Protocol I8F-MC-GPIF (c)

A Master Protocol to Investigate the Efficacy and Safety of Tirzepatide Once Weekly in Participants who have Obstructive Sleep Apnea and Obesity: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-OSA)

NCT05412004

Approval Date: 02-JUN-2023

Title Page

Master Protocol Title: A Master Protocol to Investigate the Efficacy and Safety of Tirzepatide Once Weekly in Participants who have Obstructive Sleep Apnea and Obesity: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-OSA)

Protocol Number: I8F-MC-GPIF
Amendment Number: c

List of Intervention-Specific Appendices (ISAs):
I8F-MC-GPI1: Participants with OSA unwilling or unable to use PAP therapy
I8F-MC-GPI2: Participants with OSA on PAP therapy

Compound: Tirzepatide (LY3298176)

Brief Title: A Master Protocol for Tirzepatide in Participants with Obstructive Sleep Apnea and Obesity

Study Phase: 3
Acronym: SURMOUNT-OSA
Sponsor Name: Eli Lilly and Company
Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number:
IND: 157090

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

Document ID: VV-CLIN-116270

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment b	*30-Sep-2022*
Amendment a	*10-Feb-2022*
Original Protocol	*27-Jan-2022*

Amendment [c]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:
This amendment includes changes made to the primary and key secondary endpoints for change in AHI and clarification around timing of the PHQ-9 assessment. Revisions were made to clarify the role of central reading of PSG scores.

Protocol changes have been made as outlined in the following table.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis and 3. Objectives, Endpoints, and Estimands	Primary Objective: Removed "percent"	To align with change made to primary endpoint. Note, the current sample size is deemed adequate for the assessment of the updated primary endpoint and all key secondary endpoints
	Primary Endpoints: Updated primary endpoint from "Percent change in AHI from baseline to Week 52" to "Change in AHI from baseline to Week 52 (events per hour)"	In response to regulatory recommendation
	Key Secondary Endpoints: Updated first endpoint from "Change in AHI" to "Percent change in AHI"	Changed to reflect revisions in endpoint hierarchy
1.3. Schedule of Activities (SoA)	"PHQ-9" row: Added additional information to Comments: "PHQ-9 at V7 and V11 may be scheduled for any day +/- 14 days."	Clarification
5.2 Exclusion Criteria	EC#44: Added glucose-lowering medication, including metformin	Clarification

Section # and Name	Description of Change	Brief Rationale
	to the list of medications prohibited within 3 months of Visit 1	
6.8.2 Prohibited Concomitant Medications	Added glucose-lowering medication, including metformin to the list of prohibited concomitant medications	Clarification
8.1.1.1 Polysomnography	Added text, "The eligibility criteria and AHI related endpoints of the study will be assessed based on central reading of the PSG."	Clarification that PSG based endpoints are based on result determined from central reading of PSG
9.1 Statistical Hypotheses	"Percent" has been removed from the description of the treatment effect definition	To align with changes made in Section 1.1 and Section 3
9.3.1 General Considerations	A statement was added to clarify that efficacy analyses will be conducted on all participants meeting study eligibility criteria	Clarifications added to ensure consistency of text in Section 9.3.1 with the table in Section 9.2
	The first intercurrent event has been updated to include incorrect study procedures leading to invalid measurements	Clarifying how invalid measurements will be handled in the analysis.
9.3.2 Primary Analysis	"Percent" has been removed when describing the primary endpoint	To align with changes made in Section 1.1 and Section 3
9.3.3 Analysis of Key Secondary Endpoints	"Percent" has been added when describing the analysis	To align with changes made in Section 1.1 and Section 3
Throughout	Editorial corrections	Minor, therefore not described

Table of Contents

1. Protocol Summary

1.1. Synopsis

Master Protocol Title: A Master Protocol to Investigate the Efficacy and Safety of Tirzepatide Once Weekly in Participants who have Obstructive Sleep Apnea and Obesity: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-OSA)

Brief Title: A Master Protocol for Tirzepatide in Participants with Obstructive Sleep Apnea and Obesity

Rationale:

Obstructive sleep apnea (OSA) is a breathing disorder associated with significant comorbidity and mortality. Currently available therapeutic approaches have shown moderate success in treating the clinical signs and symptoms of OSA (that is, snoring and excessive daytime sleepiness) but have failed to address the underlying pathophysiology of the disease and, more importantly, the cardiovascular (CV) morbidity and mortality associated with OSA.

Tirzepatide is a dual GIP/GLP-1R agonist that has demonstrated statistically significant and clinically relevant lowering in HbA1c and dose-dependent weight loss in 5 Phase 3 trials that enrolled patients with type 2 diabetes mellitus (T2DM) (Dahl et al. 2021; Frias et al. 2021; Lilly 2021; Ludvik et al. 2021; Rosenstock et al. 2021). Data from clinical studies show that a large proportion of participants have significant body weight reduction with tirzepatide treatment, suggesting that this agent may represent a promising pharmacologic treatment option that could reduce the frequency of apnea and hypopnea events as well as reduce weight, decrease blood pressure, and improve insulin resistance and dyslipidemia, which are all features associated with the increase in CV morbidity and mortality as seen in people living with OSA.

Objectives, Endpoints, and Estimands:

The following objectives and endpoints apply to both intervention-specific appendices (ISAs).

Primary Objective	**Endpoints**
To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo for mean decrease in AHI.	Change in AHI from baseline to Week 52 (events per hour).
Key Secondary Objectives (controlled for type I error)	**Endpoints**
To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo for • Change in AHI • A hierarchical assessment of PROs • Clinically meaningful change in AHI • Achieving OSA remission or mild nonsymptomatic OSA • Change in body weight • Change in inflammatory status • Change in SBP	From baseline to Week 52 • Percent change in AHI • A hierarchical combination of the following: o Change in FOSQ-10 score o Change in FOSQ (30 items) Vigilance domain score o Change in FOSQ (30 items) Activity Level domain score • Percent of participants with ≥50% AHI reduction • Percent of participants with o AHI <5 or o AHI 5-14 with ESS ≤10 • Percent change in body weight • Change in hsCRP concentration From baseline to Week 48[a] • Change in SBP

Abbreviations: AHI = Apnea-Hypopnea Index; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; hsCRP = high-sensitivity C reactive protein; MTD = maximum-tolerated dose; OSA = obstructive sleep apnea; PROs = patient-reported outcomes; SBP = systolic blood pressure; QW = once weekly.

[a] BP will be assessed at Week 48 because PAP suspension at Week 52 may confound BP assessment.

For estimands guiding statistical analyses, see Section 9.3.1.

Overall Design:

The overall study design consists of 2 components:

- Master Protocol: defines study elements common for both populations.
- ISAs: provide detailed population-specific information.

Study I8F-MC-GPIF (GPIF) is multicenter, randomized, parallel-arm, double-blind, placebo-controlled, Phase 3 study with 52-week treatment duration conducted under a basket-design, which will investigate the effects of treatment with weekly (QW) tirzepatide at the maximum

tolerated dose (MTD) (10 mg or 15 mg), compared with placebo in participants who have moderate-to-severe OSA and obesity.

One master protocol will support 2 studies/ISAs.

- ISA 1 (GPI1) will include participants who are unwilling or unable to use PAP therapy.
- ISA 2 (GPI2) will include participants who are on PAP therapy for at least 3 months at time of screening and plan to continue PAP therapy during the study.

Participants will be assigned to the ISA which reflects their current PAP usage. The participant will then be randomly assigned 1:1 to treatment or placebo.

Number of Participants:

Approximately 412 participants will be randomly assigned to study intervention across the entire master protocol, with approximately 206 participants randomly assigned to study intervention in each ISA. See Section 9.5 for additional information.

An upper limit of approximately 70% enrollment of male participants will be used to ensure a sufficiently large sample of female participants.

Intervention Groups and Duration:

The study interventions are:

- tirzepatide at the MTD (10 mg or 15 mg) SC QW, or
- placebo.

The expected total duration of study participation for each participant, including screening and the post-treatment follow-up periods, is 60 weeks across the following study periods:

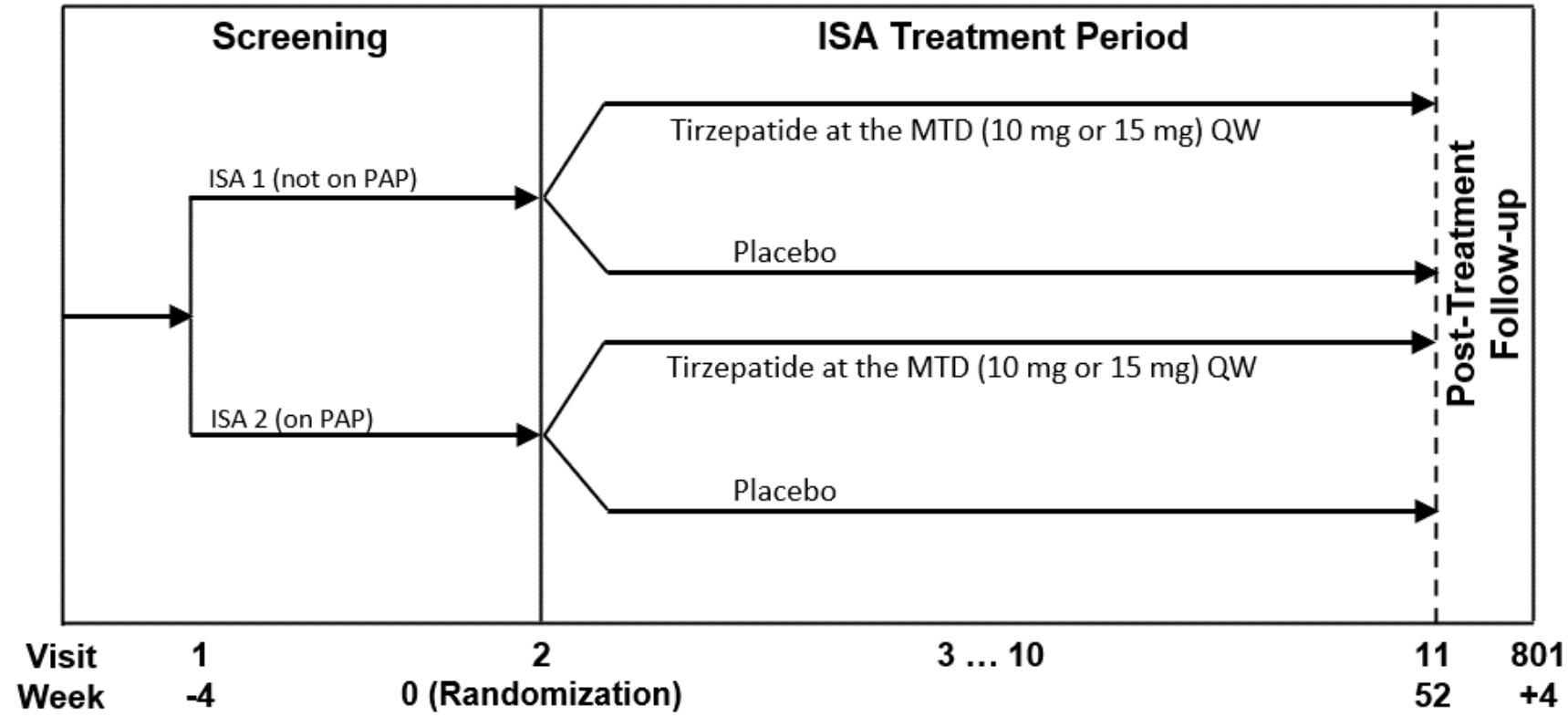
- Screening: 4 weeks
- Treatment: 52 weeks
- Post-treatment follow-up: 4 weeks

The maximum duration of treatment is 52 weeks.

