Protocol I8F-JE-GPHZ (b)

Efficacy and Safety of Once-Weekly Tirzepatide in Participants with Obesity Disease: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-J)

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Approval Date: 11-Jun-2021

Title Page

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Protocol Number: I8F-JE-GPHZ

Amendment Number: b

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Study Phase: 3

Short Title: Efficacy and Safety of Tirzepatide Once Weekly Versus Placebo in Participants with Obesity Disease (SURMOUNT-J)

Acronym: SURMOUNT-J

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Regulatory Agency Identifier Number(s): Not applicable

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

Approval Date: 11-Jun-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment (a)	*18-Jan-2021*
Original Protocol	*30-Oct-2020*

Amendment [b]

Overall Rationale for the Amendment:

The correction of inclusion criteria is the primary driver for this amendment.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities Table 3	Changed from "IWQoL-CT" To "IWQoL-Lite-CT"	Typo
5.1 Inclusion Criteria	Inclusion criteria 2a has been updated from "…and OGTT 2-hour glucose of ≥140 mg/dL…." to "…, and/or OGTT 2-hour glucose of ≥140 mg/dL…"	In order to improve enrolment feasibility without compromising scientific validity.
5.1 Inclusion Criteria	Added the following sentence to criteria 2a. "In this study, IGT is defined to include impaired fasting glucose also described as "Borderline type" according to Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020)."	Added for clarity.
5.2 Exclusion Criteria	Exclusion Criteria 1 has been updated from "...(fasting glucose or OGTT 0-hour ≥126 mg/dL, OGTT 2-hour glucose ≥200 mg/dL)…" to	Modified for clarity

Section # and Name	Description of Change	Brief Rationale
	"…(fasting glucose or OGTT 0-hour ≥126 mg/dL and/or OGTT 2-hour glucose ≥200 mg/dL)…"	
5.2 Exclusion Criteria	Exclusion Criteria 26 has been updated from "…or alternative remedies intended to promote weight loss." to "…or alternative remedies intended to promote weight loss or may cause weight reduction."	Modified for clarity
6.5 Concomitant Therapy	Description for permitted use of concomitant therapy has been updated from "Participants will be permitted to use concomitant medications on a stable dose for at least 3 months prior study entry and the dosage change is not allowed during the study other than there are concerns about the safety issue, except certain medications (for example; other medications for weight management) that may interfere with the assessment of efficacy and safety characteristics of the study treatments." to "Participants are permitted to use concomitant medications that they require during the study, with the exception of certain medications (for example; other medications for weight management) that may interfere with the assessment of efficacy and safety characteristics of the study treatments. Any concomitant medications taken for obesity-related health	Rearranged wording and sentence structure for clarity.

Section # and Name	Description of Change	Brief Rationale
	problems on a stable dose for at least a period of 3 months prior to study entry will be permitted. Dosage change during the study will only be allowed if concerns for safety issue are identified."	
7.2 Participant Discontinuation/Withdrawal from the Study	Changed from "At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the Schedule of Activities" to "When discontinuing from the study prior to Visit 21 or Visit 99, an early discontinuation visit should be conducted if possible, as described in the Schedule of Activities"	Modified for clarity
8.1.2.2 2-Hour Oral Glucose Tolerance Test	Changed from "Definition of IGT from 2-hour OGTT results: fasting glucose or 0-hour OGTT = 110-125 mg/dL (6.1-6.9 mmol/L) and 2-hour OGTT = 140-199 mg/dL (7.8-11.0 mmol/L)." to "Definition of IGT from 2-hour OGTT results: fasting glucose or 0-hour OGTT = 110-125 mg/dL (6.1-6.9 mmol/L) and/or 2-hour OGTT = 140-199 mg/dL (7.8-11.0 mmol/L)."	This change is made to reflect the change implemented in section 5.1
8.1.3 Exploratory Efficacy Assessments Incident Diabetes	Changed the laboratory evidence of diabetic type criteria for OGTT 0-hr and 2-hr glucose from: "…(fasting glucose or OGTT 0-hour glucose ≥126 mg/dL, OGTT 2-hour glucose ≥200 mg/dL)…"	Modified for clarity

Section # and Name	Description of Change	Brief Rationale
	to "…(fasting glucose or OGTT 0-hour glucose ≥126 mg/dL and/or OGTT 2-hour glucose ≥200 mg/dL)…"	
10.12 Appendix 12: 2-Hour Oral Glucose Tolerance Test Flow Chart	Changed the 0hr and 2hr OGTT condition in the flowchart from "AND" to "AND/OR" and added dashed line to separate the OGTT and HbA1c condition	This change is made to reflect the change implemented in section 5.1 and for additional clarity of the figure.
Protocol header	Study alias in the header has been changed from "Protocol I8F-JE-GPHZ(a)" to "Protocol I8F-JE-GPHZ(b)"	This change is made to reflect the amendment version of this protocol.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:
Efficacy and Safety of Once-Weekly Tirzepatide in Participants with Obesity Disease: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-J)

Short Title:

Efficacy and Safety of Once-Weekly Tirzepatide Versus Placebo in Participants with Obesity Disease (SURMOUNT-J)

Rationale:
In general, the accumulation of slight imbalances in daily energy balance causes weight gain and leads to obesity. Obesity is a major risk factor for many comorbid diseases, such as stroke, coronary artery disease, diabetes, malignant disease, and motor dysfunction, which cause a lower quality of life and shortened life expectancy (JASSO 2016; Haneda et al. 2018). In Japan, body mass index (BMI) ≥25 kg/m^2 is defined as obese, and an obese person with obesity-related health problems and medically requiring weight loss is defined as having "obesity disease" (Matsuzawa 2011). In particular, 3 metabolic disorders in the obesity-related health disorders (impaired glucose tolerance [IGT], hyperlipidemia, and non-alcoholic fatty liver disease [NAFLD]), are located upstream of the metabolic syndrome (Ito 2003), and promote the onset and progression of complications. The guidelines proposed by the Japan Society for the Study of Obesity (JASSO) also suggest that the objective of medical therapy for obesity disease is to accelerate weight loss safely, leading to improvement in complications of obesity, and to suppress the combined use of multiple drugs in patients who have difficulty achieving weight loss goals by individual efforts alone.

The gut incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are secreted after meal ingestion and mediate the incretin effect. Both hormones have effects on endocrine cells in the pancreas, increasing insulin biosynthesis and secretion, and modifying glucagon secretion (Skow et al. 2016). Based on these properties, several GLP-1 receptor (GLP-1R) agonists have been approved for pharmacological treatment of type 2 diabetes mellitus (T2DM) (Tomlinson et al. 2016).

In addition to its pancreatic effects, GLP-1R activation decreases gut motility, slows gastric emptying, and promotes satiety (presumably through a combination of GLP-1R activation in the central and peripheral nervous systems), thereby regulating food intake and body weight (Baggio and Drucker 2007). The US Food and Drug Administration and the European Medicines Agency approved the GLP-1R agonist liraglutide for the treatment of individuals who are overweight or obese (Saxenda® package insert, 2014; Saxenda® SmPc, 2015), which is not approved in Japan.

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

in body weight regulation and targeting both the GLP-1R and the GIPR simultaneously may result in additive or synergistic effects of the 2 incretins on body weight (Coskun et al. 2018).

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

As a dual GIP/GLP-1R agonist, tirzepatide could exceed the efficacy of selective GLP-1R agonists by recruiting metabolically active tissues not targeted by selective GLP-1R agonists (for example, adipose tissue as indicated by the observation of increased energy utilization) (Müller et al. 2018) and has the potential to reach higher efficacy in target tissues, such as insulin-producing pancreatic beta cells that express both GIPR and GLP-1R, before reaching its therapeutic limitation.

Study I8F-JE-GPHZ (GPHZ) is a Phase 3, multicenter, randomized, placebo-controlled, double-blinded study of the safety and efficacy of tirzepatide 10 mg and 15 mg QW, compared with placebo, when used in conjunction with a reduced-calorie diet and increased physical activity for weight management, in obesity disease participants with BMI ≥27 kg/m^2 and at least 2 obesity-related health problems or participants with BMI ≥35 kg/m^2 and at least 1 obesity-related health problem. The obesity-related health problems are defined as IGT, hyperlipidemia, and NAFLD. The co-primary endpoint will be to demonstrate that QW tirzepatide 10 mg and/or 15 mg are superior to placebo in both mean percent changes in body weight and proportion of participants who achieve ≥5% body weight reduction from baseline to 72 weeks in participants with obesity disease.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate that once-weekly tirzepatide, at doses of 10 mg and/or 15 mg, is superior to placebo in terms of body weight reduction from BL to 72 weeks in Japanese participants with obesity disease	○ Mean percent change in body weight at Week 72 and ○ Proportion of participants who achieve ≥5% body weight reduction at Week 72
Secondary	
To compare the efficacy of once-weekly tirzepatide 10 mg and/or 15 mg with placebo for	
○ Improvement in obesity-related health problems (72 weeks)	○ Proportion of participants who met the following criteria at 72 weeks from BL ○ Improvement in at least 2 obesity-related health problems for participants with BL BMI ≥27 and <35 kg/m^2, or ○ Improvement in at least 1 obesity-related health problem for participants with BL BMI ≥35 kg/m^2
○ Improvement in laboratory tests for obesity-related health problems (72 weeks)	○ Mean changes in the following laboratory tests at 72 weeks from BL ○ OGTT 2-hr glucose (only for participants with IGT at BL) ○ Fasting glucose (only for participants with IGT at BL) ○ Fasting lipids (TG) (only for participants with hyperlipidemia at BL) ○ HFF (only for participants diagnosed as NAFLD by MRI at BL)
○ Improvement of IGT (72 weeks)	○ Proportion of participants who achieved improvements of IGT (only for participants with IGT at BL)
○ Improvement of hyperlipidemia (72 weeks)	○ Proportion of participants who achieved improvements of hyperlipidemia (only for participants with hyperlipidemia at BL)
○ Improvement of NAFLD (72 weeks)[a]	○ Proportion of participants who achieved improvements of NAFLD (only for participants who are diagnosed as NAFLD by MRI at BL)

Objectives	Endpoints
○ **Body mass related parameters**	
○ Change in body weight (24, 52, and 72 weeks)	○ Proportion of participants who achieve the following criteria from BL ○ ≥5% body weight reduction (only at 24 and 52 weeks) ○ ≥7% body weight reduction ○ ≥10% body weight reduction ○ ≥15% body weight reduction ○ ≥20% body weight reduction ○ Mean change from BL in ○ Absolute body weight ○ BMI ○ Mean percent change from BL in body weight (only at 24 and 52 weeks) ○ Mean EWL
○ Change in VAT and SAT (72 weeks)	○ Mean change from BL in ○ VAT ○ SAT ○ VAT/SAT ratio ○ Mean percent change from BL in ○ VAT ○ SAT ○ VAT/SAT ratio ○ Proportion of participants who achieve VAT <100 cm^2 (only for participants with VAT ≥100 cm^2 at BL) from BL
○ Change in waist circumference (24, 52, and 72 weeks)	○ Mean change from BL in waist circumference
○ **IGT related parameters (only for participants with IGT at BL)**	
○ Change in IGT related parameters (24, 52, and 72 weeks)	○ Mean change from BL in ○ Fasting glucose ○ HbA1c ○ Fasting insulin ○ C-peptide ○ HOMA2-%B ○ HOMA2-%S
○ **Hyperlipidemia related parameters (only for participants with hyperlipidemia at BL)** ○ Change in fasting lipids (24, 52, and 72 weeks)	Mean change from BL in ○ TG ○ TC ○ VLDL-C ○ LDL-C (direct) ○ HDL-C ○ Non-HDL-C ○ FFA

Objectives	Endpoints
○ **NAFLD related parameters**	
○ Change in NAFLD/NASH biomarkers (24, 52, and 72 weeks)	○ Mean change from BL in ○ ALT ○ AST ○ GGT ○ AST/ALT ratio ○ K-18 (M30) ○ Pro C3 ○ ELF ○ FIB-4 index
○ **Other parameters**	
○ Change in blood pressure (24, 52, and 72 weeks)	○ Mean changes from BL in ○ Systolic blood pressure ○ Diastolic blood pressure
○ Change in uric acid (24, 52, and 72 weeks)	○ Mean change from BL in uric acid
○ **Patient-reported outcomes**	
○ Change in patient-reported physical functioning (72 weeks)	○ Mean change from BL in SF-36v2 acute form physical functioning domain score from BL ○ Mean change in IWQOL-Lite-CT Physical Function score
○ Change in patient-reported health status (72 weeks)	○ Mean change in EQ-5D-5L score from BL ○ Index score ○ VAS score
○ Change in dietary evaluation based on the meal record (24, 52, and 72 weeks)[b]	○ Mean change from BL in ○ Total fats ○ Total carbohydrates ○ Total proteins ○ Total caloric intake
○ Change in dietary evaluation based on appetite sensation (24, 52, and 72 weeks)[c]	○ Mean change (VAS) from BL in ○ Satiety ○ Fullness ○ Prospective food consumption ○ Hunger ○ Overall appetite score
To characterize the population PK of tirzepatide and explore the relationships between the tirzepatide concentration and efficacy, safety, tolerability, and pharmacogenetics measures	○ Population PK and PD parameters

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; BMI = body mass index; ELF = enhanced liver fibrosis; EQ-5D-5L = EuroQol - 5 Dimension - 5 Level; EWL = excess weight loss; FIB-4 = Fibrosis-4; FFA = free fatty acid; GGT = gamma-glutamyl transferase; HbA1c = glycated hemoglobin; HDL-C = high density lipoprotein cholesterol; HFF = hepatic fat fraction; HOMA2-%B = homeostasis model assessment estimates steady state beta cell function; HOMA2-%S = homeostasis model assessment estimates steady state insulin sensitivity; IGT = impaired glucose tolerance; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials version; K-18 (M30) = keratin-18 M30 fragment; LDL-C = low density lipoprotein cholesterol; MRI = magnetic

resonance imaging; NAFLD = non-alcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; OGTT = oral glucose tolerance test; PD = pharmacodynamics; PK = pharmacokinetics; Pro-C3 = a fragment of the NH2-terminal propeptide of type III procollagen; SAT = subcutaneous adipose tissue; SF-36v2 = Short-Form 36-item Health Survey Version 2; TC = total cholesterol; TG = triglyceride; VAS = visual analog scale; VAT = visceral adipose tissue; VLDL-C = very low density lipoprotein cholesterol

a To compare the efficacy of once-weekly tirzepatide with placebo, improvement of NAFLD at 72 weeks will be combined with all doses.

b Individual daily meal intake information (photographs and record sheet), including breakfast, lunch, dinner, and snacks, will be collected on 3 consecutive or non-consecutive days during the week before the visit. These records will be collected only from participants who agree to participate in taking these measurements.

c Appetite sensation will be measured by a 100-mm VAS for parameters of hunger, fullness, satiety, and prospective food consumption, including snacks before and after meal recorded on 3 consecutive or non-consecutive days during the week immediately before the visit. These records will be collected only from participants who agree to participate in taking these measurements.

Overall Design

Study GPHZ is a Phase 3, multicenter, randomized, placebo-controlled, double-blinded study to evaluate the safety and efficacy of tirzepatide 10 mg and 15 mg administered subcutaneously once weekly compared with placebo when used in conjunction with a reduced-calorie diet and increased physical activity for weight management, in participants who have

- A BMI of 27 kg/m^2 or greater and less than 35 kg/m^2 and at least 2 obesity-related health problems; OR
- A BMI of 35 kg/m^2 or greater and at least 1 obesity-related health problem.

Obesity-related health problems are defined as IGT, hyperlipidemia, or NAFLD.

All participants will undergo a 4-week screening period and a 72-week treatment period including a 20-week dose escalation. The safety follow-up period will be 4 weeks.

Study participants will be randomized in a 1:1:1 ratio to tirzepatide 10 mg QW, tirzepatide 15 mg QW, or placebo QW, stratified by

- baseline IGT (yes or no)
- baseline hyperlipidemia (yes or no)
- baseline NAFLD (yes or no), and
- sex (male, female).

Disclosure Statement:

This is a parallel group-treatment study with 3 arms that is participant- and investigator-blinded.

