean change in BMI (kg/m^2)
• Glycemic control	• Mean change in: o Fasting glucose (mg/dL) o HbA1c (%)
• Insulin	• Mean change in fasting insulin (pmol/L)
• Lipid parameters	• Mean change in: o Total cholesterol (mg/dL) o LDL-cholesterol (mg/dL) o HDL-cholesterol (mg/dL) o VLDL-cholesterol (mg/dL) o Triglycerides (mg/dL) o Free Fatty acids (mg/dL)
• Blood pressure	• Mean change in: o systolic blood pressure (mmHg) o diastolic blood pressure (mmHg)
• Patient-Reported Outcomes	• Mean change in SF-36 v2 acute form Physical Functioning domain score • Mean change in IWQOL-Lite-CT Physical Function composite score
To demonstrate that tirzepatide MTD is superior to placebo in change from Visit 2 (Week 0) for the following (measured at 88 weeks) for:	
• Body weight	• Mean change in body weight (kg) • Mean percent change in body weight (%) • Mean change in BMI (kg/m^2) • Percentage of study participants who achieve ≥15% body weight reduction
• Waist circumference	• Mean change in waist circumference (cm)
• Glycemic control	• Mean change in: o Fasting glucose (mg/dL) o HbA1c (%)
• Insulin	• Mean change in fasting insulin (pmol/L)

Objectives	Endpoints
• Lipid parameters	• Mean change in: o Total cholesterol (mg/dL) o LDL-cholesterol (mg/dL) o HDL-cholesterol (mg/dL) o VLDL-cholesterol (mg/dL) o Triglycerides (mg/dL) o Free fatty acids (mg/dL)
• Blood pressure	• Mean change in: o systolic blood pressure (mmHg) o diastolic blood pressure (mmHg)
• Patient-Reported Outcomes	• Mean change in SF-36 v2 acute form Physical Functioning domain score • Mean change in IWQOL-Lite-CT Physical Function composite score

Abbreviations: BMI = body mass index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite-Clinical Trials Version; LDL = low-density lipoprotein; MTD = maximum tolerated dose; SF-36 v2 acute form = Short Form-36 Version 2 Health Survey acute form; VLDL = very low-density lipoprotein.

4. Study Design

4.1. Overall Design

Study GPHN is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled, 88-week study that will investigate the impact of MTD of tirzepatide (10 mg or 15 mg QW), compared with placebo, on the maintenance of weight loss after an initial 36-week open-label tirzepatide lead-in treatment period, in study participants who do not have T2DM, and have obesity (BMI ≥30 kg/m^2) or are overweight (BMI ≥27 kg/m^2) with at least 1 weight-related comorbid condition.

Study GPHN will consist of 4 periods: a 2-week screening period; a 36-week open-label tirzepatide lead-in treatment period (including a 20-week dose-escalation period); a 52-week double-blind, placebo-controlled treatment period; and a 4-week safety follow-up period. The study participants will be randomized in a double-blind 1:1 ratio (tirzepatide MTD QW or placebo) at the end of the open-label lead-in treatment period. An upper limit of 70% enrollment of women will be used to ensure a sufficiently large sample of men.

4.1.1. Overview of Study Periods

4.1.1.1. Visit Structure for Fasting Office Visits

On all designated fasting office visits, study participants are required to report to the site in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or performing any significant physical activity. If a participant is adversely affected by the fasting condition, they are allowed to eat; however, specific study procedures need to be completed while fasting. See Section 10.8 for a suggested order of activities that occurs at office visits.

4.1.1.2. Main Study Period

4.1.1.2.1. 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 Schedule of Activities (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 any significant physical activity), Visit 1 may be conducted over more than 1 day to ensure necessary conditions are met. Patient-reported outcomes (PROs) questionnaires should be administered as early as possible, as per Suggested Visit Structure (Section 10.8). Preferred administration order is:

1. Patient Global Impression of status (PGIs) for physical activity
2. Short Form-36 Version 2 Health Survey acute form (SF-36 v2 acute form)
3. Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT)

Participants who meet all applicable inclusion criteria and none of the applicable exclusion criteria at Visit 1 will continue to Visit 2.

The Mental Health questionnaires (Patient Health Questionnaire-9 [PHQ-9], Columbia-Suicide Severity Rating Scale [C-SSRS], and C-SSRS Self-Harm Form) should be completed after the assessment for AEs.

4.1.1.2.2. Treatment Period

Open-Label Lead-In Treatment Period

Visit 2

At Visit 2, eligible participants will perform all required baseline study procedures (including the collection of all baseline laboratory measures and questionnaires) prior to enrollment and prior to taking the first dose of study drug. Participants will be provided diaries and be trained to record key study information, as appropriate.

Patient-reported outcomes questionnaires should be administered as early as possible, as per Suggested Visit Structure (Section 10.8). Preferred administration order is:

1. PGIs for physical activity
2. SF-36 v2 acute form
3. IWQOL-Lite-CT
4. EQ-5D-5L

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

Participants will receive an initial consultation with a dietician or equivalent qualified delegate, according to local standards, to set lifestyle goals for caloric intake and physical activity (Section 5.3).

End of Visit 2 to Visit 11

At the end of Visit 2, for participants that meet all the entry criteria and are enrolled in this study, study site personnel will demonstrate use of the autoinjector (also referred to as single-dose pen), using the provided demonstration device and observe the study participant inject the first dose of tirzepatide. The date, time, and location of the first dose of study drug will be recorded on the electronic case report form (eCRF).

After study enrollment, participants will undergo a 36-week open-label tirzepatide dose-escalation and lead-in treatment period (Visits 3 to 11 will occur as indicated in the SoA).

Patient-reported outcomes questionnaires should be administered as early as possible, as per Suggested Visit Structure (Section 10.8). Preferred administration order is the same as described for Visit 2. Mental Health questionnaires should be completed after the assessment of AEs.

Dietician consultations continue at Weeks 4, 8, 12, and then as indicated in the SoA (Section 1.3). Study drug and injection supplies will be returned per the SoA and according to local requirements. New supplies will be dispensed as needed.

The starting dose of tirzepatide is 2.5 mg QW for 4 weeks, then the dose is increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 to 12.5 to 15 mg) up to MTD (either 10 mg or 15 mg).

Interventions to optimize study drug tolerance and adherence may be employed throughout the study and include, but are not limited to, brief temporary interruptions and use of additional medications to manage GI symptoms (for example, nausea, vomiting, and diarrhea, see Section 6.6.2 for details). During the open-label lead-in period, participants unable to tolerate 2.5 mg or 5 mg despite the above measures will be discontinued from the study. For participants unable to tolerate any dose between 7.5 mg and 15 mg inclusive, despite the above measures, the investigator should contact Lilly to consider a dose de-escalation step with subsequent re-escalation to reach either the 10-mg or 15-mg dose on or before Week 36 as described below (only 1 cycle of dose de-escalation and re-escalation is permitted during the open-label, lead-in period):

- 7.5 mg to 5 mg, then the dose is increased by 2.5 mg every 4 weeks up to MTD (either 10 mg or 15 mg)
- 10 mg to 7.5 mg, then the dose is increased by 2.5 mg every 4 weeks up to MTD (either 10 mg or 15 mg)
- 12.5 mg to 10 mg, then the dose is increased by 2.5 mg every 4 weeks up to MTD (either 10 mg or 15 mg)
- 15 mg to 12.5 mg, then the dose is increased by 2.5 mg every 4 weeks up to MTD (either 10 mg or 15 mg)

Participants who tolerate 15 mg by Visit 11 will continue on 15 mg as their MTD dose.

Participants who tolerate 10 mg but do not tolerate 12.5 mg or 15 mg by Visit 11, even after 1 de-escalation and re-escalation attempt, will continue on 10 mg as their MTD dose.

Participants who tolerate 12.5 mg but do not tolerate 15 mg by Visit 11, even after 1 de-escalation and re-escalation attempt, will continue on 10 mg as their MTD dose.

Participants who do not tolerate up to 10 mg by Visit 11, even after 1 de-escalation and re-escalation attempt, will be discontinued from the study.

At Visit 11, those who successfully complete the open-label, lead-in period (reaching and tolerating either the 10-mg or 15-mg dose at Visit 11) will be randomized either to continue tirzepatide at MTD or placebo for the duration of the 52-week, double-blind treatment period.

Double-Blind Treatment Period

End of Visit 11 to Visit 24

Following randomization (end of Visit 11), office visits will occur as indicated in the SoA (Section 1.3). Telephone visits will occur at 4-week intervals between the office visits starting at Week 44.

Office visit procedures should be conducted according to the SoA (Section 1.3), and will include:

- weight, waist circumference, and vital signs measurements
- laboratory testing

- administration of PROs questionnaires
- collection of AEs, product complaints, and concomitant medications
- Mental Health questionnaires
- review of participant diary information (to include reinforcement and compliance assessments for study drug administration and lifestyle goals), and
- drug dispensing.

Patient-reported outcomes questionnaires should be administered as early as possible, as per Suggested Visit Structure (Section 10.8). Preferred administration order is the same as Visit 2.

Mental Health questionnaires should be completed after the assessment of AEs.

Dietician consultations continue as indicated in the SoA. Study drug and injection supplies will be returned per the SoA and according to local requirements. New supplies will be dispensed as needed.