Data Monitoring Committee: Yes

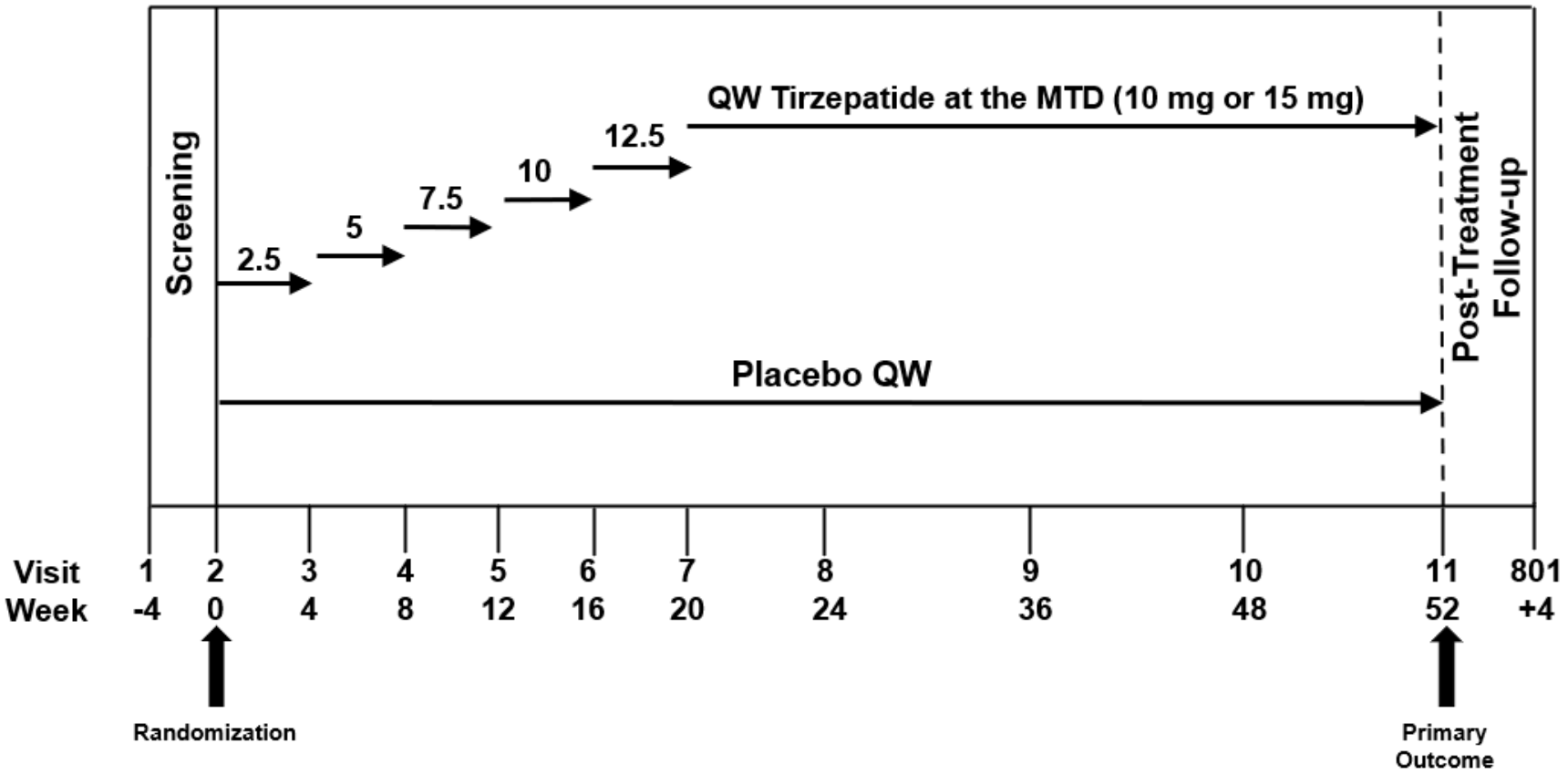
1.2. Schema

Master Protocol and ISA Schema



Abbreviations: ISA = intervention-specific appendix; MTD = maximum-tolerated dose; PAP = positive airway pressure.

Dose Escalation and Visit Schema



Abbreviations: MTD = maximum-tolerated dose; QW = once weekly.

1.3. Schedule of Activities (SoA)

If Study Period I - Screening takes longer or shorter than 4 weeks to complete, it will not be considered a protocol deviation. Study Period I - Screening should not exceed 6 weeks unless approval from the sponsor is received.

Visit procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance period of each visit.

Study Period II - Treatment: For early discontinuations (ED) from study that occur before the last visit in treatment period, see the activities listed for ED in this table.

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b.
Informed consent	X													The informed consent must be signed before any protocol-specific tests/procedures are performed.
Inclusion and exclusion criteria, review and confirm	X	X												Inclusion/Exclusion criteria should be confirmed prior to drug assignment and administration of first dose of study intervention.
Demographics	X													Includes ethnicity, year of birth, gender (sex), and race.
Preexisting conditions and medical history, including relevant surgical history	X													All conditions ongoing and relevant past surgical and medical history should be collected.
Prespecified medical history	X													Should include, but not be limited to, collecting diagnosis of OSA and obesity-related health problems.
Prior treatments for indication	X													Include OSA and obesity.
Substance use (alcohol, caffeine, tobacco use)	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 8.3.1. Additional data are collected for certain AEs.

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b.
Physical Evaluation														
Height	X													
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	Weight measurements should be obtained per the instructions in Section 10.8.
Waist circumference		X					X				X	X	X	Waist circumference should be obtained per the instructions in Section 10.8.
Hip circumference		X					X				X	X	X	Hip circumference should be obtained per the instructions in Section 10.8.
Neck circumference		X					X				X	X	X	Neck circumference should be obtained per the instructions in Section 10.8.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes PR and BP. Measured after participant has been sitting at least 5 minutes. Vital-sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing. See Sections 8.2.2 and 10.8.
Complete physical examination	X													The complete physical examination is performed (excludes pelvic, rectal, and breast examinations unless clinically indicated).
Symptom-directed physical assessment		X (refer to Comment)												Symptom-directed physical assessment from V2 through V11 and ED will be conducted at the discretion of the PI, as indicated based on participant status and standard of care.

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b.
														May be performed by qualified personnel per local regulations.
12-lead ECG (local)	X										X	X		ECG measurements should be obtained per the instructions in Section 8.2.3.
Wearable Devices and PSG Assessments														
Schedule Sleep Center Study for PSG	X					X				X				PSG results must be reviewed to confirm eligibility prior to randomization.
Sleep Center Study for PSG	X						X				X			PSG at V7 and 11 may be scheduled for any day +/- 14 days.
Participant wears the WatchPat300	X		X		X		X				X			Applicable only to participants in GPI1 (off PAP). Training documents will detail information on the dispensation, wearing, and return process.
Participant wears actigraphy (AX6) device	X		X		X		X				X			Training documents will detail information on the dispensation, wearing, and return process.
Participant Education and Supplies														
eDiary education	X													Additional training can be repeated, as needed.

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b.
Train participant on study intervention administration		X												Re-training is available anytime.
Review Lifestyle Program instructions		X	X	X	X	X	X	X	X	X	X	X		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.
Participant Diary														
Participant diary dispensed	X													Includes the following: Electronic diaries: Sleep diary; Dosing diary; Hypoglycemic events (when applicable), PAP adherence (for GPI2 only). Paper diary: Patient Diet and Exercise diary
Diary compliance check		X	X	X	X	X	X	X	X	X	X	X		
Diary return											X	X		
Patient-Reported Outcomes (Electronic) *Complete prior to any clinical-administered assessments*														
ESS	X		X		X		X				X	X		When the PROs are scheduled for visits at which the PSG will be done, they should be completed on the same day as PSG and in the following order (FOSQ, ESS, PROMIS Short Form v1.0 Sleep Disturbance 8b, PROMIS Short Form v1.0 Sleep-related Impairment 8a, PGIS, PGIC, SF-36v2 acute form, and EQ-5D-
EQ-5D-5L	X										X	X		
FOSQ	X				X		X				X	X		
PGIS (OSA Symptom Scales)	X		X		X		X				X	X		

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b.
														5L). Completing the PRO assessments on the next day after PSG is not considered a protocol violation.
PGIC (OSA Symptom Scales)			X		X		X				X	X		
PROMIS Short Form v1.0 Sleep Disturbance 8b	X		X		X		X				X	X		
PROMIS Short Form v1.0 Sleep-related Impairment 8a	X		X		X		X				X	X		
SF-36v2, acute	X						X				X	X		
PHQ-9	X	X					X				X	X		The PHQ-9 should be administered after assessment of AEs, if both collected on the same day. PHQ-9 at V7 and V11 may be scheduled for any day +/- 14 days.
Clinician-Administered Assessments (Paper)														
C-SSRS screening/baseline	X													The C-SSRS should be administered after assessment of AEs, if both collected on the same day. The C-SSRS since last visit 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		
Laboratory Tests and Sample Collections														

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b.
Hematology	X				X			X	X		X	X	X	
HbA1c	X	X			X			X	X		X	X	X	
Clinical chemistry (includes glucose)	X	X			X			X	X		X	X	X	
Lipid panel		X						X			X	X	X	
hsCRP		X						X			X	X		
Serum pregnancy	X													Only for WOCBP and females with a history of tubal ligation. See Section 10.4, Appendix 4.
Urine pregnancy (local)		X			X			X	X		X	X		A urine pregnancy test must be performed at V2 with the result available prior to first dose/injection of study intervention for WOCBP 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.
FSH	X													Optional; performed as needed to confirm postmenopausal status. See Section 10.4, Appendix 4.
Insulin		X						X			X	X	X	
C-Peptide		X						X			X	X	X	
Free fatty acids		X						X			X	X	X	

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b.
Cystatin-C	X							X			X	X	X	
Calcitonin	X										X	X	X	
Pancreatic amylase	X				X			X			X	X	X	
Lipase	X				X			X			X	X	X	
TSH	X													
eGFR	X	X			X			X	X		X	X	X	Calculated using CKD-EPI method.
UACR	X	X			X			X	X		X	X	X	
PK samples		X	X		X			X			X	X	X	PK samples to be collected predose and close to ADA samples.
Immunogenicity (ADA) samples		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 10.3.7.2 (Hypersensitivity Reactions). Immunogenicity samples and PK samples for immunogenicity must be predose.
Stored Samples														
Genetics sample		X												Sample can be obtained at or after the specified visit.
Exploratory biomarker samples		X						X			X	X	X	
Randomization and Dosing														
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b.
ISA assignment via IWRS	X													
ISA treatment randomization via IWRS		X												
Observe participant administer study intervention		X												Participants should administer their first dose of study intervention at the end of the V2, after other study procedures are completed.
Dispense study drug via IWRS		X	X	X	X	X	X	X	X	X				
Dispense study drug to participant (for at home dosing)		X	X	X	X	X	X	X	X	X				
Dispense ancillary supplies to participant		X												Dispensation of ancillary supplies may vary beyond V2 based on expiry dating of applicable supplies and/or participant needs.
Participant returns all unused study intervention			X	X	X	X	X	X	X	X	X	X		
Assess study intervention compliance			X	X	X	X	X	X	X	X	X	X		

Abbreviations: ADA = antidrug antibody; AEs = adverse events; AX6 = Axivity 6; CKD EPI = Chronic Kidney Disease Epidemiology; hsCRP = high sensitivity C-reactive protein; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol - 5 Dimension - 5 Level; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; ISA = intervention-specific appendix; IWRS = interactive web-response system; OSA = obstructive sleep apnea; PHQ = Patient Health Questionnaire-9; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Status; PK = pharmacokinetic; PSG = polysomnography; PR = pulse rate; PRO = patient reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; SF-36v2 = Short-Form 36 version 2; SoA = schedule of activities; TSH = thyroid-stimulating hormone; UACR = urinary albumin/creatinine ratio; V = visit; WOCBP = woman of childbearing potential.

a Post-treatment follow-up occurs approximately 4 weeks after the participant's final treatment period visit.

b Fasting visit: On all office visits, study participants should be reminded to report to the site before taking study intervention in a fasting condition, after a period of approximately 8 hours without eating, drinking (except minimal amount of water, as needed), or any significant physical activity.

2. Introduction

2.1. Study Rationale

Obstructive sleep apnea is a breathing disorder associated with significant comorbidity and mortality. Currently available therapeutic approaches have shown moderate success in treating the clinical signs and symptoms of OSA (that is, snoring and excessive daytime sleepiness) but have failed to address the underlying pathophysiology of the disease and, more importantly, the CV morbidity and mortality associated with OSA.

Tirzepatide is a dual GIP/GLP-1R agonist that has demonstrated statistically significant and clinically relevant lowering in HbA1c and dose-dependent weight loss in 5 Phase 3 trials that enrolled patients with T2DM (Dahl et al. 2021; Frias et al. 2021; Lilly 2021; Ludvik et al. 2021; Rosenstock et al. 2021). Data from clinical studies show that a large proportion of participants have significant body weight reduction with tirzepatide treatment, suggesting that this agent may represent a promising pharmacologic treatment option that could reduce the frequency of apnea and hypopnea events as well as reduce weight, decrease BP, and improve insulin resistance and dyslipidemia, which are all features associated with the increase in CV morbidity and mortality as seen in people living with OSA.

2.2. Background

Obstructive sleep apnea is a serious medical condition with a limited number of therapeutic options and high unmet need. OSA is a well-established risk factor for morbidity and mortality from CV and other metabolic diseases; further, it negatively affects daily life of patients (Tietjens et al. 2019; Gottlieb and Punjabi 2020).

Treatments for OSA include behavioral measures like weight loss programs, medical devices such as PAP, oral appliances or hypoglossal nerve stimulation, and surgery, including bariatric surgery in people living with obesity and OSA. Weight loss through caloric restriction and lifestyle interventions improves AHI, cardiometabolic comorbidities, and quality of life. Although a limited number of studies have investigated the effect of pharmacological weight-loss therapy, their results support that adding weight-loss medication to lifestyle intervention reduces AHI and improves sleep quality and possibly other OSA-related outcomes. As such, standard of care recommends a prioritization of weight loss for patients with OSA and obesity or who are overweight, including consideration for FDA-approved antiobesity pharmacotherapy (Hudgel et al. 2018). Bariatric surgery is available for patients with severe obesity and can dramatically improve OSA (Currie et al. 2021). However, such surgical procedures are associated with greater risk for perioperative and postoperative complications (Opperer et al. 2016).

Positive airway pressure is the first-line treatment for moderate-to-severe and symptomatic mild OSA. Despite good clinical efficacy for the signs and symptoms of OSA, randomized controlled studies in PAP therapy have failed to show improvements in nonsleep-related outcomes linked to OSA such as stroke, heart attack, diabetes and depression (AHRQ 2021). It is thought inadequate PAP therapy adherence may explain why randomized clinical trials have failed to demonstrate benefit (Gottlieb and Punjabi 2020). Nonadherence to PAP therapy is a major clinical challenge

and studies have shown wide variability in adherence, ranging from 29% to 83% (Weaver and Grunstein 2008). Currently, there are only few pharmacologic alternatives indicated for symptoms in patients with OSA and none are disease modifying.