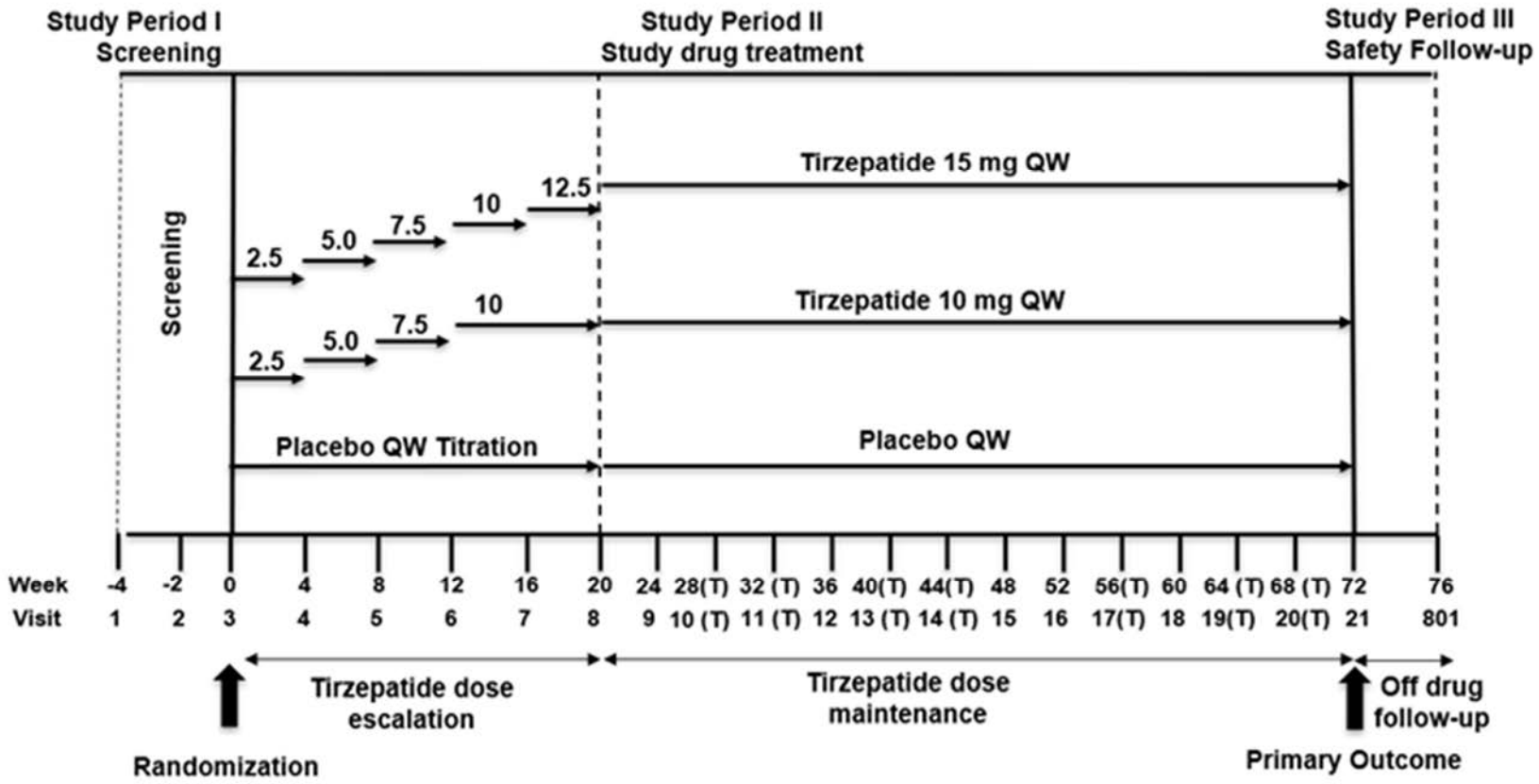
Number of Participants:

Approximately 348 participants will be screened to achieve 261 randomly assigned to study intervention for an estimated total of 87 evaluable participants per intervention group.

Intervention Groups and Duration:

All doses will be subcutaneously administered once-weekly using single-use pens. The starting dose of tirzepatide will be 2.5 mg QW (or matching placebo) for 4 weeks, then the dose will be increased by 2.5 mg (or matching placebo) every 4 weeks: 2.5 to 5 to 7.5 to 10 mg for those randomized to 10 mg, and continuing to 12.5 to 15 mg for those randomized to 15 mg.

1.2. Schema



Abbreviations: QW= once weekly; T= telephone visit.
All participants will be randomized to 72 weeks of treatment.

Figure 1. Study design for Clinical Protocol I8F-JE-GPHZ.

1.3. Schedule of Activities

Table 1. Study Period I -Screening and Randomization

Activity	Screening		Randomization	Comments
Visit number	**1**	**2**	**3**	
Week of treatment	**-4**	**-2**	**0**	
Allowable deviation (days)	**NA**	**-7/+3**	**-3/+7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window. Patients must be fasting at least 10 hours before blood sampling.
Informed consent	X			
Randomization			X	
Medical history	X			
Obesity disease assessment	X			Eleven of obesity-related health problems defined by JASSO will be utilized (Appendix 13, Section 10.13).
Adverse events and product complaints	X	X	X	At Visit 2, this activity can be performed on same day as OGTT test.
Concomitant medications	X	X	X	At Visit 2, this activity can be performed on same day as OGTT test.
Hand out diary, instruct in use			X	All training should be repeated as needed to ensure participant compliance.
Lifestyle management counseling			X	Counselling on diet and exercise, to be performed by a dietician or equivalent qualified delegate, will include calculation of individualized energy requirement and methods to change dietary composition and amount of physical activity. The lifestyle management counseling may be delivered on a separate day from the rest of that visit's study procedures but must occur within the visit window.
Review diet and exercise goals			X	
Injection training with auto-injector demonstration device			X	
Dispense study drug			X	

Activity	Screening		Randomization	Comments
Visit number	**1**	**2**	**3**	
Week of treatment	**-4**	**-2**	**0**	
Allowable deviation (days)	**NA**	**-7/+3**	**-3/+7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window. Patients must be fasting at least 10 hours before blood sampling.
Observe participant administer study drug			X	
Patient-reported outcomes measurements				
SF-36v2, acute form			X	
IWQoL-Lite-CT			X	
EQ-5D-5L			X	
Patient Global Impression of Status			X	
C-SSRS (baseline/screening version)	X			
C-SSRS (since last visit version)		X	X	At Visit 2, C-SSRS can be performed on same day as OGTT test.
PHQ-9	X		X	
Self-harm supplement form	X	X	X	At Visit 2, self-harm supplement form can be performed on same day as OGTT test.
Self-harm follow-up form	X	X	X	At Visit 2, self-harm follow up form can be performed on same day as OGTT test.
CT and MRI				
Visceral and subcutaneous adipose tissue imaging		X		Image analysis to be conducted centrally. Either CT or MRI can be used for the adipose tissue imaging. The chosen method needs to be consistent across all visits for each participant.

Activity	Screening		Randomization	Comments
Visit number	**1**	**2**	**3**	
Week of treatment	**-4**	**-2**	**0**	
Allowable deviation (days)	**NA**	**-7/+3**	**-3/+7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window. Patients must be fasting at least 10 hours before blood sampling.
Hepatic fat fraction by MRI-PDFF (only for participants who enroll as NAFLD)		X		Image analysis to be conducted centrally. For individuals where the MRI-PDFF image quality is in question, and re-capturing and assessment of the MRI image is required before 1st dose of study drug, due to the turnaround time of a central image analysis, a flexible screening window will be allowed. In such scenarios, a Visit 3 that occurs outside of the visit window will not be considered a protocol deviation.
2-Hour OGTT				
Glucose, insulin, and c-peptide		X		2-Hour OGTT test can occur 0 to 4 days prior to the visit.
Physical evaluation				
Physical examination	X			
Height	X			
Weight	X		X	Body weight must be measured in fasting state.
Waist circumference			X	
Electrocardiogram			X	Triplicate ECGs should be collected centrally at Visit 3.
Vital signs (sitting BP and PR)	X		X	Vital sign measurements should be taken before collection of blood samples for laboratory testing, at visits where required. The participant should sit quietly for 5 minutes before vital sign measurements are taken. For each parameter, 2 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart.
Clinical laboratory tests				
Hematology	X			
Clinical chemistry panel	X		X	
Other chemistry				

Activity	Screening		Randomization	Comments
Visit number	**1**	**2**	**3**	
Week of treatment	**-4**	**-2**	**0**	
Allowable deviation (days)	**NA**	**-7/+3**	**-3/+7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window. Patients must be fasting at least 10 hours before blood sampling.
Cystatin-c	X			
HbA1c	X	X	X	Collection of blood samples for HbA1c can be performed on same day as OGTT test. The collection must be before OGTT test.
Urine chemistry (albumin, creatinine, albumin/creatinine ratio)	X		X	
Urinalysis	X		X	
Hormones (females)				
Serum pregnancy test (β-HCG)	X			A serum pregnancy test will be performed by central laboratory at Visit 1 for women of childbearing potential only.
Urine pregnancy test			X	A urine pregnancy test will be performed locally for women of childbearing potential
Follicle-stimulating hormone test	X			Follicle-stimulating hormone test performed at Visit 1 for postmenopausal women at least 40 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 1 year without an alternative medical cause.
Screening liver panel	X			Refer to Exclusion Criterion 3. Hepatitis B surface antigen, anti-hepatitis C antibodies and RNA, anti-mitochondrial antibodies should be done as clinically appropriate.
Pancreas (pancreatic amylase, lipase)	X		X	
Endocrine				
Calcitonin	X			
Thyroid stimulating hormone	X			
Adiponectin (high molecular weight and total) and leptin			X	

Activity	Screening		Randomization	Comments
Visit number	**1**	**2**	**3**	
Week of treatment	**-4**	**-2**	**0**	
Allowable deviation (days)	**NA**	**-7/+3**	**-3/+7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window. Patients must be fasting at least 10 hours before blood sampling.
Insulin and C-peptide			X	
Lipid panel	X	X	X	Study eligibility was determined by laboratory TG data sampled at Visits 1 and 2, at which fasting blood samples were collected for the assessment of clinical laboratory findings if both TGs are ≥150 mg/dL. Collection of blood samples for lipid panel for Visit 2 can be performed on same day as OGTT test. The collection must be before OGTT test.
NAFLD/NASH biomarkers (K-18, Pro-C3, ELF, FIB-4 index)			X	
Inflammatory markers (hsCRP and TNFα)			X	
Other tests				
Immunogenicity			X	
Pharmacokinetics			X	
Pharmacogenetic stored sample			X	
Non-pharmacogenetic stored samples			X	
Dietary evaluation				
Meal intake			X	Individual daily meal intake information (photographs and record sheet), including breakfast, lunch, dinner, and snacks, will be collected on 3 consecutive or non-consecutive days during the week immediately before the visit. These records will be collected only from participants who agree to participate in taking these measurements.

Activity	**Screening**		**Randomization**	**Comments**
Visit number	**1**	**2**	**3**	
Week of treatment	**-4**	**-2**	**0**	
Allowable deviation (days)	**NA**	**-7/+3**	**-3/+7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window. Patients must be fasting at least 10 hours before blood sampling.
Appetite sensation			X	Appetite sensation will be measured by a 100-mm VAS for parameters of hunger, fullness, satiety, and prospective food consumption including snacks before and after meal recorded on 3 consecutive or non-consecutive days during the week immediately before the visit. These records will be collected only from participants who agree to participate in taking these measurements.

Abbreviations: β-HCG = β-human chorionic gonadotropin; BP = blood pressure; C-SSRS = Columbia-suicide severity rating scale; CT = computed tomography; ECG = electrocardiogram; ELF = enhanced liver fibrosis; EQ-5D-5L = EuroQol - 5 Dimension - 5 Level; FIB-4 = Fibrosis-4; HbA1c = glycated hemoglobin; hsCRP = high-sensitivity C-reactive protein; IWQoL-Lite-CT = Impact of Weight on Quality of Life-Lite-Clinical trials version; JASSO = Japan Society for the Study of Obesity; K-18 = keratin-18 M30 fragment; MRI = magnetic resonance imaging; MRI-PDFF = magnetic resonance imaging - proton density fat fraction; NA = not applicable; NAFLD = non-alcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; OGTT = oral glucose tolerance test; PHQ-9 = Patient Health Questionnaire-9; PR = pulse rate; Pro-C3 = a fragment of the NH2-terminal propeptide of type III procollagen; RNA = ribonucleic acid; SF-36v2 = Short-Form 36-item Health Survey Version 2; TG = triglyceride; TNFα = tumor necrosis factor-α; VAS = visual analog scale.

Table 2. Study Period II-Treatment Period

Activity	Treatment Period																		Comments
Visit number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Week of treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	
Allowable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**		**X**			**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Telephone visit							**X**	**X**		**X**	**X**			**X**		**X**	**X**		Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.
Adverse events and product complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hand out diary, instruct in use			X			X			X			X			X				
Lifestyle management counseling	X	X	X			X			X			X	X		X			X	Counseling on diet and exercise, to be performed by a dietician or equivalent qualified delegate, will include calculation of individualized energy requirement and methods to change dietary composition and amount of physical activity. The lifestyle management counseling may be delivered on a separate day from the rest of that visit's study procedures but must occur within the visit window.

Activity	**Treatment Period**																		**Comments**
Visit number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Week of treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	
Allowable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**		**X**			**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Telephone visit							**X**	**X**		**X**	**X**			**X**		**X**	**X**		Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.
Review diet and exercise goals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study drug	X	X	X	X	X	X			X			X	X		X				
Participant returns study drugs and injection supplies	X	X	X	X	X	X			X			X	X		X			X	
Review study participant diary, including study drug compliance and hypoglycemic events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient-reported outcome measures																			
SF-36v2, acute form																		X	
IWQoL-Lite-CT																		X	
EQ-5D-5L																		X	

Activity	Treatment Period																		Comments
Visit number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Week of treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	
Allowable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**		**X**			**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Telephone visit							**X**	**X**		**X**	**X**			**X**		**X**	**X**		Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.
Patient Global Impression of Status																		X	
C-SSRS (since last visit version)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PHQ-9			X			X			X			X			X			X	
Self-harm supplement form	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Self-harm follow-up form	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CT and MRI																			
Visceral and subcutaneous adipose tissue imaging																		X	Image analysis to be conducted centrally. Either CT or MRI can be used for the adipose tissue imaging. The chosen method needs to be consistent between all visits for each participant. At Visit 21, CT or MRI can be done with -28/+7 days allowance, which means this can be combined with Visit 20.

Activity	**Treatment Period**																		**Comments**
Visit number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Week of treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	
Allowable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**		**X**			**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Telephone visit							**X**	**X**		**X**	**X**			**X**		**X**	**X**		Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.
Hepatic fat fraction by MRI-PDFF (only for participants who enroll as NAFLD)																		X	At Visit 21, MRI can be done with -28/+7 days allowance, which means this can be combined with Visit 20.
2-Hour OGTT																			
Glucose, insulin, c-peptide						X							X					X	2-Hour OGTT can occur 0 to 4 days prior to the visit.
Physical evaluation																			
Weight	X	X	X	X	X	X			X			X	X		X			X	Body weight must be measured in fasting state.
Waist circumference	X	X	X	X	X	X			X			X	X		X			X	
Electrocardiogram						X												X	Single ECGs should be collected centrally at Visit 9 and Visit 21.

Activity	Treatment Period																		Comments
Visit number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Week of treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	
Allowable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**		**X**			**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Telephone visit							**X**	**X**		**X**	**X**			**X**		**X**	**X**		Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.
Vital signs (sitting BP and PR)	X	X	X	X	X	X			X			X	X		X			X	Vital sign measurements should be taken before collection of blood samples for laboratory testing, at visits where required. The participant should sit quietly for 5 minutes before vital sign measurements are taken. For each parameter, 2 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart.
Clinical laboratory tests																			
Hematology			X			X							X					X	
Clinical chemistry panel						X							X					X	
Other chemistry						X							X					X	
Cystatin-c						X							X					X	
HbA1c			X			X			X			X	X		X			X	

Activity	Treatment Period																		Comments
Visit number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Week of treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	
Allowable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**		**X**			**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Telephone visit							**X**	**X**		**X**	**X**			**X**		**X**	**X**		Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.
Urine chemistry (albumin, creatinine, albumin/creatinine ratio)			X			X			X				X		X			X	
Urinalysis			X			X			X				X		X			X	
Hormones (females)																			
Urine pregnancy test			X			X			X			X			X			X	A urine pregnancy test will be performed locally for women of childbearing potential
Pancreas (pancreatic amylase, lipase)			X			X							X					X	
Endocrine																			
Calcitonin			X			X												X	
Adiponectin (high molecular weight and total) and leptin						X							X					X	
Insulin and C-peptide			X			X			X			X	X		X			X	
Lipid panel						X							X					X	

Activity	**Treatment Period**																		**Comments**
Visit number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Week of treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	
Allowable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**		**X**			**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Telephone visit							**X**	**X**		**X**	**X**			**X**		**X**	**X**		Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.
NAFLD/NASH biomarkers (K-18, Pro-C3, ELF, FIB-4 index)						X							X					X	
Inflammatory markers (hsCRP and TNFα)						X							X					X	
Other tests																			
Immunogenicity	X		X			X							X					X	
Pharmacokinetics	X		X			X							X					X	
Non-pharmacogenetic stored samples			X			X							X					X	

Activity	Treatment Period																		Comments
Visit number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Week of treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	
Allowable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**		**X**			**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Telephone visit							**X**	**X**		**X**	**X**			**X**		**X**	**X**		Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.
Dietary evaluation																			
Meal intake						X							X					X	Individual daily meal intake information (photographs and record sheet), including breakfast, lunch, dinner and snacks, will be collected on 3 consecutive or non-consecutive days during the week immediately before the visit. These records will be collected only from participants who agree to participate in taking these measurements.

Activity	Treatment Period																		Comments
Visit number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
Week of treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	
Allowable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**		**X**			**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Telephone visit							**X**	**X**		**X**	**X**			**X**		**X**	**X**		Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.
Appetite sensation						X							X					X	Appetite sensation will be measured by a 100-mm VAS for parameters of hunger, fullness, satiety, and prospective food consumption including snacks before and after meal recorded on 3 consecutive or non-consecutive days during the week immediately before the visit. These records will be collected only from participants who agree to participate in taking these measurements.