At each of the 8 scheduled telephone visits, procedures will include:

- collection of AEs, product complaints, and concomitant medications
- administration of Mental Health questionnaires (after the AE assessment), and
- review of participant diary information (to include reinforcement and compliance assessments for study drug administration and lifestyle goals)

During all treatment periods, participants should be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties administering their study medication. Participants should also be advised about the appropriate course of action in the event that study drug is not taken at the required time (late/missing doses).

Visit 99

Visit 99 is only applicable to participants who discontinue the double-blind study treatment prematurely (after Week 36 and before Week 88) and decline to complete the remaining scheduled study visits. These participants will be asked to return for Visit 99 at 88 weeks ±7 days (see Section 7.2.1.). This visit is critical to ensure complete data collection for the primary body weight endpoint.

Participants should attend this visit in the fasting state. Procedures to be completed are:

- measurement of weight and waist circumference
- listing of concomitant medications
- assessment of AEs, and
- completion of the Mental Health questionnaires (after the AE assessment).

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

Early Discontinuation of Treatment Visit

Participants unable or unwilling to continue the study treatment for any reason will perform an early discontinuation (ED) of treatment visit (Section 7.2). If the participant is discontinuing during an unscheduled or a scheduled visit, that visit should be performed as an ED visit. Procedures should be completed according to the SoA. Patient-reported outcomes questionnaires

should be administered as early as possible, as per Suggested Visit Structure (Section 10.8). Administration of Mental Health questionnaires should be after the assessment for AEs.

4.1.1.3. Safety Follow-Up Period

Visit 801

All participants are required to complete a safety follow-up visit (Visit 801), according to the SoA. Participants discontinuing the study early and performing an ED visit will also be asked to perform the safety follow-up visit (see Section 7.2.1). During the safety follow-up period, participants will not receive study drug. Participants are also required to return any remaining study diaries to the study site at the end of this period.

Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit in the double-blind treatment period (Visit 24 or Visit 99) or 4 weeks after the ED visit for those who discontinue during the open-label lead-in period or decline to return for Visit 99.

4.1.2. Study Procedures

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

Study participants will be permitted to use concomitant medications that they require during the study, except certain excluded medications (see Section 5.2) that may interfere with the assessment of efficacy and safety characteristics of the study treatments.

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

4.2. Scientific Rationale for Study Design

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the GIPR and GLP-1R. Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety (Coskun et al. 2018). It is administered QW by SC injection.

As a dual GIP/GLP-1R agonist, tirzepatide could exceed the efficacy of selective GLP-1R analogs by recruiting metabolically active tissues not targeted by selective GLP-1R analogs (for example, adipose tissue as indicated by the observation of increased energy utilization) (Müller et al. 2018) and has the potential to reach higher efficacy in target tissues, such as insulin-producing pancreatic beta-cells that express both GIPR and GLP-1R, before reaching its therapeutic limitation. Results from a Phase 2 study (GPGB) demonstrated that tirzepatide use in participants with T2DM was associated with a substantial, dose-dependent weight loss, greater than the weight change observed with dulaglutide, a specific GLP-1R agonist. General safety characteristics of all studied doses of tirzepatide were similar to that of the GLP-1R agonist class, consisting mainly of nausea, vomiting, and diarrhea. In general, these events were transient and mild or moderate in severity, with few severe episodes. These data suggest that tirzepatide has the potential to be a pharmacologic treatment for chronic weight management.

Although GI AEs were more common in the 15-mg arm of tirzepatide in the Phase 2 study (GPGB), this dose demonstrated the highest efficacy in terms of weight loss. An optimized dose-escalation regimen proposed in the current Phase 3 study (GPHN) to improve tolerability (and supported by a dose-escalation algorithm from Study GPGF and PK/PD modeling) should enable a use of the 15-mg dose to maximize effects on body weight.

Study GPHN is designed to determine the impact of treatment with MTD of tirzepatide compared with placebo on maintenance of weight loss in participants without T2DM who have obesity or are overweight. Because obesity is a chronic relapsing progressive disease (Bray et al. 2017), the impact of a therapy on weight maintenance in addition to weight loss enables a more complete understanding of its benefit and helps to inform decisions on duration of therapy.

There is not a clear consensus on how best to define weight maintenance, weight regain, or treatment failure. Recently, some studies have attempted to evaluate different measures of weight maintenance and correlate them with clinical outcomes. Berger et al. (2019) analyzed data from over 1500 participants in the Look AHEAD study who had ≥3% initial weight loss, and defined maintenance/regain according to 5 dichotomized cut-offs (0%, 25%, 50%, 75%, and 100%). They correlated different levels of maintenance with cardiometabolic risk factors and found that those who maintained ≥75% of the initial weight loss had the most cardiometabolic benefit. Conducting a similar study in a bariatric surgery cohort, which experienced much greater initial weight loss than the Look AHEAD cohort, King et al. (2018) found that 20% or greater regain correlated the same or better than other cut-offs with most cardiometabolic risk factors. Based on these recent data, maintaining 75% to 80% of initial weight loss regardless of therapeutic modality appears to be clinically relevant. That being said, it does not seem reasonable to define therapeutic failure at the same cut-off. Perhaps a more appropriate definition of complete therapeutic failure is regaining weight to the point that an individual falls below the 5% weight loss threshold which is used to define initial success of treatment in the first place. To have a more complete picture of therapeutic benefit, an evaluation of both maintenance (at an 80% threshold of maximum weight loss) and time to complete failure (defined as returning to >95% of initial weight) is likely warranted. Therefore, both these measures are being evaluated in the randomized weight-maintenance phase of Study GPHN.

A double-blind design after 36 weeks (randomization) was selected to minimize participant and investigator bias in assessments for efficacy, safety, and study drug tolerability. In addition, the objective of Study GPHN is to evaluate maintenance of initial weight loss, and therefore, achieving a near-maximum weight loss effect and body weight plateau prior to randomization is important. Thirty-six weeks was chosen as the time point for randomization based on PK/PD modeling which shows that by 36 weeks (including 20-week dose escalation) most participants will reach a near-plateau of body weight.

A placebo comparator was selected for this trial in accordance with regulatory guidance (FDA 2007; EMA 2016). In addition, all participants, regardless of treatment assignment, will receive lifestyle-modification counseling consistent with current guidelines for weight management (Jensen et al. 2014). Specifically, participants will consult with a dietician, or equivalent qualified delegate, throughout the study to achieve an approximately 500 kcal/day energy deficit through a combination of caloric restriction and increased physical activity (see Section 5.3).

The planned duration of treatment for the primary endpoint at 88 weeks allows for a 52-week treatment period at the dose achieved following dose escalation to either 10 mg or 15 mg. This duration is considered appropriate to assess the full effects and balance of risk and benefit for tirzepatide MTD compared with placebo on body weight and is consistent with regulatory guidelines (FDA 2007; EMA 2016).

The effects of study intervention cessation will be assessed in the 4-week safety follow-up/observational period. 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.

4.3. Justification for Dose

Tirzepatide MTD (10 mg or 15 mg QW) will be evaluated in this study. These doses and associated escalation schemes were selected based on assessment of safety, efficacy (weight loss), and GI tolerability data in Phase 1 and 2 studies in patients with T2DM, followed by exposure-response modeling of the data that predicted weight loss in patients with overweight or obesity.

In a 26-week, Phase 2 study (GPGB) of participants with T2DM, tirzepatide reduced body weight by 4.8 kg, 8.7 kg, and 11.3 kg at dose levels of 5, 10, and 15 mg, respectively, whereas the weight loss observed in participants on dulaglutide, a selective GLP-1R agonist, used at the dose of 1.5 mg, was 2.7 kg (Frias et al. 2018).

Similar to the GLP-1R agonist class, most of the tirzepatide AEs were dose-dependent and GI-related, consisting mainly of nausea, vomiting, and diarrhea. In general, these events were mild or moderate in severity, with few severe episodes, and transient.

Tirzepatide doses of 10 mg and 15 mg were selected based principally on the following criteria:

- each dose provides robust weight loss relative to placebo
- the percent of patients achieving ≥10% is higher with 15 mg than 10 mg, and
- safety and tolerability were supported by Phase 2 results and/or PK/PD modeling.

Dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5-mg increments every 4 weeks should permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns. The maximum proposed dose of 15 mg maintains an exposure multiple of 1.6 to 2.4 to the no-observed adverse effect level doses in 6-month monkey and rat toxicology studies.

4.4. End of Study Definition

Section 7.2 describes the criteria used to determine if a participant has completed the study.