There is significant unmet need in treatment of patients with OSA. Tirzepatide, a GIP and GLP-1R dual agonist, has the potential to provide benefit to patients with OSA who have obesity by reducing weight, which may reduce the frequency of apnea and hypopnea events, decreasing BP, and improving insulin resistance and dyslipidemia.

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 IB.

3. Objectives, Endpoints, and Estimands

The following objectives and endpoints apply to both ISAs.

Primary Objective	**Endpoints**
To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo for mean decrease in AHI.	Change in AHI from baseline to Week 52 (events per hour).
Key Secondary Objectives (controlled for type I error)	**Endpoints**
To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo for • Change in AHI • A hierarchical assessment of PROs • Clinically meaningful change in AHI • Achieving OSA remission or mild nonsymptomatic OSA • Change in body weight • Change in inflammatory status • Change in SBP	From baseline to Week 52 • Percent change in AHI • A hierarchical combination of the following: o Change in FOSQ-10 score o Change in FOSQ (30 items) Vigilance domain score o Change in FOSQ (30 items) Activity Level domain score • Percent of participants with ≥50% AHI reduction • Percent of participants with o AHI <5 or o AHI 5-14 with ESS ≤10 • Percent change in body weight • Change in hsCRP concentration From baseline to Week 48[a] • Change in SBP
Other Secondary Objectives	**Endpoints**
To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo for • Change in excessive daytime sleepiness • Change in patient-reported functional status as assessed by FOSQ (30 items) • Change in body weight	From baseline to Week 52 • Change in ESS score • Change in all other FOSQ domain scores • Percent of participants who achieve o ≥10% body weight reduction o ≥15% body weight reduction o ≥20% body weight reduction

• Change in lipid parameters	• Change in
	  ○ HDL-cholesterol
	  ○ non-HDL-cholesterol
	  ○ triglycerides

• Change in PROs	• Change in:
	  ○ PROMIS Sleep-related impairment short form 8a score
	  ○ PROMIS Sleep disturbance short form 8b score
	  ○ SF-36v2 acute form domain scores
	• Percent of participants with improved categorical shift in:
	  ○ PGIS-OSA Sleepiness
	  ○ PGIS-OSA Fatigue
	  ○ PGIS-OSA Snoring

• Insulin • Hypoxic burden • Change in DBP	• Change in fasting insulin • Change in SASHB (% min/hour) From baseline to Week 48[a] • Change in DBP
Exploratory Objectives	**Endpoints**

To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo for
• Change in PROs
	From baseline to Week 52
	• Change in
	  ○ EQ-5D-5L utility index
	  ○ EQ-VAS scores
	• Percent of participants with improved categorical shift in:
	  ○ PGIC-OSA Sleepiness
	  ○ PGIC-OSA Fatigue
	  ○ PGIC-OSA Sleep quality
	  ○ PGIC-OSA Snoring

• To evaluate the effect of tirzepatide on sleep parameters as measured by Actigraphy (AX6)	• Mean change from baseline to endpoint assessment in
	  ○ Daytime sleep duration
	  ○ Daily step counts
	  ○ Average acceleration

Abbreviations: AHI = Apnea-Hypopnea Index; AX6 = Axivity 6; DBP = diastolic blood pressure; ESS = Epworth Sleepiness Scale; EQ-5D-5L = EuroQol - 5 Dimension - 5 Level; EQ-VAS = EuroQol Visual Analogue Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; HDL = high-density lipoprotein; hsCRP = high-sensitivity C reactive protein; MTD = maximum-tolerated dose; OSA = obstructive sleep apnea; PGIC-OSA = Patient Global Impression of Change – Obstructive Sleep Apnea; PGIS-OSA = Patient Global Impression of Status – Obstructive Sleep Apnea; PROs = patient-reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; SBP = systolic blood pressure; SF-36v2 = Short-Form 36 version 2, SASHB = sleep apnea-specific hypoxic burden; QW = once weekly.

[a] BP will be assessed at Week 48 because PAP suspension at Week 52 may confound BP assessment.

For estimands guiding statistical analyses, see Section 9.3.1.

4. Study Design

4.1. Overall Design

Study I8F-MC-GPIF (GPIF) is a multicenter, randomized, parallel-arm, double-blind, placebo-controlled Phase 3 study to evaluate the efficacy and safety of tirzepatide at the MTD (10 mg or 15 mg) QW versus placebo in participants who have obesity and moderate-to-severe OSA.

This basket-type master protocol will investigate 2 participant populations, described in 2 ISAs:

- GPI1 will include participants who are unwilling or are unable to use PAP therapy.
- GPI2 will include participants who are on PAP therapy for at least 3 months at time of screening and plan to continue PAP therapy during the study.

Participants to be assigned to whichever ISA they qualify for. Participants will then be randomly assigned to:

- tirzepatide at the MTD (10 mg or 15 mg) SC QW, or
- placebo.

The expected total duration of study participation for each participant, including screening and the post-treatment follow-up periods, is 60 weeks across the following study periods:

- Screening: 4 weeks
- Treatment: 52 weeks
- Post-treatment follow-up: 4 weeks

The maximum duration of treatment is 52 weeks. Procedures and assessments for each visit are presented in the SoA, Section 1.3.

4.2. Scientific Rationale for Study Design

The basket trial design employs a single overarching trial structure as a means to implement multiple investigations (Woodcock and LaVange 2017). Such approaches often allow for more streamlined and coordinated clinical trial logistics and consistency in data collection methods.

The 2 studies associated with the master protocol, also called “Intervention-Specific Appendices” (ISAs), will describe any objectives, endpoints and efficacy assessments specific to each study population. ISA refers to specific population and background intervention, as defined by inclusion criteria. Used together, the master protocol and the 2 ISAs will describe the investigations to be conducted.

ISA 1 and ISA 2 represent different populations with different treatment needs, and it is anticipated that tirzepatide may meet the needs of each participant group.

Inclusion of a placebo treatment arm is acceptable because there are no currently effective disease-modifying treatments for OSA; this approach is in agreement with the use of placebo described in the Declaration of Helsinki (WMA 2013). The use of a placebo comparator in Study GPIF is needed to determine the efficacy and safety of tirzepatide therapy.

4.3. Justification for Dose

Tirzepatide doses of up to 15 mg administered SC QW will be evaluated in this study. Participants may be treated with lower maintenance dose of 10 mg if they do not achieve full dose escalation to 15 mg and/or do not tolerate 15 mg.

These doses and associated escalation schemes were selected based on assessment of safety, efficacy (weight loss), and GI tolerability data in Phase 1, 2, and 3 studies in patients with T2DM, followed by exposure-response modeling of the data that predicted weight loss in patients with overweight or obesity.

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.

Similar to the GLP-1RA 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 as MTD were selected based principally on the following criteria:

- each dose provides robust weight loss relative to placebo
- the percent of participants achieving ≥10% weight loss is higher with 15 mg than 10 mg, and
- safety and tolerability were supported by Phase 3 results in T2DM.

The proposed tirzepatide maintenance dose of up to 15 mg using a dose-escalation regimen is expected to safely maximize the potential for weight loss while minimizing GI tolerability concerns as has been achieved for approved GLP-1 RA drugs. The subsequent benefit of weight loss should result in clinically meaningful improvements in AHI.

4.4. End of Study Definition

A participant is considered to have completed the study if they have completed all required phases of the study including the last visit or the last scheduled procedure shown in the SoA. The end of the study for each ISA 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. The end of study timing for each ISA is independent of the other ISA end of study timing.

5. Study Population

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

5.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Previously diagnosed moderate-to-severe OSA with an AHI ≥15, as diagnosed with PSG, home sleep apnea test (HSAT), or other method that meets local guidelines prior to Visit 1. See Section 10.10 for definitions of apnea and hypopnea.
3. AHI ≥15 on PSG as part of the trial at Visit 1.
4. In the investigator's opinion, are well-motivated, capable, and willing to
   - learn how to self-inject study intervention, 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 study intervention; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject study intervention)
   - inject study intervention (or receive an injection from a trained individual if visually impaired or with physical limitations), and
   - follow study procedures for the duration of the study, including, but not limited to: follow lifestyle advice (for example, dietary restrictions and exercise plan), maintain a study diary, and complete required questionnaires.

Weight

5. BMI ≥30 kg/m^2.
6. Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight.

Sex and Contraceptive/Barrier Requirements

7. Males and females may participate in this trial.
   Female participants must not be pregnant, intending to be pregnant, breastfeeding, or intending to breastfeed.
   Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For definitions and the contraception requirements of this protocol, see Appendix 4 (Section 10.4) .

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

Diabetes-related

9. Have T1DM or T2DM, history of ketoacidosis, or hyperosmolar state/coma.
10. HbA1c ≥ 6.5% (≥ 48 mmol/mol) at Visit 1.

OSA-related

11. Any previous or planned surgery for sleep apnea or major ear, nose or throat surgery, including tonsillectomy and adenoidectomy that still may affect breathing at time of Visit 1. Inclusion of a participant with more minor ear, nose or throat surgery (for example, deviated septum) will be at the investigator's discretion.
12. Significant craniofacial abnormalities that may affect breathing at time of Visit 1.
13. Diagnosis of Central or Mixed Sleep Apnea with % of mixed or central apneas/hypopneas ≥50%, or diagnosis of Cheyne Stokes Respiration.
14. Diagnosis of Obesity Hypoventilation Syndrome or daytime hypercapnia.
15. Active device treatment of OSA other than PAP therapy (for example, dental appliance), or other treatment, that in the opinion of the investigator, may interfere with study outcomes, unless willing to stop treatment at Visit 1 and throughout the study.
16. Respiratory and neuromuscular diseases that could interfere with the results of the trial in the opinion of the investigator.

Obesity-related

17. Have a self-reported change in body weight >5 kg within 3 months prior to screening.
18. Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty if performed more than 1 year prior to screening).
19. Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months (for example, mucosal ablation, gastric artery embolization, intragastric balloon, and duodenal-jejunal bypass sleeve).

Other medical

20. History of clinically relevant medical, behavioral, or psychiatric disorder, other than OSA, that is associated with insomnia or excessive sleepiness.
21. Impaired renal function, defined as eGFR <30 mL/min/1.73 m^2.
22. 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.
23. History of chronic or acute pancreatitis.
24. Thyroid-stimulating hormone 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.
    Note: TSH values above the normal range can, in some patients, suggest subclinical hypothyroidism. If, in the investigator's opinion, the participant has subclinical

hypothyroidism and may require initiation of thyroid hormone replacement during the course of the study, the participant should be excluded from the study.

25. 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).
26. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
27. Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS **or**
    have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS,
    and the ideation or behavior occurred within the past month.
28. PHQ-9 score of 15 or more at Visit 1 or 2, prior to randomization.
29. Uncontrolled hypertension (SBP ≥160 mmHg and/or DBP ≥100 mmHg) at Visit 1.
30. Any of the following CV conditions less than 3 months prior to randomization: acute MI, cerebrovascular accident (stroke), unstable angina, or hospitalization due to congestive heart failure.
31. History of (less than 3 months prior to Visit 1) or planned CV procedure.
32. Heart failure, including New York Heart Association Functional Classification Class IV
33. Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the central laboratory during screening:
    - ALT level >3.0X the ULN for the reference range
    - ALP level >1.5X the ULN for the reference range, or
    - TBL level >1.2X the ULN for the reference range (except for cases of known Gilbert's Syndrome).

    Note: Participants with nonalcoholic fatty liver disease are eligible to participate in this trial if their ALT level is ≤3.0X the ULN for the reference range.
34. Have a calcitonin level (at Visit 1) of:
    a. ≥20 ng/L at Visit 1, if eGFR ≥60 mL/min/1.73 m^2
    b. ≥35 ng/L at Visit 1, if eGFR <60 mL/min/1.73 m^2
35. Have a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
36. 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.
37. Have any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to GLP-1R agonists.
38. 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.
39. Have history of use of marijuana less than 3 months of V1 and unwillingness to abstain from marijuana use during the trial. Participants should also refrain from use of cannabidiol oil for the duration of the study.

40. Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant.
41. Requires the use of supplemental oxygen.

Prior/Concomitant Therapy

42. 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) in the next 12 months.

43. Have current or history of (less than 3 months prior to Visit 1) treatment with medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotic and mood stabilizers, for example:

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

Note: Selective serotonin reuptake inhibitors are permitted, except for paroxetine.

44. Have taken, less than 3 months prior to Visit 1, medications (prescribed or over-the-counter) or alternative remedies intended to promote weight loss. Examples include, but are not limited to:
    - Saxenda® (liraglutide 3.0 mg)
    - Xenical®/Alli® (orlistat)
    - Meridia® (sibutramine)
    - Acutrim® (phenylpropanolamine)
    - Sanorex® (mazindol)
    - Adipex® (phentermine)
    - BELVIQ® (lorcaserin)
    - Qsymia® (phentermine/topiramate combination)
    - Contrave® (naltrexone/bupropion)
    - Pramlintide
    - Zonisamide
    - Topiramate

- Wegovy®
- Any glucose-lowering medication, including metformin

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

45. Use of stimulants less than 3 months prior to Visit 1 (for example, modafinil, armodafinil, solriamfetol, pitolisant, amphetamine, dextroamphetamine, dexmethylphenidate, methylphenidate, and lisdexamfetamine).
46. Use of hypnotics, mirtazapine, opioids, trazodone less than 3 months prior to Visit 1.
47. Use of GLP-1 RA less than 3 months prior to Visit 1.
48. Criterion 48 is deleted.
49. Use of any over-the-counter or prescription medications that could affect the evaluation of excessive sleepiness, per investigator discretion.
50. Unwillingness to discontinue over-the-counter (herbal or supplemental) medication that, in the opinion of the investigator, can interfere with the study.