Abbreviations: BP = blood pressure; C-SSRS = Columbia-suicide severity rating scale; CT = computed tomography; ECG = electrocardiogram; EQ-5D-5L = EuroQol - 5 Dimension - 5 Level; HbA1c = glycated hemoglobin; hsCRP = high-sensitivity C-reactive protein; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite-Clinical trials version; MRI = magnetic resonance imaging; MRI-PDFF = magnetic resonance imaging - proton density fat fraction; NAFLD = non-alcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; OGTT = oral glucose tolerance test; PHQ-9 = Patient Health Questionnaire-9; PR = pulse rate; SF-36v2 = Short-Form 36-item Health Survey Version 2; TNFα = tumor necrosis factor-α; VAS = visual analog scale.

Table 3. Study Period III- Early Discontinuation and Follow-Up Period

Activity	**Early Discontinuation and Follow-Up Period**			**Comment**
Visit Number	**99**	**ED**	**801**	At ED visit, participants who are unable or unwilling to continue the study treatment for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit. At Visit 801, for participants who discontinue or complete the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit during the 72-week treatment period.
Weeks of treatment	**72**		**4 weeks post end of treatment period**	
Allowable duration (days)	**±7**		**±7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Adverse events and product complaints	X	X	X	
Hypoglycemic events	X	X	X	
Concomitant medications	X	X	X	
Lifestyle management counseling		X		Counselling on diet and exercise, to be performed by a dietician or equivalent qualified delegate, will include calculation of individualized energy requirement and methods to change dietary composition and amount of physical activity. The lifestyle management counseling may be delivered on a separate day from the rest of that visit's study procedures but must occur within the visit window.
Review diet and exercise goals		X		
Participant returns study drugs and injection supplies		X		

Activity	**Early Discontinuation and Follow-Up Period**			**Comment**
Visit Number	**99**	**ED**	**801**	At ED visit, participants who are unable or unwilling to continue the study treatment for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit. At Visit 801, for participants who discontinue or complete the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit during the 72-week treatment period.
Weeks of treatment	**72**		**4 weeks post end of treatment period**	
Allowable duration (days)	**±7**		**±7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Review study participant diary, including study drug compliance		X		
Patient-reported outcome measurements				
SF-36v2, acute form		X		
IWQoL-Lite-CT		X		
EQ-5D-5L		X		
Patient Global Impression of Status		X		
C-SSRS (since last visit version)	X	X	X	
PHQ-9	X	X	X	
Self-harm supplement form	X	X	X	
Self-harm follow-up form	X	X	X	

Activity	Early Discontinuation and Follow-Up Period			Comment
Visit Number	**99**	**ED**	**801**	At ED visit, participants who are unable or unwilling to continue the study treatment for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit. At Visit 801, for participants who discontinue or complete the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit during the 72-week treatment period.
Weeks of treatment	**72**		**4 weeks post end of treatment period**	
Allowable duration (days)	**±7**		**±7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
CT and MRI				
Visceral and subcutaneous adipose tissue imaging		X		Image analysis to be conducted centrally. Either CT or MRI can be used for the adipose tissue imaging. The chosen method needs to be consistent between all visits for each participant. At ED visit, CT or MRI should only be performed on participants who have had at least 9 months (36 weeks) study drug exposure; for those participants, the procedures should be done within 2 weeks (+2 weeks) as much as possible of the last dose of study drug.
Hepatic fat fraction by MRI-PDFF (only for participants who enroll as NAFLD)		X		Early discontinuation MRI-PDFF procedures should only be performed on participants who have had at least 9 months (36 weeks) study drug exposure; for those participants, MRI-PDFF procedures should be collected within 2 weeks (+2 weeks) as much as possible of the last dose of study drug.

Activity	Early Discontinuation and Follow-Up Period			Comment
Visit Number	**99**	**ED**	**801**	At ED visit, participants who are unable or unwilling to continue the study treatment for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit. At Visit 801, for participants who discontinue or complete the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit during the 72-week treatment period.
Weeks of treatment	**72**		**4 weeks post end of treatment period**	
Allowable duration (days)	**±7**		**±7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
2-Hour OGTT				
Glucose, insulin, c-peptide		X		Early discontinuation 2-Hour OGTT procedures should only be performed on participants who have had at least 9 months (36 weeks) study drug exposure; for those participants, 2-Hour OGTT procedures should be collected within 2 weeks (+2 weeks) as much as possible of the last dose of study drug and participant must be fasting at least 10 hours prior to start of the OGTT (samples taken at 0, 30, 60, 90, and 120 minutes).
Physical evaluation				
Weight	X	X	X	At Visit 99, participants wanting to discontinue the study before Week 72 will be asked to return for Visit 99 at 72 weeks ±7 days after randomization primarily for body weight measurement and assessment of adverse events. If the participant is unwilling to attend Visit 99, it should be documented in the participant medical record that the participant has refused to attend.

Activity	Early Discontinuation and Follow-Up Period			Comment
Visit Number	**99**	**ED**	**801**	At ED visit, participants who are unable or unwilling to continue the study treatment for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit. At Visit 801, for participants who discontinue or complete the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit during the 72-week treatment period.
Weeks of treatment	**72**		**4 weeks post end of treatment period**	
Allowable duration (days)	**±7**		**±7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Waist circumference	X	X	X	
Electrocardiogram		X	X	Single ECGs should be collected centrally at ED and Visit 801
Vital signs (sitting BP and PR)		X	X	Vital sign measurements should be taken before collection of blood samples for laboratory testing, at visits where required. The participant should sit quietly for 5 minutes before vital sign measurements are taken. For each parameter, 2 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart.
Clinical laboratory tests				
Hematology		X	X	
Clinical chemistry		X	X	
Other chemistry				
Cystatin-c		X	X	

Activity	Early Discontinuation and Follow-Up Period			Comment
Visit Number	**99**	**ED**	**801**	At ED visit, participants who are unable or unwilling to continue the study treatment for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit. At Visit 801, for participants who discontinue or complete the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit during the 72-week treatment period.
Weeks of treatment	**72**		**4 weeks post end of treatment period**	
Allowable duration (days)	**±7**		**±7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
HbA1c		X	X	
Urine chemistry (albumin, creatinine, albumin/creatinine ratio)		X	X	
Urinalysis		X	X	
Hormones (females)				
Urine pregnancy test		X		A urine pregnancy test will be performed locally for women of childbearing potential
Pancreas (pancreatic amylase, lipase)		X	X	
Endocrine				
Calcitonin		X	X	
Adiponectin (high molecular weight and total) and leptin		X	X	
Insulin and C-peptide		X	X	

Activity	Early Discontinuation and Follow-Up Period			Comment
Visit Number	**99**	**ED**	**801**	At ED visit, participants who are unable or unwilling to continue the study treatment for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit. At Visit 801, for participants who discontinue or complete the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit during the 72-week treatment period.
Weeks of treatment	**72**		**4 weeks post end of treatment period**	
Allowable duration (days)	**±7**		**±7**	The visit date after randomization visit is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit	**X**	**X**	**X**	If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Lipid panel		X	X	
NAFLD/NASH biomarkers (K-18, Pro-C3, ELF, FIB-4 index)		X	X	
Inflammatory markers (hsCRP and TNFα)		X	X	
Other tests				
Immunogenicity		X	X	
Pharmacokinetics		X	X	
Non-pharmacogenetic stored samples		X	X	

Abbreviations: BP = blood pressure; C-SSRS = Columbia-suicide severity rating scale; CT = computed tomography; ED = early discontinuation; EQ-5D-5L = EuroQol - 5 Dimension - 5 Level; HbA1c = glycated hemoglobin; hsCRP = high-sensitivity C-reactive protein; IWQoL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical trials; MRI = magnetic resonance imaging; MRI-PDFF = magnetic resonance imaging - proton density fat fraction; NAFLD = non-alcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; OGTT = oral glucose tolerance test; PHQ-9 = Patient Health Questionnaire-9; PR = pulse rate; SF-36v2 = Short-Form 36-item Health Survey Version 2; TNFα = tumor necrosis factor-α.

2. Introduction

In general, the accumulation of slight imbalances in daily energy balance causes weight gain and leads to obesity. Obesity is a major risk factor for many comorbid diseases, such as stroke, coronary artery disease, diabetes, malignant disease, and motor dysfunction, which cause a lower quality of life and shortened life expectancy (JASSO 2016; Haneda et al. 2018). In Japan, body mass index (BMI) ≥25 kg/m^2 is defined as obese, and an obese person with obesity-related health problems and medically requiring weight loss is defined as having "obesity disease" (Matsuzawa 2011). In particular, 3 metabolic disorders in the obesity-related health disorders (impaired glucose tolerance [IGT], hyperlipidemia, and non-alcoholic fatty liver disease [NAFLD]), are located upstream of the metabolic syndrome (Ito 2003), and promote the onset and progression of complications. The guidelines proposed by the Japan Society for the Study of Obesity (JASSO) also suggest that the objective of medical therapy for obesity disease is to accelerate weight loss safely, leading to improvement in complications of obesity, and to suppress the combined use of multiple drugs in patients who have difficulty achieving weight loss goals by individual efforts alone.

2.1. Study Rationale

The gut incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are secreted after meal ingestion and mediate the incretin effect. Both hormones have effects on endocrine cells in the pancreas, increasing insulin biosynthesis and secretion, stimulating beta-cell neogenesis and proliferation, and protecting beta cells from apoptosis. They also exert actions on alpha cells, modifying glucagon secretion (Skow et al. 2016). Based on these properties, several GLP-1 receptor (GLP-1R) agonists have been approved for pharmacological treatment of type 2 diabetes mellitus (T2DM) (Tomlinson et al. 2016).

In addition to its pancreatic effects, GLP-1R activation decreases gut motility, slows gastric emptying, and promotes satiety (presumably through a combination of GLP-1R activation in the central and peripheral nervous system), thereby regulating food intake and body weight (Baggio and Drucker 2007). The US Food and Drug Administration and the European Medicines Agency approved the GLP-1R agonist liraglutide for the treatment of individuals who are overweight or obese (SAXENDA® package insert, 2014; SAXENDA® SmPc, 2015); this drug is not approved in Japan.

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

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

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

Study I8F-JE-GPHZ (GPHZ) is a Phase 3, multicenter, randomized, placebo-controlled, double-blinded study, to investigate the safety and efficacy of tirzepatide 10 mg and 15 mg QW, compared with placebo, when used in conjunction with a reduced-calorie diet and increased physical activity for body weight management in participants with BMI ≥27 kg/m^2 and at least 2 obesity-related health problems or participants with BMI ≥35 kg/m^2 and at least 1 obesity-related health problem. The obesity-related health problems are defined as IGT, hyperlipidemia, or NAFLD. The co-primary endpoint will be to demonstrate that QW tirzepatide 10 mg and/or 15 mg are superior to placebo in both mean percent changes in body weight and proportion of participants who achieve ≥5% body weight reduction from baseline to 72 weeks in patients with obesity disease.

2.2. Background

In Japan, if obesity disease is diagnosed, the patients try lifestyle intervention including diet, exercise, and behavioral therapy for 3 to 6 months to improve body weight and health problems. If improvement of the health problems is achieved by lifestyle modification therapy, the therapy is continued. If not, and any of following criteria are met; 1) BMI ≥25 kg/m^2, visceral fat area ≥100 cm^2 and 2 or more health problems, 2) BMI ≥35 kg/m^2 with 1 or more health problems, medical therapy is indicated. There remains an unmet need in the pharmacologic treatment of obesity for drugs that are safe, efficacious, and well tolerated. At present in Japan, Sanorex® (mazindol) is covered only for severely obese subjects by national health insurance with a prescription limit of 3 months or less. Chinese herbal medicines are also available. Bariatric surgery is also approved for severely obese subjects, but only laparoscopic sleeve gastrectomy is covered by national health insurance and some facilities implement laparoscopic sleeve gastrectomy with duodenojejunal bypass as an advanced medical treatment (JSTO 2013). Weight loss induced by GLP-1R agonists appears to be mediated through a combination of hormonal inputs to satiety centers (van Bloemendaal et al. 2014) and has not been consistently associated with changes in mental health or with potential for addiction in long-term studies conducted to establish cardiovascular safety in patients with diabetes (Marso et al. 2016a; Marso et al. 2016b; Gerstein et al. 2019). Tirzepatide, which is both a GLP-1R and GIPR agonist, has been associated with significant dose-dependent weight loss at 5-, 10-, and 15-mg doses in Phase 2 studies (Frias et al. 2018).

Dose selection for obesity treatment has been informed by 4 clinical trials: 2 Phase 1 studies (Study I8F-MC-GPGA [GPGA] and I8F-JE-GPGC [GPGC]), and 2 Phase 2 studies (Study I8F-MC-GPGB [GPGB] and I8F-MC-GPGF [GPGF]).

Phase 1 Study GPGA was a combination of single ascending dose and multiple ascending dose studies in healthy subjects and a multiple dose study in patients with T2DM. A total of

142 participants (89 healthy subjects and 53 patients with T2DM) received at least 1 dose of treatment. Doses of tirzepatide ranged from:

- 0.25 mg to 8 mg in the single ascending dose study (with maximum tolerated dose achieved at 5 mg)
- multiple doses from 0.5 mg to 4.5 mg QW and titrated doses up to 10 mg QW for 4 weeks in healthy subjects
- multiple doses at 0.5 mg and 5 mg QW and titrated up to 15 mg QW for 4 weeks in patients with T2DM in the multiple ascending dose study

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

In addition, the safety, tolerability, and PK/PD of tirzepatide were evaluated in Study GPGC; a Phase 1, 8-week multiple ascending dose study in Japanese patients with T2DM. This study involved a comparison of 3 QW, SC dose levels of tirzepatide or placebo:

- 2.5-mg to 10-mg titration regimen for Cohort 1
- 5-mg to 15-mg titration regimen for Cohort 2
- 5-mg fixed dose for Cohort 3

The safety and tolerability data and PK/PD profiles of tirzepatide in Study GPGC supported the use of doses up to 15 mg of tirzepatide in Japanese patients.

Phase 2 Study GPGB provided initial safety, tolerability, and efficacy data in the tirzepatide 1- to 15-mg dose range when used in treatment of patients with T2DM. In the dose range of 5 to 15 mg, tirzepatide provided significantly greater reductions in hemoglobin A1c (HbA1c) and body weight compared with dulaglutide 1.5 mg QW. The most common adverse events (AEs), which were also dose dependent, were mild-to-moderate nausea, vomiting, and diarrhea (Frias et al. 2018).

Phase 2 Study GPGF showed that adjustments in the tirzepatide dose-escalation algorithms resulted in additional reduction in the frequency of gastrointestinal (GI) AEs and reduced the frequency of treatment discontinuations due to GI AEs. Dose-escalation algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5-mg increments every 4 weeks should permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns. The maximum proposed dose of 15 mg maintains an exposure multiple of 1.6 to 2.4 to the no-observed adverse-effect level doses in 6-month monkey and rat toxicology studies. Based on interim data in Study GPGC, there were no clinically meaningful differences in the PK, PD, and safety profile between Japanese patients and non-Japanese patients with T2DM. Hence, the doses and associated escalation schemes chosen for this Phase 3 Study GPHZ are the same as that chosen for global studies.

These doses and associated escalation schemes were selected based on assessment of safety, efficacy (weight loss), and GI tolerability data, followed by exposure-response modeling of data

in patients in Phase 1 and 2 studies that predicted weight loss in obese and overweight patients without T2DM.

2.3. Benefit/Risk Assessment

Because tirzepatide is a long-acting, GIP and GLP-1 receptor dual agonist, the potential risks associated with tirzepatide may be similar to the risks associated with currently available long-acting GLP-1 receptor agonists. The known risks associated with increased GLP-1 receptor activity include but are not limited to: GI effects (particularly nausea, vomiting, and diarrhea), hepatobiliary effects (gall bladder disease and hepatic safety), pancreatic safety, cardiovascular risk (heart rate and blood pressure), hypoglycemic events, thyroid safety, developmental safety, and allergic/hypersensitivity reactions.