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

5. Study Population

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

5.1. Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Have a BMI of:
    - ≥30 kg/m^2 or
    - ≥27 kg/m^2 and previously diagnosed with at least 1 of the following weight-related comorbidities:
        - Hypertension: treated or with systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg
        - Dyslipidemia: treated or with 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
        - Obstructive sleep apnea
        - Cardiovascular disease (for example, ischemic cardiovascular disease, New York Heart Association [NYHA] Functional Classification Class I-III heart failure)
2. Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight
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)
    - follow study procedures for the duration of the study, including, but not limited to, following lifestyle advice (for example, dietary restrictions, exercise plan), maintaining a study diary, and completing required questionnaires

Participant Characteristics

4. Are at least 18 years of age and age of majority per local laws and regulations

a. Male participants:
   - Male participants with partners of childbearing potential should be willing to use reliable contraceptive methods throughout the study and for 5 half-lives of study drug plus 90 days, corresponding to 4 months after the last injection

b. Female participants:
   - Female participants not of childbearing potential may participate and include those who are:
     - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) or congenital anomaly (such as Mullerian agenesis)

       or
     - Postmenopausal – defined as either:
       - A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause AND a follicle-stimulating hormone (FSH) ≥40 mIU/mL; women in this category must test negative in pregnancy test prior to study entry

         or
       - A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea

         or
       - A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

   - Female participants of childbearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must
     - test negative for pregnancy at Visit 1 based on a serum pregnancy test
     - if sexually active, agree to use 2 forms of effective contraception, where at least 1 form is highly effective for the duration of the trial plus 30 days, corresponding to 2 months after the last injection, and
     - not be breastfeeding

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

Informed Consent

5. 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 study enrollment if they meet any of the following criteria:

Medical Conditions

Diabetes-Related

6. Have Type 1 diabetes mellitus (T1DM) or T2DM, history of ketoacidosis, or hyperosmolar state/coma
7. Have at least 1 laboratory value suggestive of diabetes mellitus during screening, including 1 or more of: HbA1c ≥6.5% (≥48 mmol/mol), fasting glucose ≥126 mg/dL (≥7.0 mmol/L), and random glucose ≥200 mg/dL (≥11.1 mmol/L)

Obesity-Related

8. Have a self-reported change in body weight >5 kg within 3 months prior to screening
9. Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty if performed >1 year prior to screening)
10. 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

    Examples:

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

Other Medical

11. Have renal impairment measured as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory during screening
12. 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
13. Have a history of chronic or acute pancreatitis
14. Have thyroid-stimulating hormone (TSH) outside of the range of 0.4 to 6.0 mIU/L at the screening visit

    Note: Participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 3 months and their TSH at screening falls within the range indicated above.

    Note: Participants with a history of subclinical hypothyroidism but a TSH at screening within the range indicated above, may be included if, in the investigator's opinion, the

patient is unlikely to require initiation of thyroid hormone replacement during the course of the study.

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

16. 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.

17. Have a lifetime history of suicide attempt

18. Have a PHQ-9 score of 15 or more on or before Visit 2

19. On the C-SSRS on or before Visit 2:

    - 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

20. Have uncontrolled hypertension (systolic blood pressure above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg)

21. Have any of the following cardiovascular conditions within 3 months prior to Visit 2

    - acute myocardial infarction
    - cerebrovascular accident (stroke)
    - unstable angina
    - hospitalization due to congestive heart failure (CHF)

22. Have NYHA Functional Classification Class IV CHF

23. Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or any of the following, as determined by the central laboratory during screening:

- alanine aminotransferase (ALT) level >3.0X upper limit of normal (ULN) for the reference range
- alkaline phosphatase (ALP) level >1.5X ULN for the reference range, or
- total bilirubin (TBL) level >1.2X ULN for the reference range (except for cases of known Gilbert's Syndrome)

Note: Participants with NAFLD are eligible to participate in this trial if their ALT level is ≤3.0X ULN for the reference range

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

    - ≥20 ng/L, if eGFR ≥60 mL/min/1.73 m^2
    - ≥35 ng/L, if eGFR <60 mL/min/1.73 m^2

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

26. 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

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

28. 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

29. Have 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.

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

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

Prior/Concomitant Therapy

32. Are receiving or have received within 3 months prior to screening chronic (>2 weeks or >14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, 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, intra-articular, or inhaled preparations) during the course of the study

33. Have current or history of (within 3 months prior to Visit 2) treatment with 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), or
    - lithium

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

34. Have taken, within 3 months prior to Visit 2, medications (prescribed or over-the-counter) or alternative remedies that promote weight loss

    Examples include, but are not limited to:

    - Saxenda (liraglutide 3.0 mg)
    - Xenical®/Alli® (orlistat)
    - Meridia® (sibutramine)
    - Acutrim® (phenylpropanolamine)
    - Sanorex® (mazindol)
    - Apidex® (phentermine)
    - BELVIQ® (lorcaserin)
    - Bontril® (phendimetrazine)
    - Qsymia™ (phentermine/topiramate combination), or
    - Contrave® (naltrexone/bupropion)

    Note: Use of metformin or any other glucose-lowering medication, whether prescribed for polycystic ovary syndrome (PCOS) or diabetes prevention, is not permitted.

35. Have started implantable or injectable contraceptives (such as Depo Provera®) within 18 months prior to screening

Prior/Concurrent Clinical Study Experience

36. 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

37. 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

38. Have previously completed or withdrawn from this study or any other study investigating tirzepatide after receiving at least 1 dose of IP

Other Exclusions

39. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

40. Are Lilly employees

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), participants will consult with a dietician, or equivalent qualified delegate, according to local standards, to receive lifestyle management counseling at Weeks 0, 4, 8, and 12 during dose escalation and then at Weeks 24, 36, 40, 52, 64, 76, and 88.

Diet and exercise goals established during the lifestyle consultation and the importance of adherence to the lifestyle component of the trial will be reinforced at each trial contact by study staff.

5.3.1. Meals and Dietary Restrictions

At Visit 2 and subsequent visits, study participants will receive dietary counseling by a dietitian, or equivalent qualified delegate, according to local standard. Dietary counseling will consist of advice on healthy food choices and focus on calorie restriction using a hypocaloric diet with macronutrient composition of:

- maximum 30% of energy from fat,
- approximately 20% of energy from protein,
- approximately 50% of energy from carbohydrates, and
- an energy deficit of approximately 500 kcal/day compared to the participant's estimated total energy expenditure (TEE).

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

The hypocaloric diet will be continued throughout the treatment period. If a BMI $\leq$22 kg/m^2 is reached, the recommended energy intake should be recalculated with no kcal deficit for the remainder of the trial.

Total energy expenditure is calculated by multiplying the estimated basal metabolic rate (BMR) (see table below) with a Physical Activity Level value of 1.3 (Food and Agriculture Organization of the United Nations/World Health Organization [WHO]/United Nations University 2004), which reflects an inactive lifestyle. This calculation provides a conservative estimate of caloric requirements:

TEE (kcal/day) = BMR X 1.3

Equations for Estimating BMR in kcal/Day*

Sex	Age	BMR (kcal/day)
Men	18 to 30 years	15.057 X actual weight in kg + 692.2
	31 to 60 years	11.472 X actual weight in kg + 873.1
	>60 years	11.711 X actual weight in kg + 587.7
Women	18 to 30 years	14.818 X actual weight in kg + 486.6
	31 to 60 years	8.126 X actual weight in kg + 845.6
	>60 years	9.082 X actual weight in kg + 658.5

Abbreviation: BMR = basal metabolic rate; FAO = Food and Agriculture Organization of the United Nations; UNU = United Nations University; WHO = World Health Organization.
*Revised WHO equations (adapted from: FAO/WHO/UNU 2004).

5.3.2. Physical Activity

At Visit 2 and all subsequent visits, participants will be advised to increase their physical activity to moderate intensity (for example, brisk walking) for at least 150 minutes per week.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not 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.

6.1. Study Intervention(s) Administered

ARM Name	Tirzepatide MTD	Placebo
Dose	10 mg or 15 mg QW	N/A
Route of Administration	SC	
Sourcing	Provided centrally by the sponsor and dispensed via IWRS	
Packaging and Labeling	Study intervention will be provided in autoinjectors (single-dose pens) packaged in cartons to be dispensed. Clinical study materials will be labeled according to country regulatory requirements.	

Abbreviations: IWRS = interactive web-response system; MTD = maximum tolerated dose; N/A = not applicable; QW = once weekly; SC = subcutaneous.

There are no restrictions on the time of day each weekly dose of study drug is given, but it is advisable to administer the SC injections on the same day and same time each week. The actual date, time, and injection-site location of all dose administrations will be recorded in the diary by the participant. 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, in which case that dose should be skipped, and the next dose should be taken at the appropriate 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 in the abdomen or thigh using the injection supplies provided; a caregiver may administer the injection in the participant's upper arm. The injection-site location of all dose administrations will be recorded in the diary by the participant. A new autoinjector will be used for each injection. If study drug is to always be injected in the same body region, participants should be advised to rotate injection sites each week.

6.1.1. Medical Devices

The combination products provided for use in the study are tirzepatide investigational autoinjector (or matching placebo). Any AE resulting from device deficiencies, misuse, or malfunctions must be detected, documented, and reported by the investigator throughout the study (see Section 10.4.3).

6.2. Preparation/Handling/Storage/Accountability

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind, randomized study.

Participants will undergo a 36-week open-label tirzepatide lead-in treatment period. Those who successfully complete the lead-in period (reaching either a 10-mg or 15-mg dose) will be randomized (1:1) in a double-blind fashion to either continue tirzepatide at MTD or switch to placebo for the duration of the double-blind treatment period. Assignment to treatment groups will be determined by a computer-generated random sequence using the interactive web-response system (IWRS).

The randomization will be stratified by country, sex (female, male), tirzepatide MTD dose at 36 weeks (10 mg versus 15 mg), and percent weight loss at 36 weeks (<10% versus ≥10%).

Investigators, site staff, clinical monitors, and participants will remain blinded to the treatment assignments of the double-blinded treatment period until the study is complete.

Emergency unblinding for AEs 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 emergency 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 Lilly clinical research physician (CRP) for the participant to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit.

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 cartons at the next office visit to the study site for the purpose of performing drug accountability.

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

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 diaries, and any other parameters the investigator considers necessary.