Prior/Concurrent Clinical Study Experience

51. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
52. Previously randomly assigned to study intervention in this study or any other study investigating tirzepatide.
53. Have participated, within the last 30 days in a clinical trial involving a study intervention. If the previous study intervention is scientifically or medically incompatible with this study and has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to screening (participation in observational studies may be permitted upon review of the observational study protocol and approval by the sponsor).
54. Are Lilly employees or employees of third-party organizations involved with the study.
55. 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.
56. Have any medical condition that, in the opinion of the investigator, would be a contraindication to participation in the trial

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), participants will consult with study personnel experienced in diet and exercise counseling to receive lifestyle program instructions at timepoints indicated in the SoA.

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

5.3.1. Meals and Dietary Restrictions

At Visit 2 and subsequent visits, participants will consult with study personnel experienced in diet and exercise counseling to receive lifestyle program instructions at timepoints indicated in the SoA. 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
- an energy deficit of approximately 500 kcal/day compared to the participant's estimated TEE

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

The hypocaloric diet is continued after randomization and 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 (FAO/WHO/UNU 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[a]

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

Abbreviations: BMR = basal metabolic rate; WHO = World Health Organization.
[a]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 at least 150 minutes per week.

5.4. Screen Failures

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

Individuals who have history of marijuana use less than 3 months of Visit 1 may be rescreened once provided the individual is willing to abstain from marijuana use during the trial. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

See Section 5.4 of the respective ISA's for additional rescreening guidelines.

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

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Interventions Administered

Intervention Name	Tirzepatide (LY3298176)	Placebo
Type	Drug	Drug
Dose Formulation	Single-dose pen	Single-dose pen
Dosage Level(s)	10 mg QW, 15 mg QW	Not applicable
Route of Administration	SC	SC
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
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: IMP = investigational medicinal product; IWRS = interactive web-response system; NIMP = non-investigational medicinal product; QW = once-weekly; SC = subcutaneous.

There are no restrictions on the time of day each weekly dose of study intervention 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 details of all dose administrations will be recorded in the diary by the participant. If a dose of study intervention 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 intervention subcutaneously in the abdomen or thigh using the injection supplies provided; a caregiver may administer the injection in the participant's upper arm. A new autoinjector will be used for each injection. If study intervention is to always be injected in the same body region, participants should be advised to alternate injection sites each week.

6.1.1. Medical Devices

The combination products provided for use in the study are tirzepatide autoinjector (or matching placebo). Any medical-device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 10.3).

6.2. Preparation, Handling, Storage, and Accountability

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

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally randomly assigned to study intervention using an IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits summarized in SoA.

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

This is a double-blind study in which participants and study personnel, are blinded to study intervention. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately within 24 hours of this occurrence. The date and reason that the blind was broken must be recorded.

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

Stratification

Participants will be stratified at randomization per ISA by country/geographic region, baseline AHI (moderate/severe), and gender.

6.4. Study Intervention Compliance

A record of the number of single-dose pens dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

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

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. Dose Modification

Dose modification is permitted for management of intolerable GI symptoms during the first 24 weeks of the treatment period (Section 6.5.1).

Participants who do not tolerate at least 10 mg even after the described measures, including 1 de-escalation and re-escalation attempt, will be discontinued from the study intervention but remain in the study for continued follow-up.

Interventions to optimize study intervention tolerance and adherence may be employed throughout the study and include, but are not limited to, brief temporary interruptions (Section 7.1.2) and use of additional medications to manage GI symptoms (for example, nausea, vomiting, and diarrhea).

6.5.1. Management of Participants with Gastrointestinal Symptoms

In participants who experience intolerable GI symptoms (for example, nausea, vomiting, or diarrhea) at any time during the study, the following measures are recommended:

- counselling 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 despite #1, prescribing symptomatic medication (for example, antiemetic or antidiarrheal medication), at the investigator's discretion.
- if symptoms persist despite #1 and #2, interrupting study intervention for 1 dose, provided the participant has taken the last 3 weekly doses. Study treatment should be resumed at the assigned dose immediately, either alone or in combination with symptomatic medication, which can also be utilized to manage symptoms (Section 6.8).

During the first 24 weeks of the treatment period (20-week dose escalation plus 4 weeks), participants unable to tolerate 2.5 mg or 5 mg (despite the interventions mentioned above) will be discontinued from the study intervention but remain in 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 by 2.5 mg every 4 weeks in a blinded fashion, to reach either the 10-mg or 15-mg dose as described below.

Only 1 cycle of dose de-escalation and re-escalation is permitted during the first 24 weeks of the treatment period. MTD is either 10 mg or 15 mg. Dose modifications after the first 24 weeks of the treatment period are not permitted. For temporary study treatment discontinuation, see Section 7.1.2.

Participants who tolerate

- 10 mg, but do not tolerate 12.5 mg or 15 mg even following the above measures, including 1 de-escalation and re-escalation attempt, will continue on 10 mg as their MTD dose.
- 12.5 mg, but do not tolerate 15 mg even after the above measures, including 1 de-escalation and re-escalation attempt, will continue on 10 mg as their MTD dose.
- 15 mg will continue on 15 mg as their MTD dose.

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

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

6.7. Treatment of Overdose

Study intervention overdose (more than the specified number of injections in less than 72 hours) will be reported as an AE.

In the event of an overdose, the treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention no longer has a clinical effect.

6.8. Concomitant Therapy

Participants will be permitted to use concomitant medications that they require during the study, except certain medications (Section 6.8.2) that may interfere with the assessment of efficacy and safety characteristics of the study treatments.

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 randomly 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.

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

- Reason for use
- Dates of administration including start and end dates

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

6.8.1. Management of Incident Diabetes

Incident diabetes is defined when any 1 of the following occur after randomization (American Diabetes Association 2020):

- unequivocal hyperglycemia (random glucose ≥200 mg/dL) with signs or symptoms of hyperglycemia
- within a 4-week period, any 2 of the following criteria are observed or 1 abnormal value is observed and confirmed:
  - HbA1c ≥6.5% (48 mmol/mol)
  - FG or 0-hour serum glucose from 2-hour OGTT ≥126 mg/dL (7.0 mmol/L)
  - 2-hour glucose ≥200 mg/dL (11.1 mmol/L) by a 2-hour OGTT
  - initiation of any medication for the treatment of diabetes

Participants who develop type 2 diabetes during the study will be

- provided with and trained to use a glucometer
- educated on the signs and symptoms of hypoglycemia and its treatment (see Section 10.3.7.1), and
- provided a diary to record hypoglycemic episodes per Section 10.3.7.1.

Participants will be referred to their usual care provider and provided with a letter showing the study results indicative of diabetes. The decision to further evaluate, to initiate antihyperglycemic therapy, and the choice of antihyperglycemic medication will be at the discretion of the participant's usual care provider, with the exception of use of DPP-4 inhibitors and open-label GLP-1R agonists, which are prohibited in the study (Section 6.8.2). Monitoring for hypoglycemia includes capture of events as defined in Section 10.3 (Appendix 3). Date of diabetes diagnosis will be captured in the AE CRF.

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, polycystic ovary syndrome and diabetes prevention).

6.8.2. Prohibited Concomitant Medications

The following medications are prohibited during the study:

- DPP-4 inhibitors
- Open-label GLP-1R agonists
- Stimulants (for example, modafinil, armodafinil, solriamfetol, pitolisant, amphetamine, dextroamphetamine, dexmethylphenidate, methylphenidate, and lisdexamfetamine)
- medications that may cause significant weight gain (such as, but not limited to, paroxetine, tricyclic antidepressants, atypical antipsychotic and mood stabilizers).
- Medications that may cause weight loss (such as, but not limited to, liraglutide, semaglutide, orlistat, sibutramine, phenylpropanolamine, mazindol, phentermine, lorcaserin, naltrexone/bupropion, phentermine/topiramate combination, pramlintide, zonisamide, and topiramate)
- OTC, herbal, or supplemental medications that, in the opinion of the investigator, may interfere with the study
- hypnotics, mirtazapine, opioids, trazodone, pramlintide, sibutramine, orlistat, and zonisamide
- Systemic glucocorticoid therapy, per discussion with sponsor
- Use of any over-the-counter or prescription medications that could affect the evaluation of excessive sleepiness, per investigator discretion (such as, but not limited to, CBD oil, THC, etc.)
- Any glucose-lowering medication, including metformin

In addition,

- Active device treatment of OSA other than PAP therapy (for example, dental appliance), or other treatment that, in the opinion of the investigator, may interfere with study outcomes.

Participants who initiate and will not or cannot discontinue a prohibited medication, device, or other treatment will be permanently discontinued from study intervention per Section 7.1.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

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

A participant who prematurely discontinues study intervention is strongly encouraged to remain in the study for safety and efficacy assessments through the treatment period and post-treatment follow-up.

If a participant who discontinues the double-blind study treatment prematurely declines to complete the remaining scheduled study visits, then the participant should complete the early ED procedures indicated in the SoA. Participants should be encouraged to come back for the last treatment visit (Visit 11) to complete the end-of-treatment phase procedures and return for the post-treatment follow-up Visit 801.

Possible reasons leading to permanent discontinuation of study intervention:

- **participant decision**
  - the participant requests to discontinue study intervention
- **clinical considerations**
  - initiation of a prohibited medication (Section 6.8.2), if participants will not or cannot discontinue them
  - BMI ≤18.5 kg/m^2 is reached at any time during the treatment period, study intervention discontinuation should be considered
  - TEAE
    - intolerable GI symptoms despite management (Section 6.5.1)

      Note: The investigator should contact the Sponsor CRP to discuss whether it is medically appropriate for the participant to continue study treatment.
    - significant elevation of calcitonin

- If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor
- occurrence of any other TEAE, SAE, or clinically significant finding for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken

- Diagnosis of
  - T1DM
  - Thyroid C-cell hyperplasia, MTC or MEN Syndrome type 2 after randomization
  - acute or chronic pancreatitis
  - an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
- onset of pregnancy in a female participant (see Sections 7.2 and 8.3.2)
- Suicidal Ideation and Behavior
  - 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 intervention. 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 randomly assigned therapy.
  - in addition, study intervention may be discontinued if participants:
    - answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or**
    - answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant. The participant should be referred to a MHP for further evaluation and care.

7.1.1. Liver Chemistry Stopping Criteria

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

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/ discontinuation decisions rather than TBL>2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL > 2x ULN	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/ discontinuation decisions rather than TBL>2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Source: FDA 2009 and other consensus guidelines, with minor modifications

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

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

Participants who are discontinued from study intervention due to a hepatic event or liver test abnormality should have additional hepatic safety data collected as described in Section 10.6, Appendix 6.

7.1.2. Temporary Discontinuation

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

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

If study intervention interruption is…	then…
2 consecutive doses or less	participant restarts study intervention at last administered dose, as per escalation schedule.
3 consecutive doses or more	participant restarts study intervention (at 5 mg, managed by IWRS) and repeats dose escalation scheme.
Due to an AE	the event is to be documented and followed according to the procedures in Section 8.3 of this protocol.
Due to intolerable persistent GI AE	participants should be treated as suggested in Section 6.5.1.

Abbreviations: AE = adverse event; GI = gastrointestinal; IWRS = interactive web-response system.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- a participant will be withdrawn from the study in case of inadvertent enrollment
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
    - If the participant becomes pregnant during the study (see Section 8.3.2 for additional details)
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

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

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

7.3. Lost to Follow up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

8.1.1.1. Polysomnography

The primary efficacy assessment in this study is AHI. AHI measurements will be collected via polysomnography.

Polysomnography assessments (including AHI, blood oxygen saturation parameters, PR, sleep parameters) will be performed during 1-night, overnight clinic stays, per the SoA. Data from the PSGs will be read and scored centrally using the AASM 1B hypopnea scoring method (when there is ≥4% oxygen desaturation from pre-event baseline; see Section 10.10, Appendix 10 for definitions) (Hamilton et al. 2021).

The eligibility criteria and AHI related endpoints of the study will be assessed based on central reading of the PSG.

8.1.2. Secondary Efficacy Assessments

8.1.2.1. Patient-Reported Outcomes

8.1.2.1.1. Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ will be included to assess change in FOSQ domains and total score from baseline to Week 52. The FOSQ is a 30-item sleep-specific, participant-completed questionnaire used to assess the effect of disorders associated with excessive daytime sleepiness (EDS) on daily functioning in adults. It assesses the following 5 domains of

- General productivity (8 items)
- Activity level (9 items)
- Vigilance (7 items)
- Social outcomes (2 items)
- Intimate and sexual relationships (4 items)

The FOSQ items assess participant's current status with each item rated on a scale of 1 (extreme difficulty) to 4 (no difficulty), with an additional not applicable (0 = "I don't do this activity for

other reasons") also available. Individual domain scores are calculated by taking the mean of answered, non-zero items within each domain and a total score can be calculated by first computing the mean score for each domain, then multiplying the mean of the domain scores by 5 (Weaver et al. 1997). The total score for the FOSQ 10-item short form (FOSQ-10) can also be calculated.