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

Considering the measures taken to minimize risks to participants in this study, the identified potential risks in association with Study GPHZ are justified by the anticipated benefits that may be afforded to participants with obesity disease.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate that once-weekly tirzepatide, at doses of 10 mg and/or 15 mg, is superior to placebo in terms of body weight reduction from BL to 72 weeks in Japanese participants with obesity disease	○ Mean percent change in body weight at Week 72 and ○ Proportion of participants who achieve ≥5% body weight reduction at Week 72
Secondary	
To compare the efficacy of once-weekly tirzepatide 10 mg and/or 15 mg with placebo for	
○ Improvement in obesity-related health problems (72 weeks)	○ Proportion of participants who met the following criteria at 72 weeks from BL ○ Improvement in at least 2 obesity-related health problems for participants with BL BMI ≥27 and <35 kg/m^2, or ○ Improvement in at least 1 obesity-related health problem for participants with BL BMI ≥35 kg/m^2
○ Improvement in laboratory tests for obesity-related health problems (72 weeks)	○ Mean changes in the following laboratory tests at 72 weeks from BL ○ OGTT 2-hr glucose (only for participants with IGT at BL) ○ Fasting glucose (only for participants with IGT at BL) ○ Fasting lipids (TG) (only for participants with hyperlipidemia at BL) ○ HFF (only for participants diagnosed as NAFLD by MRI at BL)
○ Improvement of IGT (72 weeks)	○ Proportion of participants who achieved improvements of IGT (only for participants with IGT at BL)
○ Improvement of hyperlipidemia (72 weeks)	○ Proportion of participants who achieved improvements of hyperlipidemia (only for participants with hyperlipidemia at BL)
○ Improvement of NAFLD (72 weeks)[a]	○ Proportion of participants who achieved improvements of NAFLD (only for participants who are diagnosed as NAFLD by MRI at BL)

Objectives	Endpoints
○ **Body mass related parameters**	
○ Change in body weight (24, 52, and 72 weeks)	○ Proportion of participants who achieve the following criteria from BL ○ ≥5% body weight reduction (only at 24 and 52 weeks) ○ ≥7% body weight reduction ○ ≥10% body weight reduction ○ ≥15% body weight reduction ○ ≥20% body weight reduction ○ Mean change from BL in ○ Absolute body weight ○ BMI ○ Mean percent change from BL in body weight (only at 24 and 52 weeks) ○ Mean EWL
○ Change in VAT and SAT (72 weeks)	○ Mean change from BL in ○ VAT ○ SAT ○ VAT/SAT ratio ○ Mean percent change from BL in ○ VAT ○ SAT ○ VAT/SAT ratio ○ Proportion of participants who achieve VAT <100 cm^2 (only for participants with VAT ≥100 cm^2 at BL) from BL
○ Change in waist circumference (24, 52, and 72 weeks)	○ Mean change from BL in waist circumference
○ **IGT related parameters (only for participants with IGT at BL)**	
○ Change in IGT related parameters (24, 52, and 72 weeks)	○ Mean change from BL in ○ Fasting glucose ○ HbA1c ○ Fasting insulin ○ C-peptide ○ HOMA2-%B ○ HOMA2-%S

Objectives	Endpoints
○ **Hyperlipidemia related parameters (only for participants with hyperlipidemia at BL)** ○ Change in fasting lipids (24, 52, and 72 weeks)	Mean change from BL in ○ TG ○ TC ○ VLDL-C ○ LDL-C (direct) ○ HDL-C ○ Non-HDL-C ○ FFA
○ **NAFLD related parameters**	
○ Change in NAFLD/NASH biomarkers (24, 52, and 72 weeks)	○ Mean change from BL in ○ ALT ○ AST ○ GGT ○ AST/ALT ratio ○ K-18 (M30) ○ Pro C3 ○ ELF ○ FIB-4 index
○ **Other parameters**	
○ Change in blood pressure (24, 52, and 72 weeks)	○ Mean changes from BL in ○ Systolic blood pressure ○ Diastolic blood pressure
○ Change in uric acid (24, 52, and 72 weeks)	○ Mean change from BL in uric acid
○ **Patient-reported outcomes**	
○ Change in patient-reported physical functioning (72 weeks)	○ Mean change from BL in SF-36v2 acute form physical functioning domain score from BL ○ Mean change in IWQOL-Lite-CT Physical Function score
○ Change in patient-reported health status (72 weeks)	○ Mean change in EQ-5D-5L score from BL ○ Index score ○ VAS score
○ Change in dietary evaluation based on the meal record (24, 52, and 72 weeks)[b]	○ Mean change from BL in ○ Total fats ○ Total carbohydrates ○ Total proteins ○ Total caloric intake
○ Change in dietary evaluation based on appetite sensation (24, 52, and 72 weeks)[c]	○ Mean change (VAS) from BL in ○ Satiety ○ Fullness ○ Prospective food consumption ○ Hunger ○ Overall appetite score

Objectives	Endpoints
To characterize the population PK of tirzepatide and explore the relationships between the tirzepatide concentration and efficacy, safety, tolerability, and pharmacogenetics measures	○ Population PK and PD parameters
Exploratory	
To compare the efficacy of once-weekly tirzepatide 10 mg and/or 15 mg with placebo for	
○ Improvement in obesity-related health problems at 72 weeks	○ Proportion of participants who met the following criteria at 72 weeks from BL ○ improvement in ≥2 obesity-related health problems for participants with BL BMI ≥27 and <35 kg/m^2 ○ improvement in ≥1 obesity-related health problems for participants with BL BMI ≥35 kg/m^2 ○ Proportion of participants who achieved the following number of improvements of obesity-related health problems regardless of BMI at BL ○ Achieved 2 or 3 improvements (only for participants with 3 defined obesity-related health problems) ○ Achieved 2 improvements (only for participants with 2 defined obesity-related health problems) ○ Achieved 1 improvement (only for participants with 1 defined obesity-related health problems)
○ **IGT related parameters (all participants)** ○ Change in OGTT (24, 52, and 72 weeks)	○ Mean change from BL in ○ OGTT 2-hr glucose ○ fasting glucose ○ insulin ○ C-peptide
○ **Hyperlipidemia related parameters (all participants)** ○ Change in fasting lipids (24, 52, and 72 weeks)	○ Mean change from BL in ○ TG ○ TC ○ VLDL-C ○ LDL-C (direct) ○ HDL-C ○ non-HDL-C ○ FFA

Objectives	Endpoints
○ **Other parameters**	
○ Change in laboratory tests (24, 52, and 72 weeks)	○ Mean change from BL in ○ Adiponectin ○ Leptin ○ hs-CRP ○ TNFα ○ Mean change from BL in ○ eGFR ○ Urinary albumin/creatinine ratio
○ **Patient-reported outcomes**	
○ Change in SF-36v2 acute scores other than physical functioning (72 weeks)	○ Mean change from BL in ○ role-physical score ○ bodily pain score ○ general health score ○ vitality score ○ social functioning score ○ role-emotional score ○ mental health score ○ physical component summary ○ mental component summary
○ Change in IWQOL-Lite-CT scores other than physical functioning (72 weeks)	○ Mean change from BL in ○ physical score ○ psychosocial score ○ total score
○ Change in Patient Global Impression of Status (72 weeks)	○ Shift of the ordinal response category from BL
To compare once-weekly tirzepatide (all doses combined) with placebo for participants with IGT at BL	
○ Delayed progression to T2DM at 72 weeks	○ Time to onset of T2DM during 72-week treatment period from BL
To explore once-weekly tirzepatide (all participants combined) 10 mg and/or 15 mg and placebo for	
○ Immunogenicity assessment	○ The frequency and percentage of participants with preexisting ADA, with TE ADA, and with neutralizing TE ADA to tirzepatide

Abbreviations: ADA = antidrug antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; BMI = body mass index; ELF = enhanced liver fibrosis; EQ-5D-5L = EuroQol – 5 Dimension – 5 Level; EWL = excess weight loss; FIB-4 = Fibrosis-4; FFA = free fatty acid; GGT = gamma-glutamyl transferase; HbA1c = glycated hemoglobin; HDL-C = high density lipoprotein cholesterol; HFF = hepatic fat fraction; HOMA2-%B = homeostasis model assessment estimates steady state beta cell function; HOMA2-%S = homeostasis model assessment estimates steady state insulin sensitivity; hs-CRP = high-sensitivity C-reactive protein; IGT = impaired glucose tolerance; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials version; K-18 = keratin-18 M30 fragment; LDL-C = low density lipoprotein cholesterol; MRI = magnetic resonance imaging; NAFLD = non-alcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; OGTT = oral glucose tolerance test; Pro-C3 = a fragment of the

NH2-terminal propeptide of type III procollagen; PD = pharmacodynamics, PK = pharmacokinetics, SAT = subcutaneous adipose tissue; SF-36v2 = Short-Form 36-item Health Survey Version 2; T2DM = type 2 diabetes mellitus; TC = total cholesterol; TE = treatment-emerged; TG = triglyceride; TNFα = tumor necrosis factor-α; VAS = visual analog scale; VAT = visceral adipose tissue; VLDL-C = very low density lipoprotein cholesterol.

a To compare the efficacy of once-weekly tirzepatide with placebo, improvement of NAFLD at 72 weeks will be combined with all doses.

b Individual daily meal intake information (photographs and record sheet), including breakfast, lunch, dinner, and snacks, will be collected on 3 consecutive or non-consecutive days during the week before the visit. These records will be collected only from participants who agree to participate in taking these measurements.

c Appetite sensation will be measured by a 100-mm VAS for parameters of hunger, fullness, satiety, and prospective food consumption including snacks before and after meal recorded on 3 consecutive or non-consecutive days during the week immediately before the visit. These records will be collected only from participants who agree to participate in taking these measurements.

4. Study Design

4.1. Overall Design

Study GPHZ is a Phase 3, multicenter, randomized, placebo-controlled, double-blinded study to evaluate the safety and efficacy of subcutaneously administered tirzepatide 10 mg and/or 15 mg QW compared with placebo when used in conjunction with a reduced calorie diet and increased physical activity for weight management, in obesity disease participants with BMI ≥27 and <35 kg/m^2 and at least 2 obesity-related health problems or BMI ≥35 kg/m^2 and at least 1 obesity-related health problem. The obesity-related health problems are IGT, hyperlipidemia, or NAFLD.

The study population will be enriched for participants who have NAFLD and IGT, such that more than 40% of the total study population will consist of participants with NAFLD, and more than 60% of the total study population will consist of participants with IGT.

Study GPHZ will consist of 3 periods: a 4-week screening period, followed by a 72-week treatment period including a 20-week dose escalation, and a 4-week safety, off-drug, follow-up period. Approximately, 261 participants will be randomized in a 1:1:1 ratio to tirzepatide 10 mg, 15 mg, or placebo.

4.2. Scientific Rationale for Study Design

This study is designed to determine the comparative benefits and risks of tirzepatide 10 mg and/or 15 mg QW versus placebo in participants with obesity disease who have obesity-related health problems (see Table 4).

Table 4. Scientific Rationale for Study Design

Study Design Element	Scientific Rationale
Double blinded parallel-group study	It is appropriate to minimize participant and investigator bias in assessments for efficacy, safety, and study drug tolerability.
Placebo-controlled study	It was chosen to determine the comparative benefits and risks of tirzepatide 10 mg and/or 15 mg QW versus placebo in participants who have obesity disease with obesity-related health problems defined as glucose intolerance, hyperlipidemia (hypertriglyceridemia), or non-alcoholic fatty liver disease.
Conjunction with a reduced calorie diet and increased physical activity for weight management	It follows the JASSO guideline that the obesity disease patients may initiate medical therapy, if despite adequate lifestyle interventions including diet, exercise, and behavioral therapy for 3 to 6 months body weight and associated health problems are not improved.
Primary and secondary endpoints	This study is based on the regulatory guidance (JASSO Guideline for the management of obesity disease [JASSO 2016]). JASSO guideline for the management of obesity disease emphasizes the importance of improving obesity-related health problems as a secondary endpoint, although reducing body weight loss is set as the primary endpoint.
Study duration	The planned duration of treatment for the primary endpoint at 72 weeks includes a dose escalation period to either 10 or 15 mg and at least 52-week

	treatment period with the assigned dose. This duration is considered appropriate to assess the full effects and benefit/risk of each maintenance dose of tirzepatide compared with placebo on body weight and improvement of associated obesity-related comorbidities. It is consistent with regulatory guidelines (FDA 2007; EMA 2016) and agreed by PMDA.
Concomitant medications	Participants will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study treatment. (Section 6.5).

Abbreviations: JASSO = Japan Society for the Study of Obesity; PMDA = Pharmaceuticals and Medical Devices Agency; QW = once weekly.

4.3. Justification for Dose

Tirzepatide doses of 10 and 15 mg QW will be evaluated in this study.

These doses and associated escalation schemes were selected based on assessments of safety, efficacy (glycemic and weight loss effect), and GI tolerability data, followed by data from exposure response modeling in participants with T2DM in Phase 1 and 2 studies.

Dosing scheme starting at a low dose of 2.5 mg accompanied by a gradual dose escalation of 2.5-mg increments every 4 weeks should allow the development of tolerance to GI events and intends to minimize GI AEs.

The maximum proposed dose of 15 mg maintains an exposure multiple of 1.6 to 2.4 to the no observed adverse-effect level doses in 6-month monkey and rat toxicology studies.

The selected dose and escalation scheme would enable further evaluation of benefit/risk considerations for 10-mg and 15-mg doses of tirzepatide.

4.4. End of Study Definition

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

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

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 20 years or older at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Have BMI of
   - ≥27 kg/m^2 and <35 kg/m^2 with at least 2 obesity-related health problems or
   - ≥35 kg/m^2 with at least 1 obesity-related health problems
   - Health problems are IGT, hyperlipidemia, or NAFLD at screening (Visit 1 and Visit 2).
     a. IGT: have oral glucose tolerance test (OGTT) 0-hour glucose of ≥110 mg/dL and/or OGTT 2-hour glucose of ≥140 mg/dL at Visit 2 and do not meet diagnostic criteria for diabetes mellitus (DM) at Visit 1 and Visit 2. In this study, IGT is defined to include impaired fasting glucose also described as "Borderline type" according to Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020).
     b. hyperlipidemia: have fasting triglyceride ≥150 mg/dL at screening at Visit 1 and 2
     c. NAFLD (participants with NAFLD can be enrolled ONLY at clinical sites which have magnetic resonance imaging [MRI] – proton density fat fraction [PDFF] availability and/or can obtain support from imaging sites for MRI-PDFF)
        i. have hepatic fat fraction (HFF) ≥5% as measured by MRI-PDFF imaging (central evaluation) at Visit 2
3. Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight
   a. 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)
   and
   b. inject study intervention (or receive an injection from a trained individual if visually impaired or with physical limitations)
   and
   c. 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

Sex

4. Male and/or female

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

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

b. Female participants:
   i. Female participants of childbearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must:
      A. test negative for pregnancy at Visit 1 based on a serum pregnancy test,
      B. if sexually active, agree to use 2 forms of effective contraception, where at least 1 form is highly effective, for the duration of the trial and for 30 days thereafter, and
      C. not be breastfeeding
   ii. Women not of childbearing potential may participate and include those who are:
      A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Mullerian agenesis; or
      B. post-menopausal – defined as either
         - A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL; women in this category must test negative in pregnancy test prior to the study entry

      or

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

      or

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

Informed Consent

5. 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 informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

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

Medical Conditions

1. Have DM according to Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020), history of ketoacidosis or hyperosmolar state/coma, or laboratory evidence of diagnostic of DM during screening including either HbA1c ≥6.5%, or glucose levels (fasting glucose or OGTT 0-hour ≥126 mg/dL and/or OGTT 2-hour glucose ≥200 mg/dL);
    a. Diagnosis of DM
        i. Both glucose level and HbA1c meets diabetic type criteria
        ii. Only glucose level meets diabetic type criteria at Visit 1
            - With typical symptoms of DM or definite diabetic retinopathy
            - Without typical symptoms of DM or definite diabetic retinopathy, re-exam at Visit 2 and
                - Both glucose level and HbA1c meet diabetic type criteria
                - Only glucose level meets diabetic type criteria
                - Only HbA1c meets diabetic type criteria
        iii. Only HbA1c meets diabetic type criteria, re-exam at Visit 2 and
            - Both glucose level and HbA1c meet diabetic type criteria
            - Only glucose level meets diabetic type criteria
            - Only HbA1c meets diabetic type criteria
    b. Prior treatment (within 3 months prior to Visit 1) with DPP-4 inhibitors, oral GLP-1 RA, or any injectable therapy for T2DM
2. Alcohol consumption >7 units (140 g of pure alcohol)/week for women and >10.5 units (210 g of pure alcohol)/week for men (JSG 2014)
3. Evidence of acute or chronic liver disease other than NAFLD
    a. Alcoholic liver disease
    b. Hepatitis B as defined by presence of hepatitis B surface antigen (HBsAg)
    c. Hepatitis C as defined by presence of hepatitis C virus (HCV) ribonucleic acid (RNA) or positive hepatitis C antibody (anti-HCV). Participants treated for hepatitis C (and diagnosed as cured) must be RNA negative for at least 3 years prior screening in order to be eligible for the study
    d. Primary biliary cirrhosis as defined by the presence of at least 2 of the following:
        i. Biochemical evidence of cholestasis based mainly on alkaline phosphatase (ALP) elevation

ii. Presence of anti-mitochondrial antibody
iii. Historical evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts

e. Evidence of autoimmune liver disease as defined by compatible liver histology
f. Primary sclerosing cholangitis
g. Current drug-induced liver disease as defined on the basis of typical exposure and history
h. Suspected or proven liver cancer
i. Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than NAFLD, or any of the following, as determined by the central laboratory during screening:
   - alanine aminotransferase (ALT) level >3.0× the upper limit of normal (ULN) for the reference range

     or

   - ALP level >1.5× the ULN for the reference range

     or

   - total bilirubin (TBL) level >1.2× the ULN for the reference range (except for cases of known Gilbert's Syndrome)

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

4. Have a self-reported change in body weight >5 kg within 3 months prior to screening
5. Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months

   Examples:
   - mucosal ablation
   - gastric artery embolization
   - intragastric balloon
   - duodenal-jejunal bypass sleeve endoluminal liner
6. Have renal impairment measured as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, calculated by Japanese Society of Nephrology coefficient-modified Chronic Kidney Disease-Epidemiology equation as determined by central laboratory during screening
7. 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
8. Have had a history of chronic or acute pancreatitis
9. Have thyroid-stimulating hormone outside of the range of 0.4 to 6.0 µIU/mL at 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: Thyroid-stimulating hormone values above the normal range can, in some participants, 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.