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

6.5. Concomitant Therapy

Participants will be permitted to use concomitant medications that they require during the study, except certain medications (for example, other medications for weight management, see Section 5.2) that may interfere with the assessment of efficacy and safety characteristics of the study treatments.

Participants who develop diabetes during the study may initiate medication for glucose control, with the exception of dipeptidyl-peptidase-4 (DPP-4) inhibitors or GLP-1R agonists. Initiation of metformin for the treatment of diabetes is permitted, but metformin should not be initiated during the study for the treatment of other metabolic conditions (for example, PCOS, diabetes prevention). Management of incident diabetes should be performed by participants' usual care providers.

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.

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

6.6. Dose Modification

6.6.1. Tirzepatide

Tirzepatide is given QW by SC injection. There are no restrictions on the time of day each weekly dose of tirzepatide is given, but it is advisable to administer the SC injections on the same day of the week and similar time each week. If a dose of tirzepatide is missed, the participant should take it as soon as possible unless it is within 72 hours of the next dose, in which case, that dose should be skipped and the next dose should be taken at the appropriate time (see Section 6.1).

Study drug dose modification is not permitted, except for management of intolerable GI symptoms during the 36-week lead-in period (see Section 6.6.2).

6.6.2. Management of Participants with Gastrointestinal Symptoms

Participants who experience intolerable GI symptoms (for example, nausea, vomiting, or diarrhea) at any time during the study, should first be counseled on dietary behaviors that may help mitigate nausea and vomiting (for example, eating smaller meals, splitting 3 daily meals into 4 or more smaller ones, and stopping eating when they feel full). If symptoms persist, the participant should be prescribed, at the investigator's discretion, symptomatic medication (for example, antiemetic or antidiarrheal medication). A temporary interruption of study drug for 1 dose is permitted, provided the participant has taken the last 3 weekly doses. Study treatment should be resumed immediately, either alone or in combination with symptomatic medication, which can also be utilized to manage symptoms. Management of study drug after interruptions >1 dose is discussed in Section 7.1.1.

During the 36-week open-label tirzepatide lead-in treatment period, if intolerable GI symptoms (for example, nausea, vomiting, or diarrhea) persist despite the above measures, the investigator should contact Lilly to consider a dose de-escalation step with subsequent re-escalation (Section 4.1.1.2.2). During the 52-week, post-randomization treatment period, dose de-escalation with subsequent re-escalation or dose de-escalation to a lower maintenance dose is not permitted. Those with intolerable GI symptoms that develop after randomization and persist despite the above measures (for example, dietary counseling, symptomatic medication, and interruption of study drug for 1 dose) should discontinue study drug but remain in the study for continued follow-up.

6.7. Intervention after the End of the Study

Tirzepatide 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 intervention. If study intervention is definitively discontinued during the open-label lead-in period, the participant will not be randomized and will be permanently discontinued from study. If study intervention is definitively discontinued after randomization, the participant will remain in the study to be evaluated for any trial endpoint at the end of the study. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Possible reasons leading to permanent discontinuation of study intervention:

- **Participant decision**
  - The participant requests to discontinue study intervention
- **Clinical considerations**
  - Initiation of open-label GLP-1R agonist or DPP-4 inhibitor, if participant will not or cannot discontinue them
  - Intolerable GI symptoms despite management as described in Section 6.6.2
  - BMI ≤18.5 kg/m^2 is reached at any time during the treatment period

    Note: The investigator should contact the sponsor CRP to discuss whether it is medically appropriate for the participant to continue study treatment.

  - Diagnosis of T1DM
  - Diagnosis of MTC or MEN syndrome type 2
  - Significant elevation of calcitonin (Section 8.3.2.4)
  - 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)
  - If the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction has occurred related to study drug administration, the participant should be permanently discontinued from the investigational drug
  - Onset of pregnancy in a female participant
  - Occurrence of any other 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
  - Inadvertent enrollment if continued treatment with study drug would not be medically appropriate
  - 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 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 intervention due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF
  - Discontinuation of the study intervention for abnormal liver tests **should be** considered by the investigator when a participant meets one of the following conditions after consultation with the Lilly-designated medical monitor:
    - ALT or aspartate aminotransferase (AST) >8X ULN
    - ALT >2X baseline value **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 upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Participants who stop the study drug permanently postrandomization and prior to 88 weeks should continue to attend all scheduled study visits to collect all planned efficacy and safety

measurements. Participants who stop the study treatment postrandomization and prior to 88 weeks, but are unwilling to attend remaining scheduled visits, should return for Visit 99 for a final weight measurement. If these participants are unwilling to attend Visit 99, their refusal to attend should be documented in the patient medical record.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

In certain situations, the investigator may need to temporarily interrupt study drug. Every effort should be made by the investigator to maintain participants on study drug and to restart study drug after any temporary interruption, as soon as it is safe to do so. Distribution of study medication at the correct dose will be per IWRS instructions.

If study drug interruption is….	and…	then participant…
2 consecutive doses or less	occurs between Weeks 0 and 36	restarts study drug at last administered dose, as per escalation schedule.
2 consecutive doses or less	occurs between Weeks 36 and 88	restarts study drug at chosen MTD at randomization.
3 consecutive doses or more	occurs between Weeks 0 and 36	is not randomized and will be discontinued from study.
3 consecutive doses or more	occurs between Weeks 36 and 88	restarts study drug at 5 mg and repeats dose-escalation scheme to achieve the same MTD assigned at randomization.

Abbreviation: MTD = maximum tolerated dose.

If study drug interruption is due to an AE, then the event is to be documented and followed according to the procedures in Section 10.4 of this protocol.

If study drug interruption is due to intolerable persistent GI AE, participants should be treated as suggested in Section 6.6.2.

Investigators should inform Lilly 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.

7.2. Participant Discontinuation/Withdrawal from the Study

To minimize the amount of missing data and to enable assessment of study objectives as planned in the study protocol, every attempt will be made to keep randomized participants in the study irrespective of the following:

- adherence to or discontinuation from study drug

- adherence to visit schedule
- missing assessments
- study drug discontinuation due to AE
- development of comorbidities
- development of clinical outcomes

The circumstances listed above are ***not*** valid reasons for discontinuation from the study.

A participant may withdraw from the study:

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

A participant will withdraw from the study:

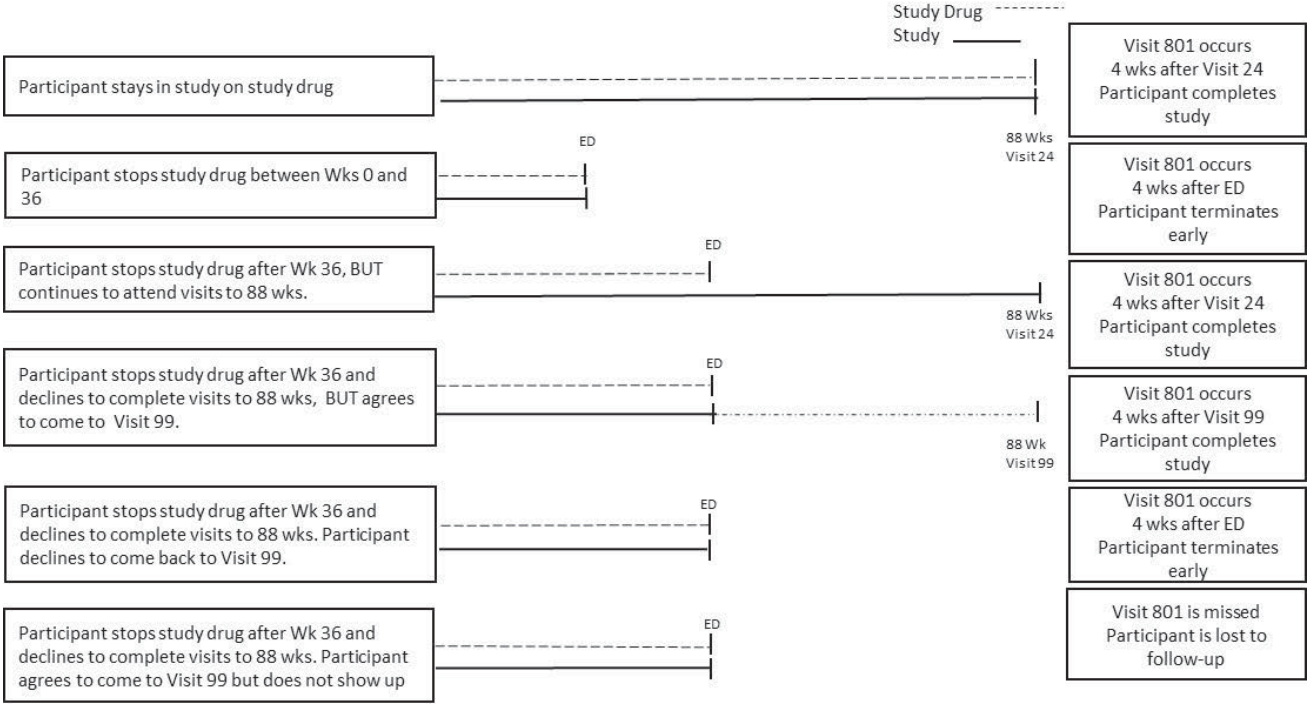
- if a female participant becomes pregnant
- if study intervention is definitively discontinued during the open-label lead-in period, the participant will not be randomized and will be permanently discontinued from study.