8.1.2.1.2. PROMIS Short Form v1.0 Sleep-related Impairment 8a

The PROMIS Short Form v1.0 Sleep-related Impairment 8a assesses self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments associated with sleep problems or impaired alertness. The PROMIS Short Form v1.0 Sleep-related Impairment 8a consists of 8 items each rated on a 5-point scale ranging from "not at all" to "very much." Items have a recall period of "in the past 7 days." Individual item scores are totaled to obtain a raw score, with higher scores indicating more sleep-related impairment. Raw scores can be converted to a T-score, which is standardized with a mean of 50 and a SD of 10. (Northwestern, 2016a)

8.1.2.1.3. PROMIS Short Form v1.0 Sleep Disturbance 8b

The PROMIS Short Form v1.0 Sleep Disturbance 8b assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep, including perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. The PROMIS Short Form v1.0 Sleep Disturbance 8b consists of 8 items each rated on a 5-point scale ranging from "not at all" to "very much, " "never" to "always," or "very poor" to "very good." Items have a recall period of "in the past 7 days." Individual item scores are totaled to obtain a raw score, with higher scores indicating more sleep disturbance. Raw scores can be converted to a T-score, which is standardized with a mean of 50 and a SD of 10. (Northwestern, 2016b)

8.1.2.1.4. Epworth Sleepiness Scale

The ESS will be included to assess improvements in excessive daytime sleepiness from baseline to Week 52. The ESS is an 8-item participant-completed measure that asks the participant to rate on a scale of 0 (would never doze) to 3 (high chance of dozing), their usual chances of dozing in 8 different daytime situations, with a recall period of "in recent times." The ESS total score is the sum of the 8-item scores and ranges from 0 to 24, with higher scores indicating greater daytime sleepiness (Johns 1991).

8.1.2.1.5. Short-Form 36 Version 2 Health Survey, Acute Form, 1-week Recall Version

The SF-36v2 will be included to assess health-related quality of life from baseline to Week 52. The SF-36v2 acute form, 1-week recall version is a 36-item generic, participant-completed measure designed to assess the following 8 domains over "the past week."

- Physical functioning
- Role-physical
- Bodily pain
- General health
- Vitality
- Social functioning

- Role-emotional, and
- Mental health

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

8.1.2.1.6. Patient Global Impression of Status – Obstructive Sleep Apnea (PGIS-OSA) Symptoms Scales

Three patient global impression of status scales will be included to assess categorical shift in participant self-rated assessment of their OSA symptom severity from baseline to Week 52.

PGIS-OSA Fatigue

This is a single-item, participant self-rated assessment of their overall level of fatigue due to OSA, "over the past 7 days." The item is rated on a 4-point scale ranging from "No fatigue" to "Severe fatigue."

PGIS-OSA Sleepiness

This is a single-item, participant self-rated assessment of their overall level of sleepiness due to OSA during waking hours, "over the past 7 days." The item is rated on a 4-point scale ranging from "Not at all sleepy" to "Very sleepy."

PGIS-OSA Snoring

The PGIS-OSA Snoring scale consists of two items. The first item is a participant self-rated assessment of their overall perception of the severity of their snoring due to OSA, "over the past 7 days," with respect to how much their snoring has affected their sleep. The item is rated on a 4-point scale ranging from "Not at all affected" to "Very affected." For the second item, participants will be asked on a 3-point scale ("Not at all" to "All the time") if they have ever been told by someone else that they snore in their sleep.

8.1.3. Exploratory Efficacy Assessments

8.1.3.1. Actigraphy

The actigraphy device (AX6) will be utilized in the OSA trial to objectively evaluate the effect of tirzepatide on various sleep and physical activity parameters including but not limited to change of daytime sleep time, sleep efficiency, and change in daytime physical activity from baseline. The actigraphy device is a data logger capable of recording raw data from a suite of integrated sensors and can be configured to collect movement-relevant data in an uninterrupted fashion for up to 2 months, thus is ideal for collecting longitudinal movement data (for example, physical activity, sleep, etc.) in real-world health research and well-defined clinical trials. The actigraphy device meets the CE (Conformite Europeenne) mark requirements. Participants should wear the actigraphy device for 7 consecutive days, 5 times during the study, per the SoA.

Lack of participation in actigraphy collections at any time is not considered a protocol deviation.

8.1.3.2. Patient Global Impression of Change – Obstructive Sleep Apnea (PGIC-OSA) Symptoms Scales

Four patient global impression of change scales will be included to assess categorical shift in participant self-rated assessment of change in their OSA symptom severity from baseline to Week 52.

PGIC-OSA Fatigue

This is a single-item, participant self-rated assessment of the change in their overall level of fatigue due to OSA, "since you started taking the study medication." The item is rated on a 5-point scale ranging from "Much worse" to "Much better."

PGIC-OSA Sleepiness

This is a single-item, participant self-rated assessment of the change in their overall level of sleepiness due to OSA during waking hours, "since you started taking the study medication." The item is rated on a 5-point scale ranging from "Much more sleepy" to "Much less sleepy."

PGIC-OSA Sleep Quality

This is a single-item, participant self-rated assessment of the change in their overall sleep quality due to OSA, "since you started taking the study medication." The item is rated on a 5-point scale ranging from "Much worse" to "Much better."

PGIC-OSA Snoring

This is a single-item, participant self-rated assessment of the overall change in how their snoring has affected their sleep, "since you started taking the study medication." The item is rated on a 5-point scale ranging from "My sleep is much more affected" to "My sleep is much less affected."

8.1.3.3. EQ-5D-5L

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

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

The 5L version, scores each dimension at 5 levels:

- no problems
- slight problems
- moderate problems
- severe problems, and
- unable to perform/extreme problems.

A total of 3125 health states is possible. 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 less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). In addition, the EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analog scale. The participant rates his/her perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health). In conjunction with the health state data, it provides a composite picture of the respondent's health status.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the CV, respiratory, gastrointestinal and neurological systems as well as a thyroid examination. Height, weight, and waist circumference will also be measured and recorded.

A symptom-directed physical assessment will be performed as indicated in the SoA, as clinically indicated.

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

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3).

8.2.3. Electrocardiograms (ECG)

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

A local single 12-lead ECG will be collected at designated visits. ECGs should be collected prior to collection of blood samples for laboratory testing, including PK samples. Participants should be supine for at least 5 minutes before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit.

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

8.2.4. Clinical Safety Laboratory Tests

See Section 10.2, Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

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

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

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, Appendix 2 must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

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

8.2.5. Pregnancy Testing

See the SoA (Section 1.3) for testing for pregnancy and timepoints.

See Appendix 4 (Section 10.4) for additional information for pregnancy.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Patients with obesity may occasionally develop suicidal ideation or behavior.

Participants should be monitored appropriately and observed closely for SIB or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

Baseline assessment of suicidal ideation and behavior/intervention emergent suicidal ideation and behavior will be monitored using the C-SSRS and PHQ-9.

8.2.6.1. C-SSRS

Columbia Suicide-Severity Rating Scale (C-SSRS) is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health (NIMH) trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events. (The Columbia Lighthouse Project, 2013)

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.

8.2.6.2. PHQ-9

The PHQ-9 is a validated self-report screening tool that assesses the presence and intensity of depressive symptoms. The PHQ-9, which incorporates the 9 Diagnostic and Statistical Manual-IV depression criteria as "0" (not at all) to "3" (nearly every day), was developed for use in primary care settings (Kroenke et al. 2001).

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

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

- AEs
- SAEs
- PCs

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

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

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

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

8.3.1. Timing and Mechanism for Collecting Events

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

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
SAE					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	start of intervention	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	until 1 month after the last dose of study intervention	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
PCs					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A

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

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

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

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading AE collection should occur prior to the collection of the C-SSRS and PHQ-9, if AE and C-SSRS/PHQ-9 collections done on the same day.

If a suicide-related event is discovered *during the C-SSRS or PHQ-9* but was not captured during the nonleading AE collection, sites should not change the AE form.

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After learning of a pregnancy in the female partner of a study participant, the investigator will
  - obtain a consent to release information from the pregnant female partner directly, and
  - within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the study follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Events of Special Interest

Adverse events of special interest are prospectively defined to include

- severe hypoglycemia
- MACE (adjudicated); includes, but not limited to CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, and hospitalization for heart failure
- treatment-emergent arrhythmias and cardiac conduction disorders
- hepatobiliary disorders; includes biliary colic, cholecystitis, and other gallbladder disease
- severe GI events
- acute renal events

- Major Depressive Disorder/suicidal behavior and ideation
- pancreatitis (adjudicated)
- c-cell hyperplasia and thyroid malignancies
- allergic/hypersensitivity reactions; includes ISRs and ADA formation

If these events are reported, investigators may be prompted to collect additional data about the event. Sections 10.1.5.1 and 10.1.5.2 (Appendix 1), outline additional information on CV and pancreatic adjudication. Section 10.3.7 (Appendix 3) outline additional information on hypoglycemia, hypersensitivity reactions, and ISRs.

8.4. Pharmacokinetics

Blood samples will be obtained from all participants enrolled in the 2 ISAs to enable the characterization of tirzepatide PK and exposure response relationships, as permissible. Samples will be collected with concurrent immunogenicity samples at timepoints indicated in the SoA (Section 1.3).

Blood samples collected from participants in the placebo arms will not be included in the bioanalyses of drug concentrations.

- Plasma samples will be collected for measurement of plasma concentrations of tirzepatide as specified in the SoA
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

8.4.1. Bioanalytical Methods

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

8.5. Pharmacodynamics

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

8.6. Genetics

A whole blood sample will be collected for pharmacogenetic analysis where local regulations allow.

8.7. Biomarkers

Blood samples will be collected to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of study participant response (including safety), and clinical outcome. Biomarkers will include measurement of biomolecules including proteins, lipids, and other cellular elements.

Samples will be collected according to the schedule described in the SoA and as detailed in the laboratory manual provided separately to sites.

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

Lilly may store samples after the end of the study to achieve study objectives. Additionally, with participant's consent, samples may be used for further research by Lilly or others such as universities or other companies to contribute to the understanding of OSA, obesity, or other diseases, the development of related or new treatments, or research methods.
See Section 10.1.12, Appendix 1 for details related to sample retention.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected for analysis to determine antibody production against tirzepatide. Antibodies may be further characterized for: cross-reactive binding to native GIP and GLP-1, neutralizing activity of tirzepatide on the GIP and GLP-1 receptors, and neutralizing activity to native GIP and/or GLP-1. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of tirzepatide. All samples for immunogenicity should be taken predose when applicable and possible.

Treatment-emergent ADAs are defined in Section 10.3, Appendix 3.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of tirzepatide at a laboratory approved by the sponsor. The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Section 10.2, Appendix 2. Samples may also be used for development and control of an immunogenicity assay.

For details related to sample retention, see Section 10.1.12, Appendix 1.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. The SAP will include more technical and detailed description of the statistical analyses described in this section.

Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

9.1. Statistical Hypotheses

For each ISA, the primary objective is to demonstrate that tirzepatide at the MTD (10 mg or 15 mg) is superior to Placebo in treating participants with OSA with respect to AHI endpoint. Thus the null and alternative hypotheses will be defined as below.

Null hypothesis: tirzepatide at the MTD (10 mg or 15 mg) is not different from the placebo with respect to the mean percent change from baseline in AHI at 52 weeks.

Alternative hypothesis: tirzepatide at the MTD (10 mg or 15 mg) is superior to the placebo with respect to the mean percent change from baseline in AHI at 52 weeks.

The treatment effect will be defined as the difference between the estimates of the mean change from baseline at 52 weeks for tirzepatide at the MTD (10 mg or 15 mg) and placebo.

9.1.1. Multiplicity Adjustment

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints will be carried out based on a graphical approach for multiple comparisons within each ISA (Bretz et al. 2011). The graphical approach is a closed testing procedure; hence, it strongly controls the familywise Type I error rate (2-sided alpha level of 0.05) across the primary and key secondary objectives (Alosh et al. 2014). Details about the graphical approach will be described in the SAP.

9.2. Analyses Sets

This table describes the populations that will be used for statistical analyses within each ISA of the master protocol. Additional intervention-specific populations for analyses may be described in the respective ISA.

Analysis Set or Population	Description
mITT population	All randomly assigned participants who are exposed to at least 1 dose of study intervention.
FAS	Data obtained during treatment period from the mITT population excluding those discontinuing study due to inadvertent enrollment, regardless of adherence to study intervention
EAS	Data obtained during treatment period from the mITT population excluding those discontinuing study due to inadvertent enrollment, excluding data after discontinuation of study intervention (last dose + 7 days)
SS	Data obtained during treatment period plus safety follow-up period from mITT population, regardless of adherence to study intervention

Abbreviations: EAS = efficacy analysis set; FAS = full analysis set; mITT = modified intent-to-treat; SS = safety analysis set.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis will be the responsibility of the sponsor or its designee. Statistical analysis for each ISA will be conducted individually and a combined analysis with both ISAs is not planned.

The SAP will be finalized prior to the unblinding of the first ISA.

Changes to the data analysis methods will require an amendment only if a principal feature of the master protocol is changed. Any other change to the data analysis methods, and the justification for making the change, will be described in the SAP or the CSR for each respective ISA. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Efficacy analyses will be conducted on all participants meeting study eligibility criteria randomly assigned to study intervention according to the treatment to which the participants are assigned and were exposed to at least one dose. The primary and key secondary efficacy analysis will be guided by 2 estimands, the “treatment regimen” estimand and the “efficacy” estimand to support global regulatory submissions and publications. For the “treatment regimen” estimand, the analysis will be conducted using FAS. To minimize missing data, participants randomly assigned to study intervention who prematurely discontinue study treatment will be encouraged to remain in the study, however, some participants may choose to permanently discontinue from the study which will lead to missing endpoints. Details on handling missing values can be found in Missing Value Imputation section. For the “efficacy” estimand, the analysis will be conducted using the EAS.