10. Have obesity induced by other endocrinologic disorders (for example, Cushing's Syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome)
11. Have a history of significant active or unstable major depressive disorder or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years

    Note: Participants with major depressive disorder or generalized anxiety disorder whose disease state is considered stable for the past 2 years and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications
12. Have any lifetime history of a suicide attempt
13. Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more at Visit 1 or 3, prior to randomization
14. On the Columbia-Suicide Severity Rating Scale (C-SSRS) at Visits 1 or 3, prior to randomization:
    a. a "yes" answer to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan)

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

       or
    c. a "yes" answer to any of the suicide-related behaviors (Actual Attempt, Interrupted Attempt, Aborted Attempt, Preparatory Act or Behavior) on the "Suicidal Behavior" portion of the C-SSRS

       and
    d. the ideation or behavior occurred within the past month
15. Have any of the following cardiovascular conditions within 3 months prior to randomization:
    - acute myocardial infarction
    - cerebrovascular accident (stroke)
    - unstable angina
    - hospitalization due to congestive heart failure
    - uncontrolled hypertension (systolic blood pressure above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg)
16. Have New York Heart Association Functional Classification IV congestive heart failure
17. Have a serum calcitonin level (at Visit 1) of 35 ng/L or more, as determined by central laboratory at Visit 1

18. Have a family or personal history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia Syndrome type 2
19. 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
20. Have any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to GLP-1R agonists
21. 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
22. Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant
23. Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle cell disease)

Prior/Concomitant Therapy

24. Have current or potential needs of glucocorticoid therapy:
    a. 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)
    b. Have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) during the study
25. Have current or history of (within 3 months prior to randomization) treatment with medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotics 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 other than paroxetine are permitted.

26. Have taken within 3 months prior to randomization, medications (prescribed, imported or over the counter) or alternative remedies intended to promote weight loss or may cause weight reduction. Examples include, but are not limited to:
    - Sanorex® (mazindol)
    - Bofu-tsusho-san® (Chinese herbal medicine)
    - Saxenda® (liraglutide 3.0 mg)
    - Xenical® (orlistat)
    - Meridia® (sibutramine)
    - Acutrim® (phenylpropanolamine)
    - Adipex® (phentermine)
    - BELVIQ® (lorcaserin)
    - Qsymia® (phentermine/topiramate combination)
    - Contrave® (naltrexone/bupropion)

    Note:
    - Use of metformin or any other glucose-lowering medication, whether prescribed for polycystic ovary syndrome or diabetes prevention is not permitted.
    - Use of semaglutide that may cause significant weight reduction is not allowed within 12 months prior to randomization.
27. Have started implantable or injectable contraceptives (such as Depo-Provera®) within 18 months prior to screening

Prior/Concurrent Clinical Study Experience

28. Are currently enrolled in any other clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study
29. Within the last 30 days prior to screening, have participated in a clinical study and received treatment, whether active or placebo. If the study involved an IP, 5 half-lives or 30 days, whichever is longer, should have passed
30. Have previously completed or withdrawn from this study or any other study investigating tirzepatide

Other Exclusions

31. Are investigator site personnel directly affiliated with this study and/or their immediate family. Immediate family is defined as a spouse, legal partner, parent, child, or sibling, whether biological or legally adopted
32. Are Eli Lilly and Company (Lilly) employees

5.3. Lifestyle Considerations

Per the Schedule of Activities (Section 1.3), participants will consult with a dietician, or equivalent qualified delegate, according to local standards, to receive lifestyle management

counseling at Weeks 0, 4, 8, and 12 during dose escalation and then at Week 24, 36, 48, 52, and 60 through 72 weeks as defined in the Schedule of Activities (Section 1.3).

Diet and exercise goals (based on JASSO guidelines) established during the lifestyle management counseling and the importance of adherence to the lifestyle component of the trial will be reinforced at each trial contact by study staff.

5.3.1. Meals and Dietary Restrictions

Per the Schedule of Activities (Section 1.3), study participants will receive diet counselling by a dietician/nutritionist, or equivalent qualified delegate, according to JASSO guidelines. Dietary counseling will consist of advice on healthy food choices and focus on calorie restriction using a hypocaloric diet with macronutrient composition of

- Approximately 50% to 60% of energy from carbohydrate
- Approximately 15% to 20% of energy from protein
- Approximately 20% to 25% of energy from fat, and
- Daily energy intake up to 25 kCal/kg × standard body weight (as determined by BMI = 22 kg/m^2) for the participant whose BMI is ≥27 kg/m^2 and 20 to 25 kcal/kg × standard body weight for the participant whose BMI is ≥35 kg/m^2.

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 recommended diet is continued after randomization and throughout the treatment period. Dietary evaluation and appetite sensation are described in Sections 8.1.2.9.5.1 and 8.1.2.9.5.2, respectively.

5.3.2. Caffeine, Alcohol, and Tobacco for PK/PD Visits

1. During each dosing session at the site visit, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for at least 10 hours before the start of dosing until after collection of the final PK and/or PD sample.
2. During each dosing session at the site visit, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or PD sample.
3. Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit. Use of tobacco products will be abstained for 8 hours before the start of dosing until after collection of the final laboratory sampling.

5.3.3. Physical Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during onsite study procedures (e.g., watching television, reading).

At Visit 3 and all subsequent visits, participants will be advised to increase their physical activity to at least 150 minutes per week. Please see Appendix 13 (Section 10.13) for detail guidance of physical activity.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure), will have an opportunity to have 1 additional screening visit with repeat screening laboratory tests at the discretion of the investigator. Before rescreening is performed, the patient must sign a new ICF and receive a new identification number. If, in the opinion of the investigator, an ineligible laboratory test result is the result of an error or extenuating circumstance, then that parameter can be retested once without the patient having to be rescreened.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

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

Abbreviations: IWRS = interactive web response service; 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 site location 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. The injection site location of all dose administrations will be recorded by the participant. 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 rotate injection sites each week.

6.1.1. Medical Devices

The product provided for use in the study is tirzepatide investigational 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 10.9).

All product complaints (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature 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 and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- Study site staff must regularly assess whether the participant is correctly administering the assigned study intervention and storing study drug according to the provided instructions
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the study training documents.

6.3. Measures to Minimize Bias: Randomization and Blinding

Interactive web-response system

All participants will be randomly assigned to study intervention using a central interactive-web response system (IWRS) at the end of Visit 3 after participant's eligibility is confirmed. 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 the Schedule of Activities (Section 1.3).

The randomization will be stratified by

- baseline IGT (yes or no)
- baseline hyperlipidemia (yes or no)
- baseline NAFLD (yes or no), and
- sex

Blind break

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

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

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

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, reviewing the study diary, and counting of unused study drug and/or empty cartons returned.

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

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

6.5. Concomitant Therapy

Participants are permitted to use concomitant medications that they require during the study, with the exception of certain medications (for example; other medications for weight management) that may interfere with the assessment of efficacy and safety characteristics of the study treatments.

Any concomitant medications taken for obesity-related health problems on a stable dose for at least a period of 3 months prior to study entry will be permitted. Dosage change during the study will only be allowed if concerns for safety issue are identified.

Participants who develop DM during the study may initiate medication for glucose control, with the exception of dipeptidylpeptidase-4 (DPP-4) inhibitors or GLP-1 receptor agonists. Initiation of metformin for the treatment of DM is permitted, but metformin should not be initiated during the study for the treatment of other metabolic conditions (for example, polycystic ovarian syndrome, diabetes prevention).

Investigative site staff will inform participants that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the study. This may not be possible when initiated for treatment of medical emergencies, in which case, the participant will inform the investigator or a designated site staff member as soon as possible.

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

- Reason for use

- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

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

6.6. Dose Modification

Study drug dose modification is not permitted, except for management of intolerable GI symptoms (see Section 6.7.1).

6.7. Management of Incident Diabetes

Participants who develop diabetes during the study will be

- provided and trained to use a glucometer
- educated on the signs and symptoms of hypoglycemia and its treatment, and
- provided a diary to record hypoglycemic episodes per Section 10.4.7.1.

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 GLP-1R agonists, which are prohibited in the study. Monitoring for hypoglycemia includes capture of events as defined in Section 10.4.7.1. Date of diagnosis of diabetes will be captured in the electronic case report form (eCRF).

6.7.1. Management of Participants with Gastrointestinal Symptoms

Participants who experience intolerable GI symptoms (for example; nausea, vomiting, or diarrhea) at any time during the study, should first be counselled on dietary behaviors that may help mitigate nausea and vomiting, (for example, eating smaller meals, splitting 3 daily meals into 4 or more smaller ones, and stopping eating when they feel full). If symptoms persist, the participant should be prescribed, at the investigator's discretion, symptomatic medication (for example, antiemetic or antidiarrheal medication).

Temporary interruption

A temporary interruption of study intervention for 1 dose is permitted, provided the participant has taken the last 3 weekly doses. Study treatment should be resumed immediately, either alone or in combination with symptomatic medication, which can also be utilized to manage symptoms. Management of study intervention after interruptions >1 dose is discussed in Section 7.

Dose modification

If intolerable GI symptoms (for example, nausea, vomiting, or diarrhea) persist despite the above measures, the investigator should contact Lilly to consider reinitiating study intervention at the next lowest maintenance dose in a blinded fashion (for example, 15 mg and 12.5 mg reduced to 10 mg, 10 mg or lower reduced to placebo). Only 1 dose reduction per participant will be permitted during the course of the study. The dose modification is not allowed without prior discussion with Lilly's CRP and/or CRS.

6.8. Intervention after the End of the Study

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

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

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

Possible reasons leading to permanent discontinuation of IP:

- **participant decision**
  - the participant requests to discontinue IP
- **clinical considerations**
  - initiation of GLP-1R agonist or DPP-4 inhibitor, if participants will not or cannot discontinue them
  - intolerable GI symptoms despite management as described in Section 10.8

    Note: If intolerable GI symptoms persist despite symptomatic treatment, temporary drug interruption, and resumption at a lower dose of study intervention, the participant should be discontinued from the study intervention.
  - BMI ≤18.5 kg/m^2 with clinically significant health condition is reached at any time during the treatment period

    Note: The investigator should contact the sponsor CRP and/or CRS to discuss whether it is medically appropriate for the participant to continue study treatment.
  - diagnosis of type 1 diabetes mellitus
  - diagnosis of medullary thyroid cancer after randomization
  - significant elevation of calcitonin (Section 10.4.7.3)
  - diagnosis of acute or chronic pancreatitis
  - diagnosis of an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
  - development of any significant study intervention-related hypersensitivity reaction
  - onset of pregnancy in a female participant
  - occurrence of any other treatment-emergent adverse event (TEAE), SAE, or clinically significant finding for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken
  - inadvertent enrollment if continued treatment with study intervention would not be medically appropriate (Section 7.2.1)
  - PHQ-9 score ≥15

        - Participants should be referred to a mental health professional to assist in deciding whether the subject should be discontinued from study intervention. If a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the subject, at the discretion of the investigator (in agreement with the mental health professional), may be continued in the trial on randomized therapy.
    - in addition, study intervention may be discontinued if participants:
        - answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS

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

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

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

- **discontinuation due to a hepatic event or liver test abnormality**
    - Participants who are discontinued from IP due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.
    - Discontinuation of the IP for abnormal liver tests **should be** considered by the investigator when a participant meets 1 of the following conditions after consultation with the Lilly designated medical monitor:
        - ALT or aspartate aminotransferase (AST) >8× ULN
        - ALT>2× baseline value OR ≥300 U/L, whichever occurs first, if baseline ALT≥2× ULN
        - ALT or AST >5× ULN for more than 2 weeks
        - ALT or AST >3× ULN and TBL >2× ULN or international normalized ratio (INR) >1.5
        - ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
        - ALP >3× ULN
        - ALP >2.5× ULN and TBL >2× ULN
        - ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

7.1.1. Temporary Study Drug Discontinuation

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

If study drug interruption is…	then…
2 consecutive doses or less	participant restarts study drug at last administered dose, as per escalation schedule.
3 consecutive doses or more	participant restarts study drug (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 10.8.

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

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

7.2. Participant Discontinuation/Withdrawal from the Study

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

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

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

Participants will be withdrawn from the study in the following circumstances:

- enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP)
- participant requests to be withdrawn from the study and clearly indicates that there will be no further contact of any kind with the site

Participants who agree to provide information relevant to any trial endpoint at the end of the study are not considered to have discontinued from the study.

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)

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

Discontinuation is expected to be uncommon.

When discontinuing from the study prior to Visit 21 or Visit 99, an early discontinuation visit should be conducted if possible, as described in the Schedule of Activities. See Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

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

7.3. Lost to Follow-Up

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

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the Schedule of Activities.
- 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 Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessments

The primary efficacy assessment in this study is body weight. Body weight measurements will be collected at specific clinic visits as summarized in the Schedule of Activities (Section 1.3).

Participants will be weighed on an electronic scale in light clothing at approximately the same time after an overnight fast (or fast of at least 10 hours) and evacuation of any bowel and bladder contents (Appendix 11, Section 10.11). The scale's performance will be monitored at least monthly using standard weights, and records of these assessments will be kept in the study binder.

8.1.2. Secondary Efficacy Assessments

The following secondary efficacy assessments will be collected according to the Schedule of Activities (Section 1.3).

8.1.2.1. Defined Obesity-Related Health Problems

The definition of improvements of defined obesity-related health problems are:

- **IGT** (only for participants with IGT at baseline)
  - Return to normal blood glucose range
    - OGTT 0-hour glucose <110 mg/dL AND
    - OGTT 2-hour glucose <140 mg/dL
- **Hyperlipidemia** (only for participants with hyper-triglyceridemia [triglyceride (TG) ≥150 mg/dL] at baseline)
  - Return to normal range (TG <150 mg/dL) OR
  - Reduced by 30% from baseline
- **NAFLD** (only for participants with diagnosis of NAFLD [HFF ≥5%] by MRI at baseline)
  - Return to normal range (HFF <5%) OR

- Reduced by 30% from baseline

The assessments will include:

- Proportion of participants who met the following criteria
  - improvement in at least 2 obesity-related health problems for participants with baseline BMI ≥27 and <35 kg/m^2, or
  - improvement in at least 1 obesity-related health problem for participants with baseline BMI ≥35 kg/m^2
- Proportion of participants who had improvement in IGT (only for participants with IGT at baseline)
- Proportion of participants who had improvement in hyperlipidemia (only for participants with hyper-triglyceridemia [TG ≥150 mg/dL] at baseline)
- Proportion of participants who had improvement in NAFLD (only for participants with a diagnosis of NAFLD [HFF ≥5%] by MRI-PDFF at baseline and all tirzepatide dose combined)

8.1.2.2. 2-Hour Oral Glucose Tolerance Test

All participants attending Screening Visit 2 will undergo a 2-hour OGTT test as outlined in the Schedule of Activities (Section 1.3). These results, in combination with those obtained from Screening Visit 1 and 2, will be used to determine study eligibility and randomization glycemic status.

Definition of IGT from 2-hour OGTT results: fasting glucose or 0-hour OGTT = 110-125 mg/dL (6.1-6.9 mmol/L) and/or 2-hour OGTT = 140-199 mg/dL (7.8-11.0 mmol/L).

8.1.2.3. Hepatic Fat Fraction Determined from Magnetic Resonance Imaging

Hepatic fat fraction will be determined using MRI-PDFF. The fat fraction is the proportion of mobile protons in liver tissue attributable to fat and is a noninvasive MRI-based biomarker of liver triglyceride concentration. The participants who are diagnosed NAFLD by MRI can be enrolled ONLY at clinical sites which have MRI-PDFF availability and/or can obtain support from imaging sites for MRI-PDFF as outlined in the Schedule of Activities (Section 1.3). See Appendix 11 (Section 10.11). Even if someone has been previously diagnosed NAFLD, they cannot be considered as a NAFLD patient unless their NAFLD was defined by MRI measurement. MRI images will be transmitted to a central reader for evaluation of the MRI-based efficacy endpoints.

8.1.2.4. Body mass related parameters

8.1.2.4.1. Body Weight

Absolute body weight will be measured as described above (see Section 8.1.1).

Body mass index (kg/m^2) will be derived using body weight in kilograms divided by the square height in meters.

Excess weight loss (%) will be derived using [(initial weight) – (current weight)]/[(initial weight) – (ideal weight)] x 100), with ideal weight considered as the weight corresponding to a BMI = 22 kg/m^2.

8.1.2.4.2. Measurement of Visceral Adipose Tissue (VAT), Subcutaneous Adipose Tissue (SAT), and VAT/SAT Ratio

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) will be collected according to the Schedule of Activities (Section 1.3).

Single slice imaging will be performed at the umbilicus level in a supine position using computerized tomography (CT) or MRI scanner at each site. The assessments will include VAT, SAT, and VAT/SAT ratio and will be calculated using software. Measurements of the adipose area will be performed centrally.