Participation in the study can be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). Participants who agree to provide information relevant to any trial endpoint at the end of the study are not considered to have discontinued from the study.

At the time of discontinuing from the study, if possible, an ED 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/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Participant Disposition and Timing of Safety Follow-Up



Abbreviations: ED = early discontinuation; Wk = Week; wks = weeks.

7.2.2. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, the investigator and the sponsor CRP must agree whether continuing the study treatment is medically appropriate. Continuation of inadvertently enrolled participants in the study, with or without study drug treatment, requires documented approval from the sponsor CRP. Safety follow-up should be performed as outlined in Section 1.3 (SoA), Section 8.3 (Adverse Events, Serious Adverse Events, and Product Complaints), and Section 8.2 (Safety Assessments) of the protocol.

7.3. Lost to Follow-up

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

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get IP. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented, and the participant will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

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

8. Study Assessments and Procedures

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

8.1.1. Primary Efficacy Assessments

The primary efficacy measurement in this study 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 10.7.

8.1.2. Secondary Efficacy Assessments

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

- BMI (derived using body weight in kilograms divided by the square of height in meters)
- Waist circumference (measuring method is described in Section 10.7)
- Fasting insulin (measured through central lab)
- HbA1c (measured through central lab)
- Fasting glucose (measured through central lab)
- Blood pressure (measuring method is described in Section 10.7)
- Lipids (measured through central lab)

8.1.3. Patient-Reported Outcomes Assessments

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

8.1.3.1. Short Form-36 Version 2 Health Survey Acute Form, 1-Week Recall Version

The SF-36 v2 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
- 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-, 5-, or 6-point scales). Scoring of each domain and both summary scores are norm-based and presented in the form of T-scores, with a mean of 50 and standard deviation (SD) of 10; higher scores indicate better levels of function and/or better health (Maruish 2011).

8.1.3.2. Impact of Weight on Quality of Life-Lite Clinical Trials Version

The IWQOL-Lite-CT is a 20-item, obesity-specific PRO instrument developed for use in obesity clinical trials. It assesses 2 primary domains of obesity-related and HRQoL: physical (7 items) and psychosocial (13 items). A 5-item subset of the physical domain, the physical-function composite is also supported. Items in the physical-function composite describe physical impacts related to general and specific physical activities. All items are rated on either a 5-point frequency ("never" to "always") scale or a 5-point truth ("not at all true" to "completely true") scale (Kolotkin et al. 2017, 2019).

8.1.3.3. EQ-5D-5L

Generic HRQoL will be assessed using the EQ-5D-5L (EuroQoL Research Foundation 2019). The EQ-5D-5L is a standardized 5-item instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, or unable to perform/extreme problems), for a total of 3125 possible health states. In addition to the health profile, a single health-state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between <0 (where 0 is a health-state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health) (Dolan 1997). In addition, the EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated (0 to 100) scale. In conjunction with the health-state data, it provides a composite picture of the respondent's health status.

The EQ-5D-5L is used worldwide and is available in more than 170 different languages. Details on the instrument, and scoring, organizing, and presenting the data collected can be found in the EQ-5D-5L User Guide (EuroQoL Research Foundation 2019).

8.1.3.4. Patient Global Impression of Status for Physical Activity

Study participants will be asked to complete a PGIs 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."

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems, as well as thyroid exam. Height, weight, and waist circumference will also be measured and recorded, per Section 10.7.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, vital signs should be measured according to the SoA (see Section 1.3) and Section 10.7.

Any clinically significant findings from vital sign measurements that result in a diagnosis should be reported to Lilly or its designee as an AE via the eCRF.

8.2.3. Electrocardiograms

For each participant, single-tracing 12-lead electrocardiograms (ECGs) should be collected according to the SoA and Section 10.7.

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 should be reported to Lilly or its designee as an AE via the eCRF.

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

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2, Appendix 2: "Clinical Laboratory Tests" for the list of clinical laboratory tests to be performed, and to the SoA for the timing and frequency.

Note: See Section 10.2, Appendix 2: "Clinical Laboratory Tests" for clinical laboratory tests reported or not reported to the investigator.

- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from nonprotocol-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, AE, or dose modification), then report the information as an AE.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

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 10.6), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyltransferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if 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 patients 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 patients with Gilbert's syndrome)

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

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 patients 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 patients with Gilbert's syndrome)

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

* 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-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 case report forms (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. Depression, Suicidal Ideation, and Behavior Risk Monitoring

Patients 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 and observed closely 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 intervention in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

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):

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints (PCs)

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For 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.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the informed consent form (ICF)	The safety follow-up visit OR participation in study has ended	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the ICF	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	The safety follow-up visit OR 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	Four months after the last injection for female partners of male participants and 2 months after the last injection for female participants	Within 24 hours of learning of the pregnancy	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
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 event.

8.3.2. Special Safety Topics

8.3.2.1. Hypoglycemia

Upon ICF signing, all participants will be educated about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia. 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 diabetes during the study will be provided with glucometers. Participants without diabetes may be given glucometers to assist in the evaluation of reported symptoms consistent with hypoglycemia at the investigator's discretion. Participants receiving glucometers will be provided a diary to record relevant information (for example, glucose values, symptoms).

All hypoglycemic episodes will be recorded on a specific eCRF (Hypoglycemic Events eCRF) and should not be recorded on the AE eCRF, 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. All posttreatment hypoglycemic events collected on the hypoglycemic eCRF will be considered as treatment-emergent and included in the analysis of incidence and rate of hypoglycemic events.

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 (American Diabetes Association 2020):

Glucose Alert Value (Level 1):

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of <70 mg/dL (<3.9 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG <70 mg/dL (<3.9 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured BG <70 mg/dL (<3.9 mmol/L).

Clinically Significant Hypoglycemia (Level 2):

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of <54 mg/dL (<3.0 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia but with a measured BG <54 mg/dL (<3.0 mmol/L).

- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available but with a measured BG <54 mg/dL (<3.0 mmol/L).

Severe hypoglycemia (Level 3):

- **Severe hypoglycemia** is defined as an episode with severe cognitive impairment, requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.

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 tirzepatide, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 2006; Koizumi et al. 2006):

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

If acute pancreatitis is suspected, the investigator should:

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

  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 diagnosed, the participant must discontinue use of the study intervention.

Case Adjudication and Data Entry

An independent clinical endpoint committee (CEC) will adjudicate all suspected cases of acute pancreatitis. In addition, AEs of severe or serious abdominal pain of unknown etiology will also

be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease.

Asymptomatic Elevation of P-Amylase and/or Lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (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 tirzepatide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

8.3.2.4. 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 participant encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude any serious adverse effect 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 participant 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 participant recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist to exclude any serious adverse effect on the thyroid.

8.3.2.5. Major Adverse Cardiovascular Events

Deaths and nonfatal cardiovascular AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment. The nonfatal cardiovascular AEs to be adjudicated include

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

8.3.2.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG, which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 10.4 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 Assessments for Hypersensitivity Events." 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 Injection Site Reaction eCRF.

At the time of AE occurrence, samples will be collected for measurement of tirzepatide antidrug antibodies (ADAs) and tirzepatide 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 biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.2.5.1.

8.3.2.11. Severe Gastrointestinal Adverse Events

Tirzepatide 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 form. For detailed information concerning the management of GI AEs, please refer to Section 6.6.2.

8.3.2.12. Acute Renal Events

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

8.3.2.13. 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. Participants will be referred to an 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

Study drug overdose (more than the specified number of injections) will be reported as an AE. In the event of an overdose, refer to the IB for tirzepatide.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Samples to assess the PD properties of tirzepatide are included in the efficacy measures and not applicable in this section.

8.7. Genetics

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

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to tirzepatide and to investigate genetic variants thought to play a role in obesity. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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 investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or Ethical Review Boards (ERBs)/Institutional Review Boards (IRBs) impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of tirzepatide or after tirzepatide becomes 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, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

8.8. Biomarkers

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

Serum and plasma samples for biomarker research (nonpharmacogenetic stored samples) 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 target, disease process, variable response to tirzepatide, pathways associated with obesity, mechanism of action of tirzepatide, and/or research method or in validating diagnostic tools or assay(s) related to obesity.

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 investigator site personnel.

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

8.9. Immunogenicity Assessments

Where local regulations and ERBs allow, blood samples for immunogenicity testing will be collected to determine antibody production against tirzepatide as specified in the SoA (Section 1.3).

For immunogenicity testing, venous blood samples will be collected from each participant according to the SoA (Section 1.3) to determine antibody production against tirzepatide. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the plasma concentrations of tirzepatide. All samples for immunogenicity should be taken predose when applicable and possible.

In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional unscheduled samples should be collected as detailed in Section 8.3.2.7 (Hypersensitivity Reactions). Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded. Samples collected at Visit 801 will assess immunogenicity at washout of tirzepatide (5 half-lives post end of treatment).

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of tirzepatide at a laboratory approved by the sponsor. Antibodies may be further characterized for their ability to neutralize the activity of tirzepatide on GIPR and GLP-1R. Positive tirzepatide ADA samples will be tested for cross-reactivity with native GIP and GLP-1, and, if positive, may then be tested for neutralizing antibodies against native GIP and/or GLP-1. In vivo laboratory indicators for effect on weight loss and PK will be utilized to detect potential neutralizing effect of ADAs against tirzepatide.