Safety analysis will be conducted using the SS. Selected safety analyses may be conducted after excluding the data after permanent discontinuation of the study intervention.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval will be calculated at 95%, 2-sided. In statistical summaries and analyses, participants will be analyzed as randomized. Countries in similar geographic regions with fewer than 10 participants, based on the all-randomized population, will be pooled to achieve a pooled country of at least 10 participants. All analyses using country in the model will use a pooled country, unless otherwise specified. The final pooling by country and geographic region will be finalized prior to data lock.

Baseline is defined as the last non missing measurement at or before the randomization visit (Visit 2) unless otherwise specified.

Analysis of covariance will be used to analyze continuous variables collected only at baseline and endpoint. The model will include treatment and strata (pooled country/geographic region, AHI stratum [moderate (AHI ≥15 and AHI <30), severe (AHI ≥ 30)] and gender) as fixed effects and baseline as a covariate. The ANCOVA model for AHI analysis will include baseline AHI instead of the AHI stratum as a fixed covariate.

The MMRM analysis, a restricted-maximum-likelihood-based model, will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model will include the fixed class effects of treatment, strata (pooled country/geographic region and gender), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline value. For analyses of variables other than AHI, the AHI stratum will also be included in the model. Significance tests will be based on least-squares means and Type III tests.

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

For categorical measures, summary statistics may include sample size, frequency, and percentages. Fisher's exact test or Pearson's chi-square test will be used for treatment comparisons unless otherwise specified.

Missing values for the primary and multiplicity adjusted endpoints at Week 52 and at Week 48 for SBP will be handled as follows. For efficacy analysis relative to the "efficacy" estimand, no explicit imputation will be performed. For efficacy analysis relative to the "treatment regimen" estimand, missing values will be imputed using multiple imputation based on the reason of intercurrent events. The statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987). The intercurrent events and the resulting missing values will be handled as follows:

Intercurrent events	**Strategy to handle intercurrent events**	**Assumptions for missing values**	**Methods to handle missing values**

Study DC due to the COVID-19 pandemic (after other reasons for missing data are ruled out) or incorrect study procedure leading to invalid measurements ascertained while on treatment	Hypothetical	MAR	Use observed data without any imputation
All other study discontinuations	Treatment policy	MNAR	Multiple imputation. Details will be indicated in SAP

Abbreviations: COVID-19 = coronavirus disease-2019; DC = discontinuation; MAR = missing at random; MNAR = missing not at random.

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

9.3.2. Primary Analysis

The primary objective of this study is to test the hypothesis that tirzepatide at the MTD (10 mg or 15 mg) is superior to placebo for participants with moderate to severe OSA on the mean AHI reduction from baseline to Week 52.

The primary analysis guided by the "treatment regimen" estimand will use FAS. Missing values will be imputed based on the strategy to handle intercurrent events described in Section 9.3.1, and more details about the imputation methods will be provided in the SAP. After the imputation, the primary efficacy comparison will be based on the contrast between tirzepatide at the MTD (10 mg or 15 mg) and placebo from the ANCOVA analysis of mean change from baseline to Week 52 in AHI using FAS as described in Section 9.3.1.

The primary analysis guided by the "efficacy" estimand will use EAS. The efficacy comparison will be based on the contrast between tirzepatide at the MTD (10 mg or 15 mg) and placebo at Week 52 (Visit 11) from the MMRM analysis of mean change from baseline in AHI using EAS as described in Section 9.3.1. More details about the model will be provided in the SAP.

Analysis aligned to each estimand will be evaluated at the full significance level of 0.05.

9.3.3. Analysis of Key Secondary Endpoints

The analyses for key secondary endpoints as in Section 3 will be performed for both the "treatment regimen" and "efficacy" estimand as described in Section 9.3.1 using the graphical testing scheme. The details of graphical testing scheme will be described in the SAP.

The analysis of the hierarchical combination PRO endpoint will be performed with the Finkelstein-Schoenfeld method, and the win ratio (Pocock et al. 2012) will be reported as the measure of treatment effect.

The last measurement prior to randomization for all three PRO endpoints will be used as baseline. For the "treatment regimen" estimand, missing values at Week 52 will be imputed through multiple imputations based on the reason of missingness as described in Section 9.3.1.

Analysis of percent change in AHI, percent change from baseline in body weight, CRP at the 52-week visit and change in SBP at the 48-week visit will be conducted in a manner similar to the primary efficacy analyses with baseline AHI stratum added in the model, and baseline of the corresponding variable as a covariate. Analysis of percent change in AHI will not include the baseline AHI stratum.

Comparisons at the 52-week visit between the treatments relative to the proportion of participants achieving ≥ 50% AHI reduction and AHI< 5 or (AHI ≥ 5 and AHI ≤ 14 and ESS ≤ 10) will be conducted using logistic regression analysis including terms for treatment, pooled country, gender, and baseline AHI as a covariate.

Analysis aligned to each estimand will be evaluated at the full significance level of 0.05 contingent on reaching statistical significance of the primary objective.

9.3.4. Treatment Group Comparability

9.3.4.1. Participant Disposition

Participants who discontinue from the study will be identified, and the extent of their participation in the study will be reported for each ISA. A detailed description of participant disposition and the reasons for discontinuation will be summarized by treatment group for each ISA at the end of the study. Intervention-specific analyses will be detailed in each respective ISA.

9.3.4.2. Participant Characteristics

Participant characteristics and baseline clinical measures will be summarized for each treatment . For all participant characteristics, the summaries will include descriptive statistics for continuous measures (for example, sample size, mean, standard deviation, median, minimum, and maximum) and for categorical measures (for example, sample size, counts and percentages). Additional intervention-specific analyses will be specified in each respective ISA.

9.3.4.3. Concomitant Therapy

Concomitant medications used during the study will be summarized for each ISA.

9.3.5. Safety Analyses

Unless specified otherwise, safety assessments will compare safety of tirzepatide at the MTD (10 mg or 15 mg) with placebo irrespective of adherence to study intervention. Thus, safety analyses will be conducted using the SS.

9.3.5.1. Adverse Events

Adverse events will be classified by system organ class and preferred term as defined by the Medical Dictionary for Regulatory Activities.

All conditions existing prior to randomization at Visit 2 will be used as baseline. The postbaseline visits during the placebo-controlled phase will be included as the postbaseline period for analysis.

For events that are gender specific, the denominator and computation of the percentage will only include participants of the given gender.

9.3.5.2. Hypoglycemic Events

Incidence of documented symptomatic hypoglycemia events and severe hypoglycemia will be summarized and compared between tirzepatide at the MTD (10 mg or 15 mg) and placebo. Rate of hypoglycemic episodes will also be analyzed. Some analyses may be conducted excluding data after introducing another antihyperglycemic therapy.

9.3.5.3. Gastrointestinal Events

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

9.3.5.4. Adjudicated Cardiovascular Events

Listings of deaths, myocardial infarctions, strokes, and hospitalizations for unstable angina or heart failure confirmed by an independent Clinical Endpoint Committee (CEC) will be provided.

9.3.5.5. Central Laboratory Measures and Vital Signs

Values and change from baseline to postbaseline values of central laboratory measures and vital signs will be summarized and compared between tirzepatide at the MTD (10 mg or 15 mg) and placebo at each scheduled visit.

9.3.5.6. Analysis of C-SSRS Data

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (The Columbia Lighthouse Project, 2013).

9.3.6. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with 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 with 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 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.

9.3.7. Other Analyses

9.3.7.1. Health Economics

Analyses of actual and change from baseline in PRO scores will be conducted using linear models with baseline PRO scores, treatment, stratification factors and other factors that may be considered relevant. These variables will be specified in the SAP.

9.3.7.2. Subgroup Analyses

The following subgroups will be analyzed using the "efficacy" estimand on percent change in AHI values from baseline to 52 week visit if there are sufficient numbers of participants in each treatment by subgroup (for example, 10%):

- Age (<50 years, ≥50 years),
- Baseline OSA severity (Moderate, Severe),
- Race,
- Ethnicity,
- Country,
- Gender (Male or Female),
- Baseline BMI (<30, ≥30 and <35, ≥35 and <40, ≥40 kg/m^2), and
- Baseline ESS (ESS≤10, ESS>10).

Analyses for percent change from baseline in AHI will be performed using an MMRM model that includes the same fixed effects given for the primary analysis model plus factors of subgroup, 2-way interaction of subgroup and treatment, 2-way interaction of subgroup and visit, and 3-way interaction of treatment, visit and subgroup. The interaction of subgroup and treatment at the primary endpoint (Week 52) will be evaluated to assess the treatment by subgroup interaction. When analyzing OSA severity (Moderate, Severe) as a subgroup, the baseline AHI will be not be included as a covariate to avoid confounding. Additional subgroup analyses may also be performed.

More details on other analyses will be described in the SAP.

9.4. Interim Analysis

Based on the projected enrollment, approximately 3 interim analyses of safety will be conducted. The first interim analysis is planned to occur when approximately 20% of the anticipated number of participants are randomly assigned to study intervention or 6 months after the first participant is randomly assigned to study intervention, whichever occurs later, from one of the ISAs. Subsequent reviews will follow approximately every 6 months throughout the study.

Only the DMC is authorized to evaluate unblinded interim analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants.

Unblinding details are specified in SAP and/or a separate unblinding plan document.

The DMC charter will describe the specific parameters of the planned interim analysis.

See Section 10.1.5, Appendix 1 And the DMC Charter for details related to the DMC.

The timing of dissemination of data summaries based on interim analyses is addressed in Section 10.1.6, Appendix 1.

9.5. Sample Size Determination

Approximately 206 participants per ISA will be randomly assigned to either tirzepatide or placebo in a 1:1 ratio (approximately 103 participants per treatment arm), and the statistical power is evaluated for the primary efficacy endpoint and key secondary combination PRO endpoint at a 2-sided significance level of 0.05. This sample size will provide

- At least 90% power to demonstrate superiority of tirzepatide at the MTD (10 mg or 15 mg) to placebo for the mean percent change from baseline in AHI, assuming 50% improvement, with a common standard deviation of 50%, and a dropout rate of 25%
- at least 90% power to demonstrate superiority of tirzepatide at the MTD (10 mg or 15 mg) to placebo for the hierarchical combination PRO endpoint using Finkelstein-Schoenfeld method (Finkelstein and Schoenfeld 1999) with a dropout rate of 25%

An upper limit of approximately 70% enrollment of male participants will be used to ensure a sufficiently large sample of female participants.

The sample size and power for the key secondary hierarchical combination PRO endpoint is estimated through simulations under the following assumptions (Blackman et al. 2016, Weaver et al. 2021):

Variable	**Placebo**	**Tirzepatide at the MTD (10 mg or 15 mg)**	**Definition of Win**
FOSQ-10 – change from baseline (mean ± SD)	1.24 ± 1.84	1.95 ± 1.84	If the change from baseline FOSQ-10 for TZP at MTD (10 mg or 15 mg) minus change from baseline FOSQ-10 for placebo ≥2.2
FOSQ Vigilance – change from baseline (mean ± SD)	0.3 ± 0.5	0.5 ± 0.5	If the change from baseline FOSQ Vigilance for TZP at MTD (10 mg or 15 mg) minus change from baseline FOSQ Vigilance for placebo ≥0.44
FOSQ Activity Level – change from baseline (mean ± SD)	0.3 ± 0.5	0.5 ± 0.5	If the change from baseline FOSQ Activity Level for TZP at MTD (10 mg or 15 mg) minus change from baseline FOSQ Activity Level for placebo ≥0.44

Abbreviations: FOSQ = Functional Outcomes of Sleep Questionnaire; FOSQ-10 = FOSQ 10-item short form; MTD = maximum tolerated dose; SD = standard deviation; TZP = tirzepatide.

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 International Ethical Guidelines
- Applicable ICH GCP Guidelines
- International Organization for Standardization (ISO) 14155
- Applicable laws and regulations

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations , ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

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

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

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

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

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

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

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. 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 the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

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

The sponsor has processes in place to ensure 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.

10.1.5. Committees Structure

Prospective adjudication of major adverse CV events and pancreatic AEs will be performed by the independent adjudication committees for this study.

Sections 10.1.5.1 and 10.1.5.2, Appendix 1 outline additional information on pancreatic and CV adjudication.

An independent DMC for the interim analysis (Section 9.4) will include members with no conflict of financial interest. An independent DMC with members all external to the sponsor will be used to monitor participant safety in an unblinded fashion. For details on the DMC, refer to the DMC charter.

10.1.5.1. Cardiovascular Adjudicated Events

Deaths and nonfatal CV AEs will be adjudicated by a committee blinded to treatment assignment. The nonfatal CV AEs to be adjudicated include:

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

10.1.5.2. Pancreatitis Adjudicated Event

Acute pancreatitis is defined as an AE of special interest in this trial (Section 8.3.3).

The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half the cases) (Banks and Freeman 2006; Koizumi et al. 2006); the pain is often associated with nausea and vomiting
- serum amylase (total and/or pancreatic) and/or lipase ≥3X ULN, and
- characteristic findings of acute pancreatitis on CT scan or MRI.

All suspected cases of acute or chronic pancreatitis will be adjudicated by a committee blinded to treatment assignment. 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. Relevant data from participants with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed CRF page. The adjudication committee representative will enter the results of adjudication in a corresponding CRF page.

10.1.6. Dissemination of Clinical Study Data

Reports

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

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

The publication policy for Study GPIF is outlined in Section 10.1.10, Appendix 1 and further described in the Clinical Trial Agreement.