For patients participating in HFF analysis, MRI for visceral and subcutaneous assessments may be used by multiple slices acquisition during MRI, which will be captured in central vendor site acquisition manual and described in the imaging charter. For further comments, see Appendix 11 (Section 10.11).

8.1.2.4.3. Waist Circumference

Waist circumference will be collected according to the Schedule of Activities (Section 1.3). Waist circumference should be measured in the horizontal plane and at the umbilicus level according to JASSO guideline. For further comments, see Appendix 11 (Section 10.11).

8.1.2.5. IGT related parameters

The following IGT related parameters will be collected according to the Schedule of Activities (Section 1.3).

- Fasting glucose (mg/dL) (measured at central laboratory)
- HbA1c (%) (measured at central laboratory)
- Insulin (pmol/L) (measured at central laboratory)
- C-peptide (ng/mL) (measured at central laboratory)
- Homeostatic Model Assessment for Beta Cell and Insulin Sensitivity (HOMA2-%B and HOMA2-%S): Fasting glucose and insulin values will be used to calculate beta-cell function and insulin sensitivity using the updated Homeostasis Model Assessment (HOMA2) (Wallace et al. 2004).

Fasting glucose samples must be obtained after 10 hours or more without eating, drinking (other than water) or performing any significant physical activity.

8.1.2.6. Hyperlipidemia related parameters

The following hyperlipidemia related parameters will be collected according to the Schedule of Activities (Section 1.3).

- Fasting lipids (measured at central laboratory)
  - TG, TC, VLDL-C, LDL-C (direct), HDL-C, non-HDL-C (mg/dL)
  - FFA (μEq/L)

8.1.2.7. NAFLD related parameters

The following NAFLD related parameters will be collected during the study according to the Schedule of Activities (Section 1.3) and change from baseline will be analyzed.

- NAFLD/nonalcoholic steatohepatitis (NASH) biomarkers
  - ALT, AST, gamma-glutamyl transferase (GGT) (U/L) (measured and calculated by central laboratory)
  - AST/ALT ratio (measured and calculated by central laboratory)
  - K-18 (M30) (U/L) (measured at central laboratory)
  - Pro C3 (ng/mL) (measured at central laboratory)
  - Enhanced Liver Fibrosis score (ELF score = $2.278+0.851\ln(C_{HA}$ [ng/mL])$+0.751\ln(C_{PIIINP}$ [ng/mL])$+\ln(C_{TIMP\text{-}1}$ [ng/mL])). (Hyaluronic Acid, PIIINP and TIMP-1 measured and calculated by central laboratory) (Guha et al. 2008)
  - Fibrosis-4 (FIB-4 index) (AST, ALT, and platelet), (measured and calculated by central laboratory)

8.1.2.8. Other parameters

The following parameters will be collected according to the Schedule of Activities (Section 1.3).

- Blood pressure (SBP/DBP) (mmHg)
- Uric acid (mg/dL) (measured at central laboratory)

8.1.2.9. Patient-Reported Outcomes Assessments

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

8.1.2.9.1. Short-Form 36 Version 2, Acute, 1-Week Recall Version

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

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

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

standard deviation (SD) of 10; higher scores indicate better levels of function and/or better health (Maruish 2011).

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

The Impact of Weight on Quality of Life-Lite Clinical Trials version (IWQOL-Lite-CT) is a 20-item, obesity-specific patient-reported outcome instrument developed for use in obesity clinical trials. It assesses 2 primary domains of obesity-related health-related quality of life: physical (7 items), and psychosocial (13 items). A 5-item subset of the physical domain, the physical-function composite, is also supported. Items in the physical-function composite describe physical impacts related to general and specific physical activities. All items are rated on either a 5-point frequency ("never" to "always") scale or a 5-point truth ("not at all true" to "completely true") scale (Kolotkin et al. 2017, 2018).

8.1.2.9.3. EQ-5D-5L

Generic health-related quality of life will be assessed using the EuroQol – 5 Dimension – 5 Level (EQ-5D-5L) (EuroQoL Group 2015). The EQ-5D-5L is a standardized 5-item instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems), for a total of 3125 possible health states. In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between <0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health) (Dolan 1997). In addition, the EQ visual analog scale (VAS) records the respondent's self-rated health status on a vertical graduated (0 to 100) scale. In conjunction with the health state data, it provides a composite picture of the respondent's health status. The EQ-5D-5L is used worldwide and is available in more than 170 different languages. Details on the instrument, and scoring, organizing, and presenting the data collected will follow C2H guidelines (Ikeda et al. 2015; C2H 2019).

8.1.2.9.4. Patient Global Impression of Status for Physical Activity

Study participants will be asked to complete a PGIS item specifically developed for this study. This is a patient-rated assessment of current health limitation and is rated on a 5-point scale ranging from "1- not at all limited" to "5- extremely limited."

8.1.2.9.5. Dietary Evaluation

All participants fulfilling inclusion criteria will be asked to collect their meal record and appetite sensation. These records will be collected only from patients who additionally agree to participate in taking these measurements.

8.1.2.9.5.1. Meal Intake

Meal record will be collected before each meal (including breakfast, lunch, dinner, and snacks) for a day. In case if patients cannot finish them all, meal records after the meal will be collected.

Meal records will be collected on 3 consecutive or non-consecutive days during the week (at least 1 day should be working day and at least 1 day should be resting day) immediately before the visits: Visit 3 (Week 0), Visit 9 (Week 24), Visit 16 (Week 52), and Visit 21 (Week 72). The Lilly-designated vendor will calculate the volume of total fats, total carbohydrates, total protein, and total caloric intake based on the meal record.

8.1.2.9.5.2. Appetite Sensation

The subjective rating of appetite sensations is measured by a 100-mm VAS for parameters of hunger, fullness, satiety, and prospective food consumption including snacks. The meal record will be collected on 3 consecutive or non-consecutive days during the week (at least 1 day should be working day and at least 1 day should be resting day) immediately before the visits: Visit 3 (Week 0), Visit 9 (Week 24), Visit 16 (Week 52), and Visit 21 (Week 72). For each meal, including breakfast, lunch, dinner and snacks, participant should complete the VAS 10 minutes before the meal and immediately after the meal. The timing of the record should be on the same date as the meal intake record. In case of frequent snacking on each recording day, if a participant consumes several snacks a day, they will be asked to complete the meal intake record for all snacks, but will only be required to complete VAS measurement for the first afternoon snack. The VAS is a validated tool to assess appetite sensation parameters (Flint et al. 2000). The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually “extremely” and “not at all.” Participants are required to rate their subjective sensations on four 100-mm scales combined with the questions:

- “How hungry do you feel right now?”
- “How satisfied do you feel right now?”
- “How full do you feel right now?”
- “How much food do you think you could eat right now?”

A staff member will use a caliper to measure the distance from 0 to the mark that the participant placed on the VAS and record the measurement in the source document.

Overall appetite score is calculated as the average of the 4 individual scores (van Can et al. 2014) below:

[Satiety] + [Fullness] + {(100 – [Prospective food consumption]) + (100 – [Hunger])} / 4.

The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

8.1.3. Exploratory Efficacy Assessments

The following exploratory assessment will be collected at the times shown in the Schedule of Activities (Section 1.3).

Obesity-related health problems

- Proportion of participants who achieved the following improvements of obesity-related health problems at 72 weeks regardless of BMI at baseline;
  - Achieved improvement in ≥2 obesity-related health problems for participants with baseline BMI ≥27 and <35 kg/m^2
  - Achieved improvement in ≥1 obesity-related health problems for participants with baseline BMI ≥35 kg/m^2
  - Achieved 2 or 3 improvements (only for participants with 3 defined obesity-related health problems) regardless of BMI at baseline
  - Achieved 2 improvements (only for participants with 2 defined obesity-related health problems regardless of BMI at baseline)
  - Achieved 1 improvement (only for participants with 1 defined obesity-related health problem regardless of BMI at baseline)

Other parameters

- Adiponectin (μg/mL) (both high molecular weight and total adiponectin, measured at central laboratory)
- Leptin (pg/mL) (measured at central laboratory)
- high-sensitivity C-reactive protein (hsCRP) (ng/dL) (measured at central laboratory)
- TNF-α (pg/mL) (measured at central laboratory)
- eGFR (mL/min/1.73 cm^2) (creatinine measured at central laboratory) calculated using the Japanese Society of Nephrology formula: 194 × Cr 1.094 × Age 0.287 [if female; × 0.739]
- Urinary albumin/creatinine ratio (mg/gCre) (measured at central laboratory)

Incident Diabetes

- Time to onset of T2DM during the 72-week treatment period
  - Definition and Management of Incident Diabetes

    <u>Definition of incident diabetes</u>

    Incident diabetes is followed by Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020) and defined when any 1 of the following occur after randomization:

    - unequivocal hyperglycemia (random glucose ≥200 mg/dL) with signs or symptoms of hyperglycemia (e.g., dry mouth, polyposia, polyuria, body weight loss, or diabetic retinopathy).
    - within a 4-week period, the following laboratory evidence of diabetic type criteria including either HbA1c ≥6.5%, or glucose levels (fasting glucose or OGTT 0-hour glucose ≥126 mg/dL and/or OGTT 2-hour glucose ≥200 mg/dL) are observed:
      i. Both glucose level and HbA1c meets diabetic type criteria

ii. Only glucose level meets diabetic type criteria
- With typical symptoms of DM or definite diabetic retinopathy
- Without typical symptoms of DM or definite diabetic retinopathy, re-exam within 1 month and:
  - Both glucose level and HbA1c meets diabetic type criteria
  - Only glucose level meets diabetic type criteria
  - Only HbA1c meets diabetic type criteria

iii. Only HbA1c meets diabetic type criteria, re-exam within 1 month and
- Both glucose level and HbA1c meet diabetic type criteria
- Only glucose level meets diabetic type criteria

· initiation of any medication for the treatment of diabetes

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems, as well as a thyroid exam. Height, weight, and waist circumference will also be measured and recorded, per Appendix 11 (Section 10.11).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the Schedule of Activities (Section 1.3) and Appendix 11 (Section 10.11).

Vital sign measurements should be taken before obtaining an electrocardiogram (ECG) tracing and before collection of blood samples for laboratory testing, at visits where required (see Section 1.3). The participant should be required to sit quietly for 5 minutes before vital sign measurements are taken. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of blood pressure measurements (systolic and diastolic blood pressures [mmHg]).

8.2.3. Electrocardiograms

For each participant, 12-Lead ECGs should be collected according to the Schedule of Activities (Section 1.3) and Appendix 11 (Section 10.11).

Electrocardiograms will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, for immediate participant management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a

diagnosis and that occur after signing of the ICF should be reported to Lilly or its designee as an AE via the eCRF.

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

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the Schedule of Activities (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the standard collection requirements, and laboratory manual and the Schedule of Activities (Section 1.3).
- 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 (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

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

8.2.4.1. Hepatic Safety Monitoring

8.2.4.1.1. Close Hepatic Monitoring

Laboratory tests (Appendix 3 [Section 10.3]), including ALT, AST, ALP, TBL, direct bilirubin, GGT, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; 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, and
  - recent illnesses, for example, heart failure, systemic infection, hypotension, or seizures
- recent travel
- history of concomitant medications including
  - over-the-counter, and
  - 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 laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

8.2.4.1.2. 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 <1.5× ULN	ALT or AST ≥3× ULN with hepatic signs/symptoms*, or ALT or AST ≥5× ULN
ALP <1.5× ULN	ALP ≥3× ULN
TBL <1.5× ULN	TBL ≥2× ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5× ULN	ALT or AST ≥2× baseline with hepatic signs/symptoms*, or ALT or AST ≥3× baseline
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL ≥1.5× ULN	TBL ≥1.5× baseline (except for participants with Gilbert's syndrome)

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

* 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
- a thorough medical history, as outlined above
- tests for prothrombin time, INR (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
- serum 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 CRF should be performed in study participants who meet 1 or more of the following 5 conditions:

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

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

8.2.5. Depression, Suicidal Ideation and Behavior Risk Monitoring

Overweight and obese patients are at increased risk for depression (Luppino et al. 2010). Depression can increase the risk for suicidal ideation and behavior. Therefore, study participants will be screened at trial entry and monitored during the study for depression, and suicidal ideation and behavior.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing study medication in subjects who experience signs of suicidal ideation or behavior, following a risk assessment (Section 10.4.7.12).

Baseline and treatment-emergent assessment of depression, suicidal ideation and behavior will be monitored during the study using the C-SSRS and PHQ-9 (Section 10.4.7.12).

8.2.6. Special Safety Topics

Adverse events of special interest (AESIs) are AEs which the sponsor specifies as being of special interest based on standard drug registration topics, safety findings from previous studies in development program, potential risks associated with GLP-1 receptor agonists as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations.

AESIs for this program include:

a) severe hypoglycemia
b) pancreatitis (adjudicated)
c) thyroid malignancies and C-cell hyperplasias
d) major adverse cardiovascular events (adjudicated); includes, but not limited to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure
e) supraventricular arrhythmias and cardiac conduction disorders
f) hypersensitivity events
g) injection site reactions
h) allergic/hypersensitivity reactions; includes injection site reactions and antidrug antibody (ADA) formation
i) hepatobiliary disorders
j) severe GI AEs
k) acute renal events
l) depression, suicidal ideation, or behavior

If "a" to "l" above are reported, sites will be prompted to collect additional details/data.

Please see Appendix 4 (Section 10.4), for detailed information.

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

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

- AEs
- SAEs
- product complaints (PCs)

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

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and study intervention via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the IP, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's study intervention is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications or discontinuations of treatment.

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 9.4.4.3), 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 product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 10 (Section 10.10).

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Adverse Event					
AE	signing of the ICF	the follow-up visit	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	signing of the ICF	start of intervention	Within 24 hours of awareness	eCRF	SAE paper form
SAE* and SAE updates	start of intervention	participation in study has ended	Within 24 hours of awareness	eCRF	SAE paper form
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	3 months after the last dose of study drug	Within 24 hours of learning of the pregnancy	eCRF	SAE paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint Form	N/A

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	Product Complaint Form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint Form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint Form	N/A

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

8.3.2. Medical Device Incidents (Including Malfunctions)

Medical devices are being used in this study for the purposes of administering tirzepatide. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a medical device incident can be found in Section 10.9 (Appendix 9).

Note: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.1.

8.3.2.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents, or malfunctions of the device that result in an incident, will be detected, documented, and reported to the sponsor during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device used during the study, the investigator will promptly notify the sponsor through the complaints process.

The method of documenting medical device incidents is provided in Section 10.9 (Appendix 9).

8.3.2.2. Follow-Up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.1). This applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.2.3. Prompt Reporting of Medical Device Incidents and Malfunctions to Sponsor

- Medical device incidents or malfunctions will be reported to the sponsor within a business day or as determined for the study, after the investigator determines that the event or issue meets the protocol definition of a medical device incident or malfunction.
- Medical device incidents or malfunctions that result in an SAE will be reported to the sponsor within 24 hours, in the same manner as other SAEs.
- Malfunctions will be reported via the Product Complaint Form and sent to the sponsor per training and per instructions provided on the Product Complaint Form.
- The same individual at the site will be the contact for the receipt of medical device reports and SAEs.

8.3.2.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report to the sponsor all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (for example; the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

8.3.3. Pregnancy

Pregnancy (maternal or paternal exposure to study intervention) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE reporting process to collect data on the outcome for both mother and fetus.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Report Timing is provided in Section 8.3.1.

8.4. Treatment of Overdose

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

8.5. Pharmacokinetics

Pharmacokinetic samples should be collected prior to the dose administration and at the same time as the immunogenicity sample. Population PK and PD parameters may be derived. Relationship between tirzepatide exposure and safety, tolerability and efficacy measures may be explored.

8.6. Pharmacodynamics

The area under the curve from 0 to 2 hours (AUC[0-2h]) for glucose and insulin during an OGTT will be calculated using the trapezoidal rule. The AUC(0-2h) as well as other derived parameters or observed concentration at specific time points for each participant on the study day will also be baseline-adjusted. The concentrations on Day -1 will be used as baseline.

8.7. Genetics

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

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

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

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

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

8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and

clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), proteins, lipids, and other cellular elements.

Serum, whole blood, and plasma samples for biomarker research will be collected at the times specified in the Schedule of Activities (Section 1.3) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to tirzepatide, pathways associated with obesity, mechanism of action of tirzepatide, and/or research method or in validating diagnostic tools or assay(s) related to obesity.

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

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

8.9. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 1.3), venous blood samples will be collected to determine antibody production against tirzepatide.

To interpret immunogenicity results, a venous blood sample will be collected at the same time points to determine the blood concentration of tirzepatide. All samples for immunogenicity should be taken predose when applicable and possible. The actual date and time (24-hour clock time) of each sampling will be recorded. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of tirzepatide at a laboratory approved by the sponsor. Antibodies may be further characterized for cross-reactive binding to endogenous counterparts, and their ability to neutralize the activity of tirzepatide or endogenous counterparts. Sample collected at Visit 801 will assess immunogenicity at washout of tirzepatide (5 half-lives post end of treatment).

Treatment-emergent ADAs are defined in Section 9.4.5.

Long-term sample retention is defined in Section 10.1.11.