Treatment-emergent ADAs are defined in Section 9.4.5.

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 tirzepatide. Any samples remaining after 15 years will be destroyed.

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry method. Bioanalytical samples collected to measure tirzepatide concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, and/or bioanalytical method cross-validation.

8.10. Health Economics

Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The alternative hypothesis for the primary objective is the following:

H1: QW tirzepatide MTD is superior to placebo for percent change from randomization (Week 36) in body weight at 88 weeks.

The alternative hypotheses for the key secondary objectives controlling for Type 1 error rate are the following:

H2: QW tirzepatide MTD is superior to placebo for change from randomization (Week 36) in body weight (kg) at 88 weeks.

H3: QW tirzepatide MTD is superior to placebo for change from randomization (Week 36) in waist circumference (cm) at 88 weeks.

H4: QW tirzepatide MTD is superior to placebo for percentage of participants who maintain ≥80% of the body weight lost during the open-label lead-in period at 88 weeks.

H5: QW tirzepatide MTD is superior to placebo for delaying the onset of returning to >95% body weight at baseline (Week 0) during the double-blind treatment period.

H6: QW tirzepatide MTD is superior to placebo for percentage of participants who achieve ≥5% body weight reduction from Visit 2 (Week 0) at 88 weeks.

H7: QW tirzepatide MTD is superior to placebo for percentage of participants who achieve ≥10% body weight reduction from Visit 2 (Week 0) at 88 weeks.

H8: QW tirzepatide MTD is superior to placebo for percent change from randomization (Week 36) in body weight at 64 weeks.

9.2. Sample Size Determination

Approximately 1000 participants will be screened and 750 participants enrolled into the 36-week open-label tirzepatide lead-in treatment period in order to get approximately 600 participants to be randomized in a 1:1 ratio to tirzepatide MTD (300 participants) or placebo (300 participants).

The sample size determination assumes that evaluation of superiority of tirzepatide MTD to placebo will be conducted at a 2-sided significance level of 0.05 using a 2-sample t-test. Additionally, a difference of at least 6% mean body weight percentage change from randomization (36 weeks) to 88 weeks between tirzepatide MTD and placebo, a common SD of 8%, and a dropout rate of 25% are assumed for statistical power calculations. Under the assumptions above, randomizing 600 participants in a 1:1 ratio to tirzepatide MTD (300 participants) and placebo (300 participants) provides more than 90% power to demonstrate superiority of tirzepatide MTD to placebo.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent
Enrolled	All participants who are assigned to open-label tirzepatide treatment
Randomized	All participants who are randomly assigned a study treatment (double-blind)
Modified Intent-to-Treat (mITT)	All enrolled participants who are exposed to at least 1 dose of study drug.
Efficacy Analysis Set (EAS)	Data obtained during the double-blind treatment period from the mITT population, excluding data after discontinuation of study drug (last dose date + 7 days).
Full Analysis Set (FAS)	Data obtained during the double-blind treatment period from the mITT population, regardless of adherence to study drug.
Safety Analysis Set (SS)	Data obtained during the double-blind period and safety follow-up period from the mITT population, regardless of adherence to study drug.

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analysis of this study will be the responsibility of the 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 clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and all confidence intervals will be given at a 2-sided 95% level. In statistical summaries and analyses, data will be analyzed as randomized.

Unless specified otherwise, efficacy analyses will be conducted using the efficacy analysis set (EAS), and safety analyses will be conducted using the safety analysis set (SS).

Unless specified otherwise, for analyses in the double-blind treatment period, baseline is defined as the last nonmissing data collected prior to or at randomization (Week 36); for analyses in the lead-in period, baseline is defined as the last nonmissing data collected prior to or at study entry (Week 0).

Summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The analysis model to make comparisons among treatment arms relative to continuous measurements assessed over time will be a mixed-model for repeated measures (MMRM) with terms of treatment, visit, treatment-by-visit interaction, stratification factors, and baseline measurement as a covariate. An unstructured covariance structure will model the relationship of within-patient errors.

The Kaplan-Meier method will be used for estimation of cumulative event-free survival rates over time, and Cox proportional hazards regression analysis will be used to compare hazard rates among treatments.

Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Logistic regression will be used to examine the treatment difference in binary efficacy outcomes if there is a need to adjust for covariates. Otherwise, Fisher's exact test will be used to examine the treatment difference in categorical outcomes.

Summary statistics for discrete count measures will include sample size, mean, SD, median, minimum, and maximum. The negative binomial regression model will be used for the treatment comparison of discrete count measures.

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

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

A detailed description of participant disposition will be provided at the end of the study.

Frequency counts and percentages of all participants screened, enrolled, and randomized will be summarized.

Frequency counts and percentages of participants who completed the study and those who prematurely discontinued the study (and/or study drug), including reason for premature discontinuation, will be summarized for both the open-label lead-in period and the double-blind period.

A Kaplan-Meier analysis of time from randomization to premature discontinuation from study and/or study treatment during the double-blind period by treatment group will be provided.

9.4.2.2. Participant Characteristics

Demographics will be summarized for all enrolled participants.

Demographics will also be summarized by treatment group for all randomized participants.

9.4.2.3. Concomitant Therapy

Concomitant medications during the double-blind treatment period will be summarized by treatment group for all randomized participants.

Concomitant medications during the open-label lead-in treatment period may also be summarized for all enrolled participants.

9.4.2.4. Treatment Compliance

Frequency counts and percentages of participants compliant to study drug will be summarized for both the open-label lead-in period and double-blind period.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

There will be 2 estimands of interest in comparing efficacy of tirzepatide MTD with placebo.

For the FDA, the primary efficacy analysis will be guided by the "hybrid" estimand and will be conducted using the full analysis set (FAS). This assessment will analyze percent change in body weight from randomization (Week 36) to the 88-week visit using an analysis of covariance (ANCOVA). The model will include terms of treatment, stratification factors, and baseline body weight as a covariate. Missing data solely due to a pandemic or natural disaster (after other reasons for missing data are ruled out) will be considered missing at random, and missing data will be imputed using all nonmissing data of the primary outcome from the same treatment arm. Missing data of the primary outcome measurement due to all other Intercurrent Events will be imputed based on retrieved dropouts in the same treatment arm, defined as observed primary outcome measurements from participants in the same treatment group who had their efficacy assessed after early discontinuation of study drug. In cases where there are not enough retrieved dropouts to provide a reliable imputation model (for example, the model implemented by the SAS program does not converge), an alternative multiple imputation method with reference to the placebo group (that is, placebo multiple imputation) will be used. Analysis will be conducted with multiple imputations.

For all other purposes, the primary efficacy analysis will be guided by the "efficacy" estimand, which reflects efficacy prior to discontinuation of study drug and is conducted using the EAS. The primary analysis model will be an MMRM for body weight percent change over time. The response variable of MMRM will be the percent change in body weight from randomization obtained at each scheduled postbaseline visit. The independent variables are treatment group (tirzepatide MTD and placebo), visit, treatment-by-visit interaction, stratification factors, and baseline body weight as a covariate. An unstructured covariance structure will model the relationship of within-patient errors. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

9.4.3.2. Key Secondary Efficacy Analyses

- superiority of tirzepatide MTD to placebo for change from randomization (Week 36) in body weight (kg) to the 88-week visit
- superiority of tirzepatide MTD to placebo for change from randomization (Week 36) in waist circumference (cm) to the 88-week visit
- superiority of tirzepatide MTD to placebo for the percentage of participants who maintain ≥80% of the body weight lost during the open-label lead-in period to 88 weeks
- superiority of tirzepatide MTD to placebo for delaying the onset of returning to >95% body weight at baseline (Week 0) during the double-blind treatment period
- superiority of tirzepatide MTD to placebo for percentage of participants who achieve ≥5% body weight reduction from Visit 2 (Week 0) to 88 weeks
- superiority of tirzepatide MTD to placebo for percentage of participants who achieve ≥10% body weight reduction from Visit 2 (Week 0) to 88 weeks
- superiority of tirzepatide MTD to placebo for percent change from randomization (Week 36) in body weight to 64 weeks

Additional details, including analysis methods for key secondary endpoints and the strategy for controlling the overall Type 1 error rate at a 2-sided alpha of 0.05 of primary and key secondary endpoint evaluation, will be provided in the SAP.

9.4.3.3. Other Secondary Efficacy Analyses

All other efficacy analyses will be guided by the "efficacy" estimand and will be conducted using the EAS.

Efficacy outcomes during the open-label lead-in treatment period may also be summarized for all enrolled participants.

Details will be provided in the SAP.

9.4.4. Other Safety Analyse(s)

Unless specified otherwise, safety assessments will be guided by an estimand comparing the safety of tirzepatide MTD with placebo irrespective of adherence to study drug.

Safety outcomes during the open-label lead-in treatment period may also be summarized for all enrolled participants.

9.4.4.1. Study Drug Exposure

Exposure to each study treatment will be calculated for each participant and summarized. The details will be provided in the SAP.

9.4.4.2. Adverse Events

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and will be reported with Preferred Terms and System Organ Classes. Counts and proportions of participants experiencing events will be reported for each randomized treatment group, and Fisher's exact test will be used to compare the treatment groups.

The percentage of participants experiencing TEAEs, SAEs, and discontinuation due to AEs will be summarized by treatment group.