Data

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

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

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

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

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

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

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

Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the CSR.

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

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

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

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement 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 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, COA data (clinician-reported outcome instrument) for suicidality assessments will be collected by the authorized study personnel, via a paper source document and will be transcribed by the authorized study personnel into the EDC system.

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

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 or access an archival copy of pertinent data for retention.

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

Data collected on the actigraphy device will be transferred electronically to the sponsor data warehouse, via a third party.

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

10.1.8. Source Documents

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

Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator

may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Section 10.1.7, Appendix 1.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

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

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

10.1.10. Publication Policy

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

10.1.11. Investigator Information

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

10.1.12. Sample Retention

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

Sample Type	Custodian	Retention Period After Last Participant Visit[a]
Exploratory Biomarker Samples	Sponsor or Designee	15 years
PK Samples	Sponsor or Designee	2 years
Genetics	Sponsor or Designee	15 years
Immunogenicity (ADA) Samples	Sponsor or Designee	15 years

Abbreviations: ADA = antidrug antibody; PK = pharmacokinetic.
[a]Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

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

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

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

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

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

Investigators must document their review of the laboratory safety results.

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

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs)	
Differential	
Percent and/or Absolutes Count of:	
Neutrophils, segmented	
Bands	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Chloride	
Bicarbonate	

Clinical Laboratory Tests	Comments
Total bilirubin	
Direct bilirubin	
ALP	
ALT	
AST	
BUN	
Creatinine	
CK	
Uric acid	
Albumin	
Calcium	
Glucose	
Lipid Panel	Assayed by Lilly designated laboratory.
Cholesterol	
Triglycerides	
HDL-C	.
LDL-C	Generated by Lilly-designated laboratory. If Triglycerides are >400; direct LDL will be measured.
VLDL-C	Generated by Lilly-designated laboratory.
Hormones (female)	
Serum Pregnancy	Assayed by Lilly-designated laboratory.
Urine Pregnancy	Assayed and Evaluated locally
FSH	Assayed by Lilly-designated laboratory.
Urine Chemistry	Assayed by Lilly-designated laboratory.
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI)	
UACR	
PK Samples – Tirzepatide	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Immunogenicity (ADA) Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-tirzepatide antibodies OR Tirzepatide antibodies	
Anti-tirzepatide antibodies neutralization OR Tirzepatide antibodies neutralization	
Additional Testing	Assayed by Lilly-designated laboratory.
HbA1c	
Calcitonin	
Pancreatic Amylase	
Lipase	

Clinical Laboratory Tests	Comments
Insulin	Results will not be provided to the investigative sites.
C-Peptide	Results will not be provided to the investigative sites.
Free Fatty Acids	Results will not be provided to the investigative sites.
hsCRP	Results will not be provided to the investigative sites.
Cystatin-C	
TSH	
Stored Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Genetics Sample	
Exploratory Biomarker Samples	
Serum	
Plasma (EDTA)	
Plasma (P800)	

Abbreviations: ADA = antidrug antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase;; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatinine kinase, CKD-EPI = Chronic Kidney Disease-Epidemiology; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; hsCRP = C-Reactive Protein, high-sensitivity; IWRS = interactive web-response system; LDL-C = low-density lipoprotein cholesterol; PK = pharmacokinetics; RBC = red blood cells; TSH = thyroid-stimulating hormone; UACR = urine albumin/creatinine ratio; VLDL-C = very-low-density lipoprotein cholesterol; WBC = white blood cells.

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

Purpose of collecting samples after a systemic hypersensitivity event

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

When to collect samples after a systemic hypersensitivity event occurs

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

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

Timing	Sample Type	Laboratory Test [a]
Collect from 30 minutes to 4 hours after the start of the event. ● Note: The optimal collection time is from 1 to 2 hours after the start of event.	Serum	total tryptase
	Serum	complements (C3, C3a, and C5a)
	Serum	cytokine panel (IL-6, IL-1β, IL-10 or any cytokine panel that includes these 3 cytokines)
Collect only if not already collected on the same day as the event. ● Note: If collecting, collect up to 12 hours after the start of the event.	Serum	Tirzepatide ADA
	Serum/plasma	Tirzepatide concentration

Abbreviations: ADA = anti-drug antibodies; IL = interleukin.

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. • An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

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

However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect • Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
f. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
g. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product Complaint

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

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

AE, SAE, and PC Recording

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

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

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with 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 one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB in their assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee. • The investigator may change their 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 sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on an SAE paper form (see next section) or to the sponsor or designee by telephone.
- Contacts for SAE reporting can be found on the SAE form.

SAE Reporting via Paper Form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor or designee.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found on the SAE form.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will 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.

10.3.7. Special Safety Topics

10.3.7.1. Hypoglycemia

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia and 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 samples collected during study visits.

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

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

Investigators should use the following classification of hypoglycemia (ADA 2020):

Level 1 hypoglycemia:

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

Level 2 hypoglycemia:

Glucose <54 mg/dL (3.0 mmol/L): Level 2 hypoglycemia is also referred to as documented or blood glucose confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

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

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

Nocturnal hypoglycemia:

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

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

10.3.7.2. Hypersensitivity Reactions

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

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

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

10.3.7.3. Injection-Site Reactions

Symptoms and signs of a local ISR may include erythema, induration, pain, pruritus, and edema.

If an ISR is reported by a participant or parent or guardian or site staff, the ISR CRF will be used to capture additional information about this reaction, for example, injection site pain, degree and area of erythema, induration, pruritis and edema.

At the time of AE occurrence, samples will be collected for measurement of tirzepatide ADAs and tirzepatide concentration.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

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

Abbreviations: SERM = selective estrogen receptor modulators; WOCBP = woman of child bearing potential.

10.4.2. Contraception Guidance

10.4.2.1. Females

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

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

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

Topic	Condition
Pregnancy testing	Negative serum result at screening, followed by a negative urine result within 24 hours prior to treatment exposure.
Contraception	Agree to use 2 forms of effective contraception, where at least one form must be highly effective (less than 1% failure rate) for the duration of the trial and for 30 days thereafter.

Examples of different forms of contraception:

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

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

10.4.2.2. Males

The table below describes contraception guidance for all men.

Topic	**Guidance**
For all men	should refrain from sperm donation for the duration of the study and for 120 days (4 months) from the last dose of study intervention received
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study, **and** • for 120 days (4 months) from the last dose of study intervention received
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

Examples of highly effective, effective and unacceptable methods of contraception are listed in Section 10.4.2.1, Appendix 4.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

DNA samples will be used for research related to tirzepatide, OSA, obesity and related diseases. They may also be used to develop tests/assays including diagnostic tests related to tirzepatide, OSA, and obesity. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to tirzepatide or study interventions of this class to understand study disease or related conditions.

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

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

The samples will be retained while research on tirzepatide, OSA, and obesity continues but no longer than the sample retention limits described in Section 10.1.12, Appendix 1.

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

10.6.1. Hepatic Evaluation Testing

See Sections 10.6.2 and 10.6.3, Appendix 6 for guidance on appropriate test selection.

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

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

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

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

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

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

10.6.2. Close Hepatic Monitoring

Laboratory tests (Section 10.2, Appendix 2), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, 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 one or more of these conditions occur:

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

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, 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 total bilirubin level should continue until levels normalize or return to approximate baseline levels.

10.6.3. Comprehensive Hepatic Evaluation

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

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

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

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus , cytomegalovirus , Epstein-Barr virus , acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

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

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

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

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

10.7. Appendix 7: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Refer to Appendix 3 for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.8. Appendix 8: Protocol GPIF Standardized Protocols for the Measurement of Height, Weight, Neck Circumference, 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).

10.8.1. 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.

10.8.2. 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 will be measured in fasting state at all visits except Visit 1. 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.

10.8.3. Measuring Hip and Waist Circumference

- Hip circumference measurements should be obtained with the participant in the standing position. The hip circumference should be measured at the maximal circumference of the buttocks.

- 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 CRF. If the difference between the 2 measurements exceeds 1 cm, this set of measurements should be discarded and the 2 measurements repeated.

Step 1. Ask the participant to wear light 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.

10.8.4. Measuring Neck Circumference

- Participants should look straight ahead during the measurement, with shoulders down (not hunched).
- Measure the neck circumference at a point just below the larynx (Adam's Apple) and perpendicular to the long axis of the neck.
- Do not place the tape measure over the Adam's Apple.
- The tape will be as close to horizontal as anatomically feasible (the tape line in the front of the neck should be at the same height as the tape line in the back of the neck).
- Care should be taken so as not to involve the shoulder/neck muscles (trapezius) in the measurement.
- Round neck measurement up to the nearest half centimeter.

10.8.5. Vital Sign Measurements (Blood Pressure and Heart Rate)

- Vital sign measurements (BP 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 at least 5 minutes before vital signs measurements are taken
- For each parameter, 3 measurements will be taken using the same arm, preferably the nondominant arm
- The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and BP needs to be recorded in the CRF
- Blood pressure must be taken with an automated BP instrument
- If BP and pulse measurements are taken separately, pulse should be taken prior to BP.

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

10.8.6. Electrocardiogram

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

10.9. Appendix 9: Provisions for Changes in Study Conduct Due to the COVID-19 Pandemic

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.

Study disruptions due to the COVID-19 pandemic

Individual, site, or regional restrictions due to the COVID-19 pandemic may cause disruptions to the conduct of the study. These disruptions may limit the ability of the investigators or participants, or both, to attend on-site visits or to conduct planned study procedures.

Implementing changes due to the COVID-19 pandemic

After receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

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

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

Considerations for making a change

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

Informed consent

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

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

Changes in study conduct due to the COVID-19 pandemic

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

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

Remote visits

Types of remote visits

Telephone/Telemedicine

Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, collection of AEs and PCs, concomitant medications review, review study participant diary (including study intervention compliance), review diet and exercise goals, C-SSRS (Since Last Visit Assessed) and PHQ-9. PROs will be completed by the participant on the provisioned device per the SoA.

Mobile healthcare visit

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 the COVID pandemic, if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to, weight measurement, blood sample collection, vital signs (temperature, PR, BP), concomitant medication review, conducting physical assessments, collection of AEs and PCs, and collecting health information. PROs will be completed by the participant on the provisioned device per the SoA.

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

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

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

Study intervention and supplies

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

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit

- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies.

These requirements must be met before action is taken:

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

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at Visit 1 are valid for a maximum of 90 days. The following rules will be applied for active participants not randomly assigned to study intervention whose participation in the study must be paused due to the COVID-19 pandemic:

- If screening is 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.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 90 days from Visit 1 to Visit 2: the participant must be discontinued because of screening interruption due to the COVID-19 pandemic. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at Visit 1 to ensure participant eligibility by Visit 2.

Adjustments to visit windows

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

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 1 (Screening)	No change
Visit 2 (Randomization)	Within 90 days after Visit 1.
Visits 3 through 6	Within 7 days before or after the intended date.
Visits 7 through 10	Within 14 days before or after the intended date.
Visit 11	Within 14 days before the intended date, or up to 28 days after the intended date.
Visit 801	Up to 28 days after the intended date

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

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected due to the COVID-19 pandemic. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

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

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
AASM	American Academy of Sleep Medicine
Abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADA	antidrug antibody
AE	adverse event
AHI	Apnea-Hypopnea Index
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Apnea	decrease in airflow ≥90% from baseline for ≥10 seconds
AST	aspartate aminotransferase
AX6	Axivity 6
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CBD	cannabidiol
COA	clinical outcome assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	cardiovascular
Device deficiencies	Equivalent to product complaint
DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DPP-4	dipeptidyl-peptidase-4
EAS	efficacy analysis set
ECG	electrocardiogram
ED	early discontinuation
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.

enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
EQ-5D-5L	EuroQol - 5 Dimension - 5 Level
ESS	Epworth Sleepiness Scale
FAS	full analysis set
FG	fasting glucose
FOSQ	Functional Outcomes of Sleep Questionnaire
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
GLP-1RA	glucagon like peptide 1 receptor
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HSAT	home sleep apnea test
hsCRP	high-sensitivity C-reactive protein
Hypopnea	an abnormal respiratory event lasting ≥10 seconds with ≥30% reduction in thoracoabdominal movement or airflow as compared to baseline, and with ≥ 4% oxygen desaturation.
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
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.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
ISA	intervention-specific appendix
ISR	injection site reaction
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
MACE	major adverse cardiovascular events

medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MEN	multiple endocrine neoplasia
MI	myocardial infarction
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription.
MMRM	Mixed model repeated measures
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
OGTT	oral glucose tolerance test
OSA	obstructive sleep apnea
OTC	Over the counter
PAP	positive airway pressure
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
PC	product complaint
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Status
PHQ-9	Patient Health Questionnaire-9
PK/PD	pharmacokinetics/pharmacodynamics
PR	pulse rate
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PSG	polysomnography
QTc	corrected QT interval
QW	weekly
SAE	serious adverse event
SAP	statistical analysis plan
SASHB	sleep apnea specific hypoxic burden
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SF-36v2	Short-Form 36 version 2
SIB	suicidal ideation and behavior
SoA	Schedule of Activities
SS	safety analysis set
T1DM	Type 1 diabetes mellites

T2DM	Type 2 diabetes mellites
TBL	total bilirubin level
TEE	total energy expenditure
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
THC	Tetrahydrocannabinol
TSH	thyroid-stimulating hormone
UACR	urinary albumin/creatinine ratio
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.11. Appendix 11: Country-Specific Requirements

10.11.1. Germany

This section describes protocol changes applicable for adult participants in study sites in Germany.