8.10. Health Economics and Medical Resource Utilization

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The alternative hypotheses for the primary objective are the following:

- H_{10}: QW tirzepatide 10 mg is superior to placebo for percent change in body weight from randomization AND percentage of participants who achieve ≥5% body weight reduction at 72 weeks.
- H_{15}: QW tirzepatide 15 mg is superior to placebo for percent change in body weight from randomization AND percentage of participants who achieve ≥5% body weight reduction at 72 weeks.

The above 2 hypotheses will be tested in parallel, each at a 2-sided significance level of 0.025.

9.2. Sample Size Determination

Approximately, 348 participants will be screened to achieve 261 randomly assigned to study intervention (approximately 87 participants per intervention group).

The sample size determination assumes that evaluation of superiority of tirzepatide 10 mg and tirzepatide 15 mg to placebo will be conducted in parallel, each at a 2-sided significance level of 0.025 using a 2-sample t-test. Additionally, a difference of at least 11% mean body weight percentage reduction from randomization at 72 weeks for tirzepatide 10 mg and/or tirzepatide 15 mg compared with placebo, a common SD of 10%, and a dropout rate of 25% are assumed for statistical power calculations. Under the assumptions above, randomizing 261 participants in a 1:1:1 ratio to tirzepatide 10 mg, tirzepatide 15 mg, and placebo provides more than 90% power to demonstrate superiority of each tirzepatide dose to placebo.

The chosen sample size and randomization ratio also provides >90% power to establish superiority of tirzepatide 10-mg and/or tirzepatide 15-mg doses to placebo in terms of proportion of participants achieving at least 5% body weight reduction at 72 weeks, conducted in parallel using a Fisher's exact test, each at a 2-sided significance level of 0.025, assuming 25% of placebo-treated participants and 90% of tirzepatide-treated participants achieve the goal and a dropout rate of 25%.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered Participants	all participants who sign the informed consent form (ICF)
Randomized Participants	all participants who are randomly assigned to treatment
Modified Intent-to-Treat (mITT) Set	all randomly assigned participants who are exposed to at least 1 dose of study drug; participants will be included in the treatment group they were randomized to
Efficacy Analysis Set (EAS)	data obtained during treatment period from mITT, excluding data after discontinuation of study drug (last dose date +7 days)
Full Analysis Set (FAS)	data obtained during treatment period from mITT, regardless of adherence to study drug
Safety Analysis Set (SS)	data obtained during the treatment period plus safety follow-up period from mITT, regardless of adherence to study drug

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) or the clinical study report. Additional exploratory data analyses may be conducted as deemed appropriate.

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

Unless specified otherwise, efficacy and safety will be assessed using the modified intent-to-treat (mITT) population. Baseline is defined as the last nonmissing data collected at randomization (prior to first dosing of study drug). Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses with placebo irrespective of adherence to study drug. Thus, safety analysis will be conducted using SS.

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

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

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

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

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

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

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

Frequency counts and percentages of all participants screened, randomized, and receiving at least 1 dose of study drug will be presented by treatment groups. Of the participants in the mITT set, frequency counts and percentages of participants who completed the study, prematurely discontinued the study (and/or study drug), including reason for premature discontinuation, will be presented by treatment groups.

A Kaplan-Meier analysis of the following time periods by treatment group will be provided

- time from randomization to premature discontinuation from study, and
- time from randomization to premature discontinuation from study treatment.

9.4.2.2. Participant Characteristics

Demographics and other baseline characteristics related to obesity disease including comorbidities of 11 obesity-related health problems defined by JASSO guidelines in Appendix 13 (Section 10.13), socioeconomic status (such as employment status and length of education), and day life environment (such as marital and living status) will be summarized by treatment group for all randomized participants.

9.4.2.3. Concomitant Therapy

Concomitant medications, including previous therapy, will be summarized by treatment arm for SS.

9.4.2.4. Treatment Compliance

Frequency counts and percentages of participants compliant to study drug will be summarized by treatment groups and visits for FAS.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

The primary efficacy analysis will be guided by the "efficacy" estimand, which represents efficacy prior to discontinuation of study drug under missing at random assumption. The efficacy analyses will be conducted using the EAS. The primary analysis model will be a MMRM for body weight percentage change over time and longitudinal logistic regression for proportion of participants achieving at least 5% body weight reduction over time. The response variable of MMRM will be the percent change in body weight from baseline values obtained at each scheduled postbaseline visit. The response variable of longitudinal logistic regression will be the achievement of at least 5% body weight reduction at each scheduled postbaseline visit. The independent variables of both analysis models are treatment group (tirzepatide 10 mg, tirzepatide 15 mg, and placebo), visit, and treatment by visit interaction, stratification factors: baseline IGT (yes or no); baseline hyperlipidemia (based on TG; yes or no); baseline NAFLD (yes or no) and sex (female, male), and baseline body weight as a covariate. An unstructured covariance structure will model relationship of within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Since the mean percent change in body weight and the percentage of participants with ≥5% body weight reduction needs to be achieved at the same time, no multiplicity adjustment is planned for these 2 tests.

For the supplemental purpose, sensitivity analysis of the primary efficacy analysis will be performed that will be guided by the "treatment-regimen" estimand and conducted using the FAS, which represents efficacy regardless of adherence to study drug. This assessment will analyze percent change in body weight obtained at the 72-week visit using an analysis of covariance (ANCOVA) and the percentage of participants achieving at least 5% body weight reduction obtained at the 72-week visit using a logistic regression model. Both models will include terms of treatment, stratification factors, and baseline body weight as a covariate. Missing value of change in body weight at the 72-week visit will be imputed based on observed body weight change from baseline values at the visit from participants in the same treatment group who had their efficacy assessed after early discontinuation of study drug. In cases where there are not enough retrieved dropouts to provide a reliable imputation model (for example, the model implemented by the SAS program does not converge), an alternative multiple imputation method with reference to the placebo group (placebo multiple imputation) will be used. Analysis will be conducted with multiple imputations.

9.4.3.2. Secondary Analyses

Proportion of participants who achieved improvement of obesity-related health problems (IGT, hyperlipidemia, or NAFLD) for each treatment group will be compared based on "efficacy" estimand using EAS. For improvement of each obesity-related health problem, composite endpoints (improvement of >1 obesity-related health problem), logistic regression analysis with treatment and sex as factor will be used. For improvement of hyperlipidemia and other categorical efficacy endpoints, longitudinal logistic regression will be used.

Other continuous efficacy endpoints will be analyzed using a MMRM model.

Additional details will be provided in the SAP.

9.4.4. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses with placebo irrespective of adherence to study drug. Thus, safety analysis will be conducted using SS.

9.4.4.1. Study Drug Exposure

Exposure to each study treatment will be calculated for each participant and summarized by treatment group.

9.4.4.2. Adverse Events

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Counts and percentages of participants experiencing events will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

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

9.4.4.3. Adverse Event of Special Interest

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

Adverse events of special interest for this study are listed in Section 8.2.6. Summaries and analyses for incidence of AESIs will be provided by treatment. The details of analysis of AESIs will be provided in the SAP.

9.4.4.4. Other Adverse Event Assessments

9.4.4.4.1. Gastrointestinal Events

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

9.4.4.4.2. Events Related to Potential Abuse Liability

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

9.4.4.4.3. Depression, Suicidal Ideation, and Behavior

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

The analysis details will be provided in the SAP.

9.4.4.4.4. Central Laboratory Measures, Vital Signs, and Electrocardiograms

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

Change from randomization to postrandomization value will be summarized for participants who have both a randomization and at least 1 postrandomization result.

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

The analysis details will be provided in the SAP.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Tirzepatide concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM® software. The relationship between tirzepatide dose and/or concentration and efficacy, tolerability, and safety endpoints may be characterized. Additionally, the impact of intrinsic and extrinsic participant factors such as age, weight, sex, and renal function on PK and/or PD parameters may be examined as needed. If ADA titers are detected from immunogenicity testing, then the impact of immunogenicity titers on tirzepatide PK or any relevant PD parameters may also be examined.

9.4.6. 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 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, if assessed, and cross reactivity to native GIP and GLP-1 may also be tabulated in TE ADA+ participants. The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to tirzepatide may be assessed.

9.4.7. Other Analyses

9.4.7.1. Subgroup Analyses for Primary Outcome

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

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

- age (<65 years and ≥65 years)
- sex (female and male)
- baseline BMI (≥27 and <30, ≥30 and <35, ≥35 kg/m^2)
- glycemic status at screening (normoglycemia versus IGT)
- hyperlipidemia status at screening (TG; ≥150 and <150 mg/dL)
- NAFLD status at screening (HFF; ≥5% and <5%)

The outcome measures for the subgroup analyses will include

- percent change in body weight from randomization at 72 weeks, and
- percentage of participants achieving at least 5% body weight reduction at 72 weeks.

9.5. Interim Analyses

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

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., 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. ● 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 the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

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

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 his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Committees Structure

Prospective adjudication of major adverse cardiovascular events and pancreatic AEs will be performed for this study. Appendix 4 (Section 10.4) outlines additional information on pancreatic and cardiovascular adjudication committees.

10.1.6. Dissemination of Clinical Study Data

Registration

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

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.

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 United States and European Union 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, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., 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 clinical study report.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

An electronic data capture system 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 electronic data capture 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.

Data collected via the sponsor-provided data capture systems 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 systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

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

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

10.1.8. 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 the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.6.

10.1.9. Study and Site Start and Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

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

10.1.10. 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. Long-Term 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 become(s) commercially available.

Sample Type	Custodian	Retention Period After Last Patient Visit*
Non-pharmacogenetic stored samples	Sponsor or designee	15 years
Pharmacokinetics	Sponsor or designee	2 years
Pharmacogenetic stored sample	Sponsor or designee	15 years
Immunogenicity	Sponsor or designee	15 years

*Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the central laboratory unless otherwise stated.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- 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.
- Refer to Section 5.1 (Inclusion Criteria) for screening pregnancy criteria.

Investigators must document their review of each laboratory safety report.
Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Clinical Laboratory Tests

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

Urine Chemistry[a]
Albumin
Creatinine
Albumin/Creatinine Ratio

Urinalysis[a]
pH
Protein
Glucose
Blood
Leukocyte esterase

Hormones (females)[a]
Serum pregnancy test (β-HCG)[b]
Urine pregnancy test[c,d]
Follicle stimulating hormone (FSH)[e]

Screening Liver Panel[a]
Hepatitis B surface antigen (HBsAg)
Anti-hepatitis C antibodies
HCV RNA
Anti-mitochondrial antibodies

Pancreas (exocrine)[a]
Pancreatic amylase
Lipase

NAFLD/NASH Biomarkers[a,f]
K-18 (M30)
Pro-C3
ELF score (calculated from Hyaluronic Acid, TIMP-1 and PIIINP)
FIB-4 index

Clinical Chemistry[a]
Sodium
Potassium
Calcium
Chloride
Phosphate
Bicarbonate
Total bilirubin
Direct bilirubin
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Gamma-glutamyl transpeptidase (GGT)
Blood urea nitrogen (BUN)
Creatinine
Uric acid
Glucose
Total protein
Albumin
Creatine kinase (CK)[j]

Other chemistry[a]
HbA1c
Cystatin-C

Endocrine[a]
Calcitonin
Thyroid-stimulating hormone (TSH)
Adiponectin (total and high molecular weight)
Leptin
Insulin
C-peptide

Lipid Panel[a]
Total cholesterol
Direct LDL-C
HDL-C
VLDL-C
Triglycerides
Free fatty acids
Non-HDL-C

Inflammatory Markers[a]
hsCRP
TNFα[f]

	Pharmacokinetics Samples[f,h,i]
Calculations[g]	
eGFR (calculated by Japanese Society of Nephrology coefficient-modified CKD-EPI equation)	**Pharmacogenetics Sample[a]**
Urine albumin/creatinine ratio (UACR)	Whole blood (EDTA)
AST/ALT ratio	
	Nonpharmacogenetic Stored Samples[a]
Immunogenicity[f,h,i]	Serum
Anti-tirzepatide antibodies	EDTA plasma
Anti-tirzepatide neutralizing antibodies	P800 plasma

Abbreviations: ADA = antidrug antibody; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatinine kinase, eGFR = estimated glomerular filtration rate; EDTA = ethylenediaminetetraacetic acid; ELF = enhanced liver fibrosis, FIB-4 index = fibrosis-4 index, FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IWRS = interactive web-response system; LDL = low-density lipoprotein; PIIINP = N-terminal procollagen III propeptide, PK = pharmacokinetics; RBC = red blood cells; TIMP-1 = tissue inhibitor of metalloproteinase-1, TSH = thyroid-stimulating hormone; UACR = urine albumin/creatinine ratio; VLDL = very low-density lipoprotein; WBC = white blood cells.

[a] Tests will be performed by or samples stored at a Lilly-designated central laboratory, unless otherwise noted.

[b] A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only. If required per local regulations and/or institutional guidelines, pregnancy testing can also be performed at other times during the study treatment period.

[c] Evaluated locally.

[d] Urine pregnancy test will be performed and result confirmed at Visit 3 prior to randomization and first injection of study drug(s) for women of childbearing potential only. Additional pregnancy tests (beyond those required per the Schedule of Activities [Section 1.3]) 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.

[e] Follicle-stimulating hormone test performed at Visit 1 for postmenopausal women at least 40 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 1 year without an alternative medical cause.

[f] Results will not be provided to the investigative sites.

[g] Calculated by the central laboratory and result provided to investigative sites.

[h] In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional blood samples will be collected including ADA, PK, and exploratory biomarker samples. PK samples for immunogenicity must be taken prior to drug administration.

[i] Assayed by a Lilly-designated laboratory.

[j] Creatine kinase MB (CK-MB) is to be assayed if creatine kinase result >1000 U/L.

10.3. Appendix 3: Laboratory Assessments for Hypersensitivity Events

- Laboratory assessments should be performed if the participant experiences generalized urticaria or if anaphylaxis is suspected.
- Collect sample after the participant has been stabilized, and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

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

Clinical Laboratory Tests for Hypersensitivity Events

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

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

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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

10.4.1. Definition of AE

AE Definition
• 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 (e.g., 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 conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/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 (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2. Definition of SAE

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

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

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

10.4.3. Definition of Product Complaints

Product Complaint

• A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  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 product complaint or problem with the study intervention so that the situation can be assessed.
• An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate (e)CRF page and product complaint information is reported on the Product Complaint Form.
  Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE 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 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

10.4.5. Reporting of SAEs

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

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

SAE Reporting via Paper CRF

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

10.4.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

10.4.7. Special Safety Topics

10.4.7.1. Hypoglycemia

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

Hypoglycemia may be identified by spontaneous reporting of symptoms from participants (whether confirmed or unconfirmed by simultaneous glucose values) or by blood glucose 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 (e.g., glucose values, symptoms).

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

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the plasma glucose values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips) in accordance with the 2019 American Diabetes Association position statement on glycemic targets (American Diabetes Association 2019):

Glucose Alert Value (Level 1):

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

Clinically Significant Hypoglycemia (Level 2):

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a blood glucose level of <54 mg/dL (<3.0 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia but with a measured blood glucose <54 mg/dL (<3.0 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available but with a measured blood glucose <54 mg/dL (<3.0 mmol/L).

Severe Hypoglycemia (Level 3):

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

To avoid duplicate reporting, all consecutive blood glucose 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).

10.4.7.2. Pancreatitis

Acute pancreatitis is defined as an AE of interest in all trials with tirzepatide, including this trial. Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks and Freeman 2006). 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 ≥3× ULN
- characteristic findings of acute pancreatitis on CT scan or MRI.

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed). Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gall bladder ultrasound, should be performed. Abdominal ultrasound may be used as an alternative method only if CT and MRI cannot be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the participant must discontinue therapy with tirzepatide, but will continue in the study. A review of the participant's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Each AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug(s).

Each participant will have measurements of p-amylase and lipase (assessed at the central laboratory) as shown on the Schedule of Activities (Section 1.3) to assess the effects of the investigational doses of tirzepatide on pancreatic enzyme levels. Serial measurements of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in

asymptomatic participants (Nauck et al. 2017; Steinberg et al. 2017a, 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic amylase ≥3× ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition. Only cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis will be submitted for adjudication.

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent clinical endpoint committee. 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 including suspected cases and those with severe or serious abdominal pain will be entered into a specifically designed eCRF page. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

10.4.7.3. Thyroid Malignancies and C-Cell Hyperplasia (Assessed by Calcitonin Measurements)

Individuals with personal or family history of medullary thyroid carcinoma and/or multiple endocrine neoplasia type 2 will be excluded from the study. The assessment of thyroid safety during the trial will include reporting of any case of thyroid malignancy including medullary thyroid carcinoma and papillary carcinoma and measurements of calcitonin. This data will be captured in specific eCRFs. The purpose of calcitonin measurements is to assess the potential of tirzepatide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms. Tirzepatide should be discontinued, after first confirming the value, if post-randomization calcitonin value is 35 ng/L or more and has increased at least 50% over baseline. A consultation with a thyroid specialist, if not available, an endocrinologist, should be obtained.

If an increased calcitonin value (≥35 ng/L and increases by ≥50% compared with baseline) is observed in a participant who has been administered a medication that is known to increase serum calcitonin, then this medication should be stopped and calcitonin levels should be measured after an appropriate washout period. If the confirmed calcitonin value is <35 ng/L, tirzepatide should be restarted when it is safe to do so.