9.4.4.3. Special Safety Topics

This section includes areas of interest whether due to observed safety findings, potential findings based on drug class, or agreed upon consultation with regulatory agencies for the reasons previously mentioned.

The following AEs are adverse events of special interest (AESIs) for this study:

- severe hypoglycemia
- major adverse cardiovascular events (adjudicated); includes, but not limited to, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure
- treatment-emergent supraventricular arrhythmias and cardiac conduction disorders
- hepatobiliary disorders; includes biliary colic, cholecystitis, and other gallbladder disease
- severe GI events
- acute renal events
- MDD/suicidal behavior and ideation

- pancreatitis (adjudicated)
- C-cell hyperplasia and thyroid malignancies, and
- allergic/hypersensitivity reactions; includes injection site reactions and ADA formation.

Summaries and analyses for the incidence of AESIs will be provided. The details of analysis of AESIs will be provided in the SAP.

9.4.4.4. Other Adverse Events Assessments

9.4.4.4.1. Gastrointestinal Events

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

9.4.4.4.2. Events related to Potential Abuse Liability

Summaries and analyses for incidence of potential abuse liability TEAEs will be provided. The details will be provided in the SAP.

9.4.4.4.3. Depression, Suicidal Ideation, and Behavior

In addition to the summary of TEAEs, suicidal ideation and behavior will be assessed by the C-SSRS, and depression-related symptoms will be assessed using the PHQ-9.

The analysis details will be provided in the SAP.

9.4.4.4.4. Central Laboratory Measures, Vital signs, and Electrocardiograms

Actual values and change from randomization of central laboratory measures, vital signs, and selected ECG parameters will be summarized by treatment group at each scheduled visit.

The percentages of participants with treatment-emergent abnormal, high, or low measures (including lab, vital, and ECG parameters) at any time will be summarized and compared between treatment groups using Fisher's exact test.

The analysis details will be provided in the SAP.

9.4.5. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with treatment-emergent ADA positive (TE ADA+) to tirzepatide will be tabulated. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution (1:10) of the ADA assay 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 TE ADA+ participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies, if assessed, and crossreactivity to native GIP and GLP-1 may also be tabulated in TE ADA+ participants.

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

9.4.6. Other Analyse(s)

9.4.6.1. Health Outcomes

Analyses of actual and change from randomization in the domains and/or summary scores of PROs questionnaires will be conducted using the EAS. The details on questionnaire-specific analyses will be provided in the SAP.

Health outcomes during the open-label lead-in treatment period may also be summarized for all enrolled participants.

9.4.6.2. Subgroup Analyses for Primary Outcome

Details of the subgroup analyses will be provided in the SAP.

The following subgroup variables will be considered (but not limited to):

- age (<65 years and ≥65 years)
- sex (female and male)
- race
- ethnicity
- BMI at study entry (<30, ≥30 and <35, ≥35, and <40, ≥40 kg/m^2), and
- Percent body weight loss at 36 weeks (<10% and ≥10%).

The outcome measures for the subgroup analyses will include percent change in body weight from randomization at 88 weeks.

9.5. Interim Analyses

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

A database lock may occur after all enrolled participants complete or discontinue the 36-week open-label lead-in treatment period. This is not considered an interim lock since the enrolled participants who complete the 36-week open-label lead-in treatment period will be randomized to a double-blind, placebo-controlled treatment period, and there is no plan to modify the study based on the results from this open-label lead-in database lock.

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

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized 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 reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.3. Data Protection

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

10.1.4. Committees Structure

Prospective adjudication of major adverse cardiovascular events and pancreatic AEs will be performed for this study. Sections 8.3.2.5 and 8.3.2.2 outline additional information on cardiovascular and pancreatic adjudication committees.

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 GPHN is outlined in Section 10.1.9 and further described in the CTA.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF 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, 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 (COA) data (participant-focused outcome instrument) and other data (for example, diary) will be collected by the participant, caregiver, or 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(s) will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. 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

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

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

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

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

- 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
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, 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 assure appropriate participant therapy and/or follow-up.

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.

- The sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- The publication policy for Study GPHN is described in the CTA.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by a central lab, unless designated as local in the SoA and in the table below. 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 (Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria).
- Investigators must document their review of each laboratory safety report.
- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel and are denoted in the table below.

Clinical Laboratory Tests

Hematology[a]
Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume
Mean cell hemoglobin concentration
Leukocytes (WBC)
Neutrophils, segmented
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Urine Chemistries[a]
Albumin
Creatinine

Cystatin-C[a]

HbA1c[a]

Endocrine[a]
Calcitonin
Thyroid-stimulating hormone (TSH)

Nonpharmacogenetic Stored Samples[a,b]
Serum
EDTA plasma
P800 plasma

Pharmacogenetics Sample[a,b]
Whole blood (EDTA)

Free Fatty Acids[a]
Insulin[a]
C-Peptide[a]

Clinical Chemistry[a]
Bicarbonate
Sodium
Potassium
Total bilirubin
Direct bilirubin
Alkaline phosphatase
ALT
AST
BUN
Creatinine
Uric acid
Calcium
Glucose
Albumin
Creatine kinase

Hormones (females)
Pregnancy Test serum [a] and/or urine (local)
Follicle-stimulating hormone (FSH)[a]

Pancreas (exocrine)[a]
Pancreatic amylase
Lipase

Immunogenicity[a,b]
Anti-tirzepatide antibodies
Anti-tirzepatide antibody neutralization
Pharmacokinetic Sample for Immunogenicity

Lipid Panel[a]
Cholesterol
Triglycerides
VLDL-C
HDL-C
LDL-C[c]

Calculations[a]
eGFR (calculated by CKD-EPI equation)
UACR

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease-Epidemiology; eGFR = estimated glomerular filtration rate; EDTA = ethylenediaminetetraacetic acid; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RBC = red blood cells; UACR = urine albumin to creatinine ratio; VLDL-C = very low-density lipoprotein cholesterol; WBC = white blood cells.

a All tests will be performed by a Lilly-designated central laboratory, unless otherwise noted.

b Results will not be provided to the investigative sites.

c This value will be calculated. If triglycerides are >400 mg/dL, the direct LDL will be assayed.

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.
Tirzepatide ADAs (immunogenicity)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tirzepatide concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **Note:** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine sample for N-methylhistamine testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine N-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine sample following the event. Obtain a follow-up urine sample for N-methylhistamine testing at the next regularly scheduled visit or after 4 weeks, whichever is later.
N-methylhistamine	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
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, 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

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 unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent 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. • "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 an AE or SAE if they fulfill the definition of an AE or SAE.

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

that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of 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, 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.

g. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.4.3. Definition of a Product Complaint

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. Adverse event/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 the 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 the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 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, significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

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

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

Follow-up of AEs and SAEs

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

10.4.5. 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 contacts 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 an 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 an 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

Definitions:

Woman of Childbearing Potential
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered women of childbearing potential:

Article I. Premenarchal

Article II. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (for example, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Article III. Postmenopausal female

- A postmenopausal state is defined as either
    - A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND an FSH ≥40 mIU/mL; or
    - A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
    - A woman at least 55 years of age with a diagnosis of menopause prior to starting hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

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

Two forms of effective contraception, where at least 1 form is highly effective, will be used. Effective contraception may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. The use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Highly Effective Methods of Contraception:

- Combined oral contraceptive pill and mini pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo Provera)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total abstinence (if this is their preferred and usual lifestyle) or in a same-sex relationship with no sexual relationship with males (as part of their preferred and usual lifestyle), and agrees to maintain this status throughout trial follow-up

Note: Periodic abstinence (for example, calendar, ovulation, symptothermal, and postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

- Vasectomy – for men in clinical studies

Note*:* Implantable contraceptives and injectable contraceptives (such as Depo Provera) are only permitted if started more than 18 months prior to screening. Participants should not start these methods of contraception after being enrolled in the study.

Effective Methods of Contraception (Must Use Combination of 2 Methods):

- Male condom with spermicide
- Female condom with spermicide
- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

Men, regardless of their fertility status, with nonpregnant women of childbearing potential partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or effective method of contraception (such as diaphragms with spermicide or cervical sponge) for the duration of the study and for 5 half-lives of study drug plus 90 days, which is approximately 4 months after the last injection. Periodic abstinence (for example, calendar, ovulation, symptothermal, and postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in women of childbearing potential.

Men who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with females. In these situations, men are not required to use contraception.

Men should refrain from sperm donation for the duration of the study and for 5 half-lives of study drug plus 90 days after the last dose of study drug, corresponding to 4 months after the last injection.

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.
- 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) and indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy 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 intervention and be withdrawn from the study.

10.6. Appendix 6: 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:	IgA (Quantitative)
HAV total antibody	IgG (Quantitative)
HAV IgM antibody	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: 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 ASMA is tested.

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

10.7. Appendix 7: Protocol GPHN Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, Vital Signs, and Electrocardiogram

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2017).

Measuring Height

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

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

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

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

Measuring Weight

- Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms to 1 decimal place.
- All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.
- Body weight must be measured in fasting state. If the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting body weight measured.