This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name		Description of the Change	Brief Rationale
7.2.	Participant Discontinuation/ Withdrawal from the Study	Deleted references to "legally authorized representative," "legal guardian," "parents"	The German Drug Law (Arzneimittelgesetz – AMG) requires per Paragraph 40 (1-3) and Paragraph 41 (3) that adult participants act on their own behalf and provide their own written informed consent. If written consent is not possible, verbal consent with a witness is acceptable. No legal representative consent is accepted.
8.3.	Adverse Events, Serious Adverse Events, and Product Complaints		
10.1.3	Informed Consent Process		
10.10.	Abbreviations and Definitions		

The revised text in the following subsections show the changes applicable for adult participants to study sites in Germany. Additions are identified by underline. Deletions are identified by ~~strikethrough format~~.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request
- ~~at the request of the participant's designee (for example, parents or legal guardian)~~
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
    - If the participant becomes pregnant during the study (see Section 8.3.2 for additional details)
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

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

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

- AEs
- SAEs
- PCs

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

10.1.3 Informed Consent Process

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

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

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

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

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

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

10.10. Appendix 10: Abbreviations and Definitions

enter	Participants entered into a study are those who sign the informed consent form directly ~~or through their legally acceptable representatives~~.

10.12. Appendix 12: Protocol Amendment History

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

Amendment [b]: 30-Sep-2022
This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the

- safety or the rights of the study participants, and
- reliability and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:
This amendment includes the addition of a key secondary objective, "Change in AHI". The endpoint for key secondary objective "Change in SBP" and other secondary objective "Change in DBP" has been updated to Week 48 from Week 52. Changes have been made to the Schedule of Activities to reflect the synchronization of timing of C-SSRS to PHQ-9.

Protocol changes have been made as outlined in the following table.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis and 3. Objectives, Endpoints, and Estimands	Key Secondary Objectives: Added "Change in AHI" as a key secondary objective with endpoint "Change in AHI"	To align with recommendations from health authority.
	Key Secondary Objectives: Moved "change in SBP" to "From baseline to Week 48" section	BP will be assessed at Week 48 because PAP suspension at Week 52 may confound BP assessment.
	Added footnote a "BP will be assessed at Week 48 because PAP suspension at Week 52 may confound BP assessment".	For additional information.
1.3. Schedule of Activities	Removed text, "Note: Visit 10 is eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, or in combination with on-site visit) at the direction of the sponsor, according to local laws and regulations."	Vital signs will be measured at Week 48, so this visit will be on site.

Section # and Name	Description of Change	Brief Rationale
	"Fasting Visit" row: Removed text, "If V10 is remote, then the visit will not be fasting."	This instruction is no longer applicable.
	"Weight" row: Removed text, "If V10 is remote, then weight will not be obtained at the visit."	This instruction is no longer applicable.
	"Vital signs" row: Removed text, "If V10 is remote, vital signs will not be obtained at the visit."	This instruction is no longer applicable.
	"Symptom-directed physical assessment" row: Removed text, "If V10 is remote, then symptom-directed physical assessment will not be done at the visit."	This instruction is no longer applicable.
	Removed "Schedule Sleep Center Study for PSG" and "Sleep Center Study for PSG" from ED visit.	Sleep study is not required for participants who discontinue early.
	"Review Lifestyle Program instructions" row: Updated comment to "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."	To clarify the requirement.
	"ESS, EQ-5D-5L, FOSQ, and PGIS" rows: Updated comment "When the PROs are scheduled for visits at which the PSG will be done, they should be completed <u>on the same day as PSG and</u> in the following order (FOSQ, ESS, PROMIS Short Form v1.0 Sleep Disturbance 8b, PROMIS Short Form v1.0 Sleep-related Impairment 8a, PGIS, PGIC, SF-36v2 acute form, and EQ-5D-5L) ~~before the~~	To clarify the requirement.

Section # and Name	Description of Change	Brief Rationale
	~~PSG is conducted, and should be done at the same time of day for each of those visits~~. Completing the PRO assessments on the next day after PSG is not considered a protocol violation.	
	"PHQ-9", "C-SSRS screening/baseline", and "C-SSRS (since last visit version)" rows: added "if both collected on the same day" to comments.	To clarify timing and allow further flexibility for AE collection independent of PHQ-9 and C-SSRS assessments.
	"C-SSRS (since last visit version)" row: Removed assessment from Visits 3, 4, 5, 6, 8, 9, 10, and 801.	Collection schedule has been updated to align with PHQ-9 assessments.
	"Participant returns all unused study intervention" row: Removed text, "If V10 is remote, participant will return any unused study intervention dispensed at V9 during the V11 visit."	This instruction is no longer applicable.
	"Assess study intervention compliance" row: Removed text, "If V10 is remote, the next study intervention compliance will be done at V11."	This instruction is no longer applicable.
3. Objectives, Endpoints, and Estimands	Other Secondary Objectives: Moved "change in DBP" to "From baseline to Week 48" section	BP will be assessed at Week 48 because PAP suspension at Week 52 may confound BP assessment.
5.2. Exclusion Criteria	Exclusion Criterion 42: Updated formatting.	For clarification.
	Exclusion Criterion 53: Removed "(4 months for studies conducted in Japan, 3 months for studies conducted in the United Kingdom).	This information is no longer applicable.
6.5. Dose Modification	Modified text, "Dose modification is permitted for	Clarification.

Section # and Name	Description of Change	Brief Rationale
	management of intolerable GI symptoms during the first 24 weeks of the treatment period (Section 6.5.1).	
	Modified text, "Participants who do not tolerate at least 10 mg even after the described measures, including 1 de-escalation and re-escalation attempt, will be discontinued from the study intervention but remain in the study for continued follow-up."	Clarification.
6.5.1. Management of Participants with Gastrointestinal Symptoms	Modified text, "For participants unable to tolerate any dose ~~escalation~~ 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 by 2.5 mg every 4 weeks ~~up to MTD will be allowed~~ in a blinded fashion, to reach either the 10-mg or 15-mg dose as described below."	Direct the investigator to contact sponsor to ensure that dose modifications are completed according to protocol.
	Added text "Dose modifications after the first 24 weeks of the treatment period are not permitted. For temporary study treatment discontinuation see Section 7.1.2."	Clarification.
6.5.1. Management of Participants with Gastrointestinal Symptoms	Modified text, "Participants who tolerate • 10 mg, but do not tolerate 12.5 mg or 15 mg even following the above measures, including 1 de-escalation and re-escalation attempt, will continue on 10 mg as their MTD dose.	Clarification.

Section # and Name	Description of Change	Brief Rationale
	• 12.5 mg, but do not tolerate 15 mg even after the above measures, including 1 de-escalation and re-escalation attempt, will continue on 10 mg as their MTD dose."	
7.1. Discontinuation of Study Intervention	Removed text in clinical considerations section, "inadvertent enrollment if continued treatment with study intervention would not be medically appropriate"	Participants who do not meet enrollment criteria will discontinue from the study.
	Added text, "The participant should be referred to a MHP for further evaluation and care."	To provide further detail for participant care.
7.2. Participant Discontinuation/Withdrawal from the Study	Added text, "A participant will be withdrawn from the study in case of inadvertent enrollment"	Text updated to align with relevant edits in Section 7.1.
8.2.3. Electrocardiograms (ECG)	Modified instructions for timing of ECG collection. "ECGs should be collected ~~at least 30 minutes~~ prior to collection of blood samples for laboratory testing, including PK samples. Participants should be supine for at least ~~approximately~~ 5 ~~to 10~~ minutes before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit."	Clarification.
8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire	Added text, "if AE and C-SSRS/PHQ-9 collections done on the same day".	To clarify timing and allow further flexibility for AE collection independent of PHQ-9 and C-SSRS assessments.
9.2. Analyses Sets	FAS and EAS descriptions updated to include "excluding those discontinuing study due to inadvertent enrollment"	Text revised to reflect updated definitions for FAS and EAS.

Section # and Name	Description of Change	Brief Rationale
	Added "(last dose +7 days)" to the description of data excluded due to the discontinuation of study intervention in the EAS population.	Clarification.
9.3. Statistical Analysis	Modified text for "hybrid" estimand, changed "hybrid" to "treatment regimen" throughout Section 9.3.	To keep terminology consistent with the literature.
9.3.1. General Considerations	Modified text, "Efficacy analyses will be conducted on all participants randomly assigned to study intervention according to the treatment to which the participants are assigned and were exposed to at least one dose.	To add details for clarification.
	Modified text, "For the "efficacy" estimand, the analysis will ~~include data collected prior to permanent discontinuation of study intervention and will~~ be conducted using the EAS.	This was duplicate information.
	"Missing Value Imputation" information moved and modified.	To reflect that the endpoint for SBP is at Week 48 instead of Week 52 and to clarify that no explicit imputation will be performed for efficacy analysis relative to "efficacy" estimand.
	Moved description of handling of missing data for "efficacy" estimand earlier in the paragraph.	Clarification.
9.3.2. Primary Analysis	Deleted text, "There will be 2 primary analysis methods, each tested at the full significance level of 0.05"	This information has been moved to the last sentences of the primary analysis section and key secondary analysis section for clarification.

Section # and Name	Description of Change	Brief Rationale
	Modified text, "Missing values will be imputed ~~following imputation methods~~ based on the strategy to handle intercurrent events described in Section 9.3.1"	Clarification.
	Added text, "Analysis aligned to each estimand will be evaluated at the full significance level of 0.05.	To substitute the deleted text "There will be 2 primary analysis methods, each tested at the full significance level of 0.05".
9.3.3. Analysis of Key Secondary Endpoints	Updated text, "Analysis of change in AHI, percent change from baseline in body weight, ~~change in SBP, and~~ CRP at the 52-week visit and change in SBP at the 48-week visit will be conducted in a manner similar to the primary efficacy analyses with baseline AHI stratum added in the model, and baseline of the corresponding variable as a covariate.	To align with changes in Section 3.
	Added text, "Analysis of change in AHI will not include the baseline AHI stratum."	Clarification.
	Added text, "Analysis aligned to each estimand will be evaluated at the full significance level of 0.05 contingent on reaching statistical significance of the primary objective."	To substitute the deleted text "There will be 2 primary analysis methods, each tested at the full significance level of 0.05".
10.3.7.1. Hypoglycemia	Updated text, "Hypoglycemic episodes will be recorded in the eDiary ~~on a specific CRF~~ and should not be recorded as AEs unless the event meets serious criteria.	Correction.
10.3.7.3. Injection-Site Reactions	Modified text, "At the time of AE occurrence ~~in the tirzepatide group~~, samples will be collected	Correction.

Section # and Name	Description of Change	Brief Rationale
	for measurement of tirzepatide ADAs and tirzepatide concentration."	
10.8.5. Vital Sign Measurements (Blood Pressure and Heart Rate)	Modified text, " • The participant should sit quietly for <u>at least</u> 5 minutes before vital signs measurements are taken"	Clarification.
10.8.6. Electrocardiogram	Modified text, " • 12-lead ECGs should be obtained after the participant has rested in a supine position for at least <u>5</u> ~~10~~ minutes. • Electrocardiograms should be collected ~~at least 30 minutes~~ prior to collection of blood samples for laboratory testing, including PK samples. • ~~Electrocardiograms should be obtained approximately 1 minute apart, with all 3 tracings to be obtained within approximately 5 minutes. Measurements that deviate substantially from previous readings should be repeated immediately.~~"	Clarification. One tracing of ECG is considered adequate.
Throughout	Editorial corrections.	Minor, therefore not described.

Amendment a: 10-Feb-2022

Overall Rationale for the Amendment:
This amendment corrects terminology used in the protocol for intervention-specific appendix (ISA), and adds selected clarifications.

Section # and Name	Description of Change	Brief Rationale
Title Page 1.1. Synopsis 1.3. Schedule of Activities 10.10. Abbreviations and Definitions	Changed "indication-specific appendix" to "intervention-specific appendix.	Correction.
1.3. Schedule of Activities	"Symptom-directed physical assessment" row: Clarified marks for symptom-directed physical assessment during the study, and added a clarifying statement in notes.	Clarification. Original language could be interpreted to mean symptom-directed physical assessment is required at all visits. Symptom-directed physical assessment from visits 2-11 and ED will be conducted at the discretion of the PI, as indicated based on participant status and standard of care.
	"Participant diary dispensed" row: Specified which diaries are electronic versus paper.	Clarification.
	"Review Lifestyle Program instructions" row: comments updated/moved from the "Review diet and exercise goals" row, which has been deleted.	Clarification.
	"Review diet and exercise goals" row: Removed.	Clarification. This review is part of Review Lifestyle Program instructions.
5.2. Exclusion Criteria	Deleted criterion 48.	Duplicate criterion (Criterion 49).

Section # and Name	Description of Change	Brief Rationale
8.1.3.1. Actigraphy	Modified text, "Participants should wear the a~~A~~ctigraphy device for 7 consecutive days, 5 times during the study, per the SoA."	Clarification.
8.2.1. Physical Examination	Modified text, "A symptom-directed physical assessment will be performed ~~at visits~~ as indicated in the SoA, as clinically indicated."	Clarification, for consistency with changes in the "Symptom-directed physical assessment" row in the SoA.
10.8.2. Measuring Weight	Modified text, "Body weight will be measured in fasting state at all visits except Visit 1."	Clarification.
Throughout	Editorial corrections.	Minor, therefore not described.

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