10.4.7.4. Major Adverse Cardiovascular Events

Deaths and nonfatal cardiovascular AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment. Relevant data from participants who experienced death or nonfatal cardiovascular AEs will be entered into a specifically designed eCRF page by study site.

The nonfatal cardiovascular AEs to be adjudicated include

- myocardial infarction
- hospitalization for unstable angina
- hospitalization for heart failure

- coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention), and
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

10.4.7.5. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG, which should be submitted to the central reading center. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 10.4.2 must be reported as SAEs.

10.4.7.6. Hypersensitivity Events

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

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

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Appendix 3 (Section 10.3). Laboratory results are provided to the sponsor via the central laboratory.

10.4.7.7. Injection Site Reactions

Symptoms of a local injection site reaction may include erythema, induration, pain, pruritus, and edema. If an injection site event is reported, the AE will be recorded, and additional data will be provided to the sponsor in the Injection Site Reaction eCRF.

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

10.4.7.8. Antidrug Antibodies

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

10.4.7.9. Hepatobiliary Disorders

All events of TE biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.2.4.1.

10.4.7.10. Severe Gastrointestinal Adverse Events

Tirzepatide may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the eCRF/AE form. For detailed information concerning the management of GI AEs, please refer to Section 6.7.1.

10.4.7.11. Acute Renal Events

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

10.4.7.12. Depression, Suicidal Ideation, or Behavior Monitoring

Participants will be monitored for depression and suicidal ideation or behavior through AE collection and by using the C-SSRS and the PHQ-9. Participants will be referred to a mental health professional if, in the opinion of the investigator, it is necessary for the safety of the participant, or if the participant had any of the following:

- a PHQ-9 score ≥15
- C-SSRS responses of
  - A "yes" answer to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan)

    or

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

    or

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

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

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

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.
   Note: Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female is defined as, women with:
   - 12 months of amenorrhea for women >55 years of age, with no need for follicle-stimulating hormone
   - 12 months of amenorrhea for women >40 years of age with follicle-stimulating hormone ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g., oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that induced amenorrhea)

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

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

Highly Effective Methods of Contraception:

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

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

- Vasectomy – for men in clinical studies

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

Effective Methods of Contraception (must use combination of 2 methods):

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

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

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

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

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

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

Female participants who become pregnant

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

- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.3. 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 or be withdrawn from the study.

10.6. Appendix 6: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a whole blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to study intervention or indication and related diseases. They may also be used to develop tests/assays including diagnostic tests related to study intervention and indication. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report 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 study intervention or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

10.7. Appendix 7: Liver Safety: Suggested Actions and Follow-Up Assessments

Hepatic Evaluation Testing

See protocol Section 8.2.4.1 for guidance on appropriate test selection.

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

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

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

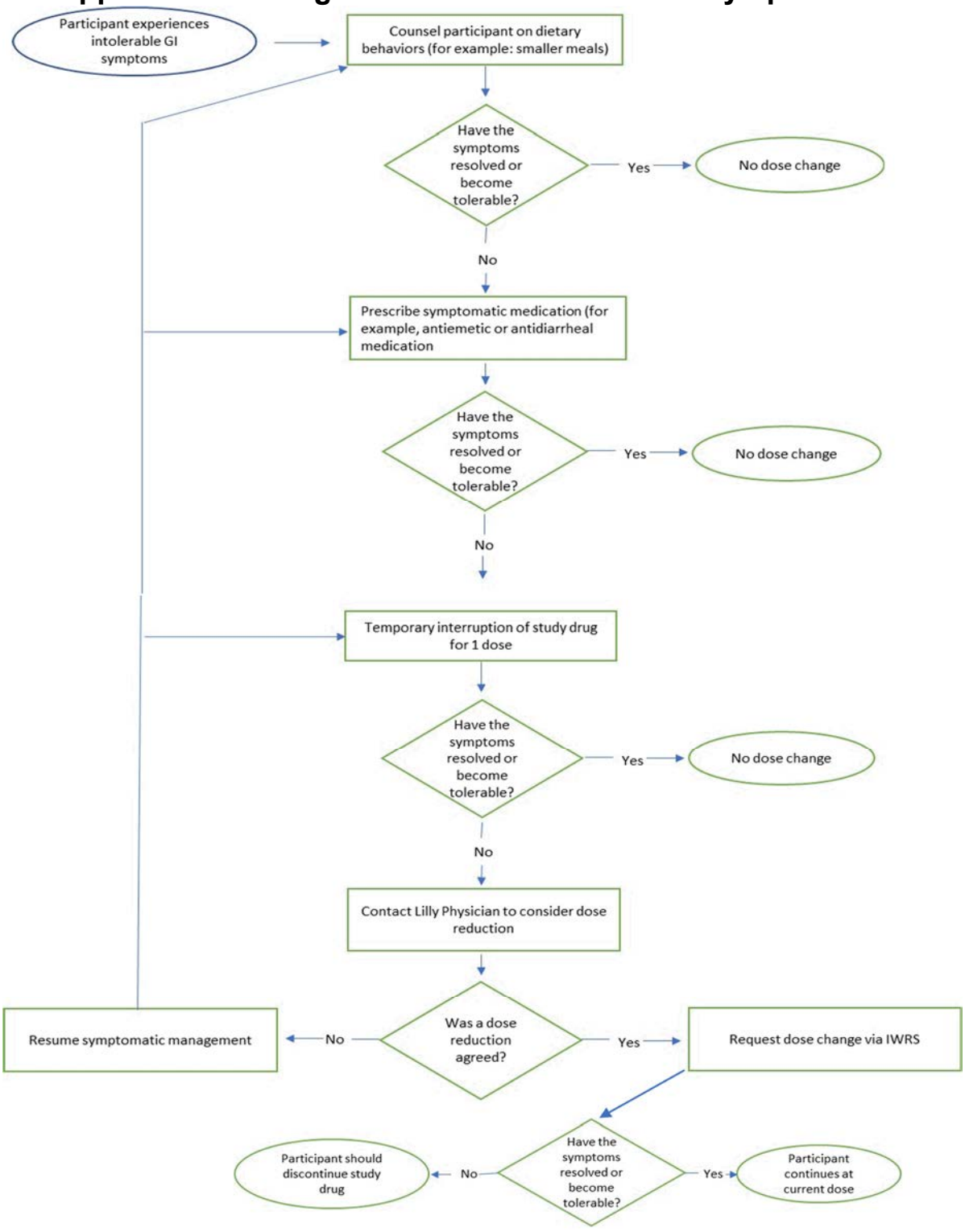
Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl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

HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA[d]
Microbiology[c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

Abbreviations: DNA = deoxyribonucleic acid; Ig = immunoglobulin; INR = international normalized ratio; RNA = ribonucleic acid.

[a] Not required if anti-actin antibody is tested.
[b] Not required if anti-smooth muscle antibody is tested.
[c] Assayed ONLY by investigator-designated local laboratory; no central testing available.
[d] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.
[e] This test should be performed locally if not available at the central laboratory.

10.8. Appendix 8: Management of Gastrointestinal Symptoms



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

10.9. Appendix 9: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow Up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study.

Medical Device Incident Definition

- A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use *which, directly or indirectly, might lead to or might have led to a serious injury, death of a participant/user/other person, or to a serious deterioration in his/her state of health.*
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.
- AND
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of Incidents

- A participant, user, caregiver, or health care professional is injured as a result of a medical device failure or its misuse.
- A participant's study intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to a medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to a medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the eCRF. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE eCRF page will be completed as described in Section 8.3. • A product complaint must be submitted describing the issue or deficiency that may have led to the incident or AE. • The eCRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

10.10. Appendix 10: 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 4 (Section 10.4) for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.11. Appendix 11: Measurement of Height, Weight, Waist Circumference, Vital Signs, Electrocardiogram, Oral Glucose Tolerance Test, Magnetic Resonance Imaging, Computed Tomography

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2008).

(Available at: https://www.who.int/ncds/surveillance/steps/Section%204%20Step%202%20Physical%20Measurements.pdf)

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 (cm) to 1 decimal place.

Measuring Weight

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

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

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

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

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

Measuring Waist Circumference

- Waist circumference should be measured in the horizontal plane and at the umbilicus level according to JASSO guideline.
- Measurements should be taken at the end of a normal expiration using a nonstretchable measuring tape. The tape should lie flat against the skin without compressing the soft tissue.
- The waist circumference should be measured twice, rounded to the nearest 0.5 cm. The measuring tape should be removed between the 2 measurements. Both measurements will be recorded in the eCRF. If the difference between the 2 measurements exceeds 1 cm, this set of measurements should be discarded and the 2 measurements repeated.

Step 1. Ask the participant to wear 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.

Vital Sign Measurements (blood pressure and heart rate)

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

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

Electrocardiogram

- All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory.
- 12-lead ECGs should be obtained after the subject has rested in a supine position for at least 10 minutes.
- Electrocardiograms should be collected at least 30 minutes prior to collection of blood samples for laboratory testing, including PK samples.
- Triplicate ECGs (obtained at Visit 3) 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.

2-Hour Oral Glucose Tolerance Test

- Participants should maintain adequate carbohydrate intake for 3 days prior to the scheduled 2-hour OGTT.
- In the 24 hours preceding the test, participants should refrain from drinking any alcohol or performing any extreme physical activity.
- Participants should fast for at least 10 hours before the administration of the test and should not eat until the test is complete.
- Placement of a venous cannula, preferably in an antecubital vein, is recommended to simplify collection of multiple blood samples for glucose, insulin, and C-peptide at time 0, 30, 60, 90, and 120 minutes.
- Immediately after collection of the time 0 sample, a 75-gram glucose dose will be given orally, using a commercial product approved for this use (and in a total volume of not more than 350 mL).
- The participant should consume the glucose load within 5 minutes.
- The participant should remain minimally active for the duration of the test.

Magnetic Resonance Imaging

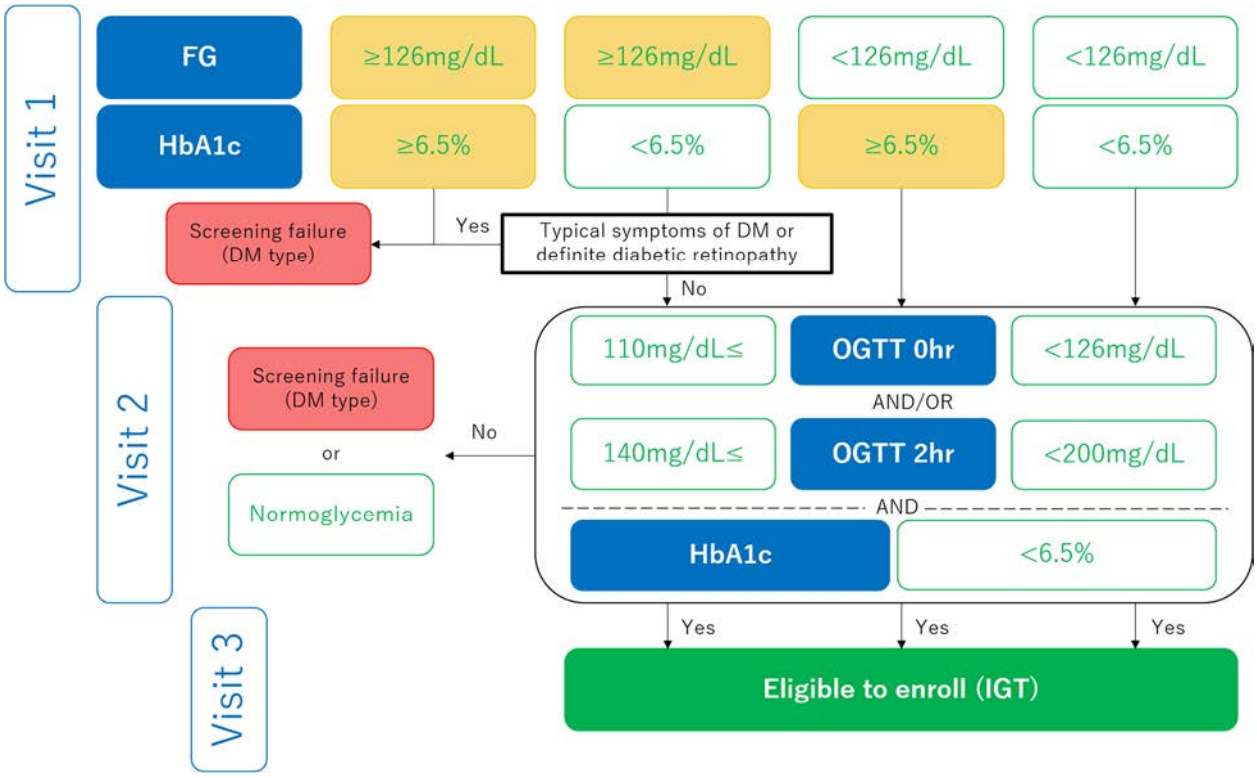
- Participants will undergo 2 liver and abdominal visceral/subcutaneous adipose tissue-directed MRI evaluations. For participant safety, images should also be over-read locally to assure there are no underlying liver pathologies other than NAFLD/NASH.
- In the event of early termination from the study drug or the study,
  - the second MRI exam may be performed when
    - the participant has been on treatment for at least 36 weeks, and
    - within 2 weeks of treatment discontinuation
- MRIs will be performed after a fast of at least 8 hours. Participants are allowed to take necessary medications and small quantities of water during the fast. Additional exclusion criteria apply for MRI examination eligibility, which do not count toward eligibility for study participation. These exclusions are:
  - a contraindication to MRI examinations
  - extreme claustrophobia
  - weight or girth exceeds the scanner capabilities
  - any condition or circumstance that, in the opinion of the investigator, would interfere with completion of MRI examinations
- For participants with claustrophobia in MRI machines, investigators may offer, at their discretion, a light sedative. However, if the participant is not willing to attempt MRI with light sedation, the participant should be excluded from the MRI evaluation but should not be excluded from the study.
- To obtain consistent and quality data for central review, investigators participating in the study will be provided with detailed instructions on the MRI acquisition protocol to be used.
- The MRI acquisition protocol will include sequences for measurement of the following:
  - Hepatic fat fraction (HFF)
  - Visceral adipose tissue (VAT) area
  - Abdominal subcutaneous adipose tissue (SAT) area
  - VAT/SAT ratio

- For patients participating in HFF analysis, they may use MRI for visceral and subcutaneous assessments by multiple slices acquisition during MRI, which will be captured in central vendor site acquisition manual and described in the imaging charter.
- Scans will be performed at 1.5 Tesla (T) or 3 T. The same scanner and imaging acquisition should be used for all subject time points. Any exceptions must be approved in advance of scanning by the imaging core laboratory. A standardized imaging acquisition will be utilized at all MRI centers and details will be provided in an MRI Site Manual.

Computed Tomography

- Single slice imaging will be performed at the umbilicus level in a supine position using CT scanner at each site.
- The CT imaging conditions will be adjusted appropriately on the basis of predefined Hounsfield unit thresholds (-190 to -30) and a slice thickness of 5 mm. To obtain consistent and quality data for central review, investigators participating in the study will be provided with detailed instructions on the CT acquisition protocol to be used.
- The CT acquisition protocol will include sequences for measurement of the following:
    - Visceral adipose tissue area (VAT)
    - Subcutaneous adipose tissue area (SAT)
    - VAT/SAT
- The system will also be divided and analyzed CT-scanned images into 2 areas (VAT and SAT) and others.
- Measurements of the adipose tissue area will be performed by a software technologist and a radiologists blinded to the clinical and pathological data.

10.12. Appendix 12: 2-Hour Oral Glucose Tolerance Test Flow Chart



Abbreviations: DM = diabetes mellitus; FG = fasting glucose; HbA1c = hemoglobin A1c; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test.

10.13. Appendix 13: JASSO guidelines

Eleven obesity-related health problems

The JASSO guideline defines 11 health disorders for diagnosis of "Obesity Disease" to subjects who need weight reduction from medical reason.

1) Glucose intolerance disorder (T2DM, IGT, and so on)

2) Dyslipidemia

3) Hypertension

4) Hyperuricemia and Gout

5) Cardiovascular disease, myocardial infarction and Angina

6) Cerebral infarction and TIA (transient ischemic attack)

7) Non-alcoholic fatty liver disease (NAFLD)

8) Menstruation disorder and infertility

9) Obstructive sleep apnea syndrome (OSAS) and obesity-hypoventilation syndrome

l0) Motor dysfunction: arthritis/osteoarthritis (knee, hip joint, supine and so on)

11) Obesity-related renal disease

Physical activity

The JASSO guideline indicated the amount of physical activity according to the purpose of weight loss;

- for prevention of weight gain; 150 to 250 minutes (1,200-2,000 kcal) per week
- for weight loss;
  - moderate-intensity physical activity less than 150 minutes per week to provide only modest weight loss
  - moderate-intensity physical activity between 225 and 420 minutes per week to provide 5 to 7.5 kg weight loss
  - greater amounts of physical activity to provide more weight loss

For example, moderate-intensity physical activities (3-6 METs) are slightly fast walking (4 km/hour) and bicycle commuting (<16 km/hour), etc.

Before starting exercise therapy, participants will be confirmed the degree of obesity-related health problems such