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

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

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

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

Measuring Waist Circumference

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

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

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

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

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

Vital Sign Measurements

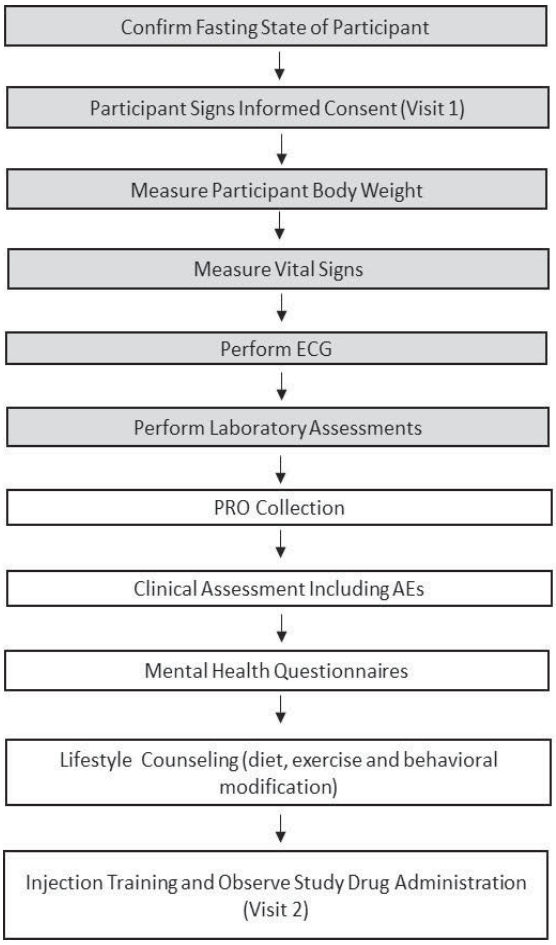
- Vital sign measurements (blood pressure and heart rate, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing.
- The participant should sit quietly for 5 minutes before vital signs measurements are taken.
- For each parameter, 2 measurements will be taken using the same arm, preferably the nondominant arm.
- The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and blood pressure needs to be recorded in the eCRF.
- Blood pressure must be taken with an automated blood pressure instrument.
- If blood pressure and pulse measurements are taken separately, pulse should be taken prior to blood pressure.

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

Electrocardiogram

- All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory.
- 12-lead ECGs should be obtained after the subject has rested in a supine position for at least 10 minutes.
- Electrocardiograms should be collected at least 30 minutes prior to collection of blood samples for laboratory testing, including immunogenicity/PK samples.

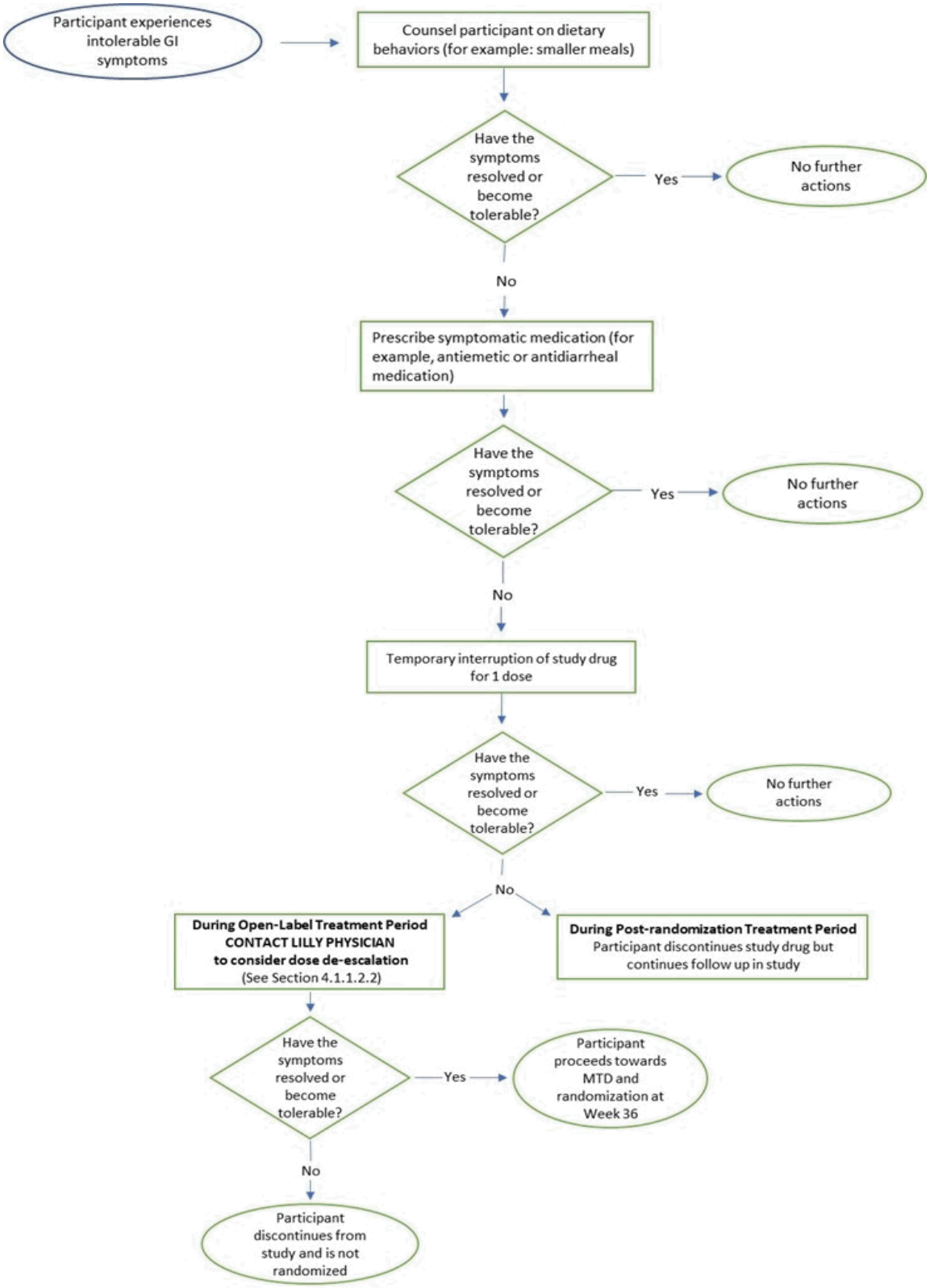
10.8. Appendix 8: Suggested Visit Structure



- Activities should be performed in the following order at the specified visits in the SOA
- Shaded areas are activities performed in a fasted state
- Non-shaded areas do not require fasting

Abbreviations: AE = adverse event; ECG = electrocardiogram; PRO = patient-reported outcome; SoA = Schedule of Activities.

10.9. Appendix 9: Management of Gastrointestinal Symptoms



Abbreviations: GI = gastrointestinal; MTD = maximum tolerated dose.

10.10. Appendix 10: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

After approval by local ERBs, 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 conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

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

Considerations for making a change

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

Informed consent

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

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

Changes in study conduct during exceptional circumstances

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

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

1. Remote visits

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

Telemedicine:
Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, concomitant medications, review of study participant diary (including study drug compliance), review diet and exercise goals, lifestyle counseling, C-SSRS (Since Last Visit Version), Self-Harm Supplement Form, Self-Harm Follow-up Form (if applicable), and 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, physical assessments, vital signs, ECG, PRO questionnaires administration, collection of blood samples and health information.

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

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

2. Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

3. Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing

protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.

- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

4. Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken prior to Visit 2 are valid for a maximum of 90 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If paused for less than 90 days from Visit 1 to Visit 2: The participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 90 days from Visit 1.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay in the CRF.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If paused for more than 90 days from Visit 1 to Visit 2: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at Visit 1 to ensure participant eligibility by Visit 2.

5. 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.

Primary endpoint visit (Visits 24 or 99) should be completed as per original schedule whenever possible and safe to do so. However, the visit windows may be brought forward no sooner than 14 days or extended up to 28 days relative to the target visit date.

For Visit 18 (key secondary endpoint visit), the visit windows may be brought forward no sooner than 7 days or extended up to 7 days relative to the target visit date, upon specific guidance from the sponsor.

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

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances.
- Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.11. Appendix 11: Abbreviations

Term	Definition
ADA	antidrug antibody
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.
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	American Medical Association
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
BMR	basal metabolic rate
CEC	Clinical endpoint committee
CFR	Code of Federal Regulations
CHF	congestive heart failure
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease-Epidemiology
CSR	clinical study report
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, GCP, and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form

CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CTA	clinical trial agreement
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl-peptidase-4
EAS	efficacy analysis set
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
enroll	The act of assigning a patient to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment. In this study enroll refers to all participants who are assigned to the open-label treatment period.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIPR	glucose-dependent insulinotropic polypeptide receptor
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor

HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
informed consent	A process by which a patient 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 patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IP	Investigational product; a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite-Clinical Trials Version
IWRS	interactive web-response system
LDL	low-density lipoprotein
MAD	multiple-ascending dose
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MEN	multiple endocrine neoplasia
MHP	mental health professional
MMRM	mixed-model for repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma

MTD	maximum tolerated dose
NAFLD	nonalcoholic fatty liver disease
NYHA	New York Heart Association
p-amylase	pancreatic amylase
PCOS	polycystic ovarian syndrome
PGIs	Patient Global Impression of status
PHQ-9	Patient Health Questionnaire-9
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
PRO	patient-reported outcome
QW	once weekly
randomized	All participants who are indiscriminately assigned a study drug.
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SF-36 v2	Short Form-36 Version 2 Health Survey
SoA	Schedule of Activities
SS	safety analysis set
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TEE	total energy expenditure

THC	tetrahydrocannabinol
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WHO	World Health Organization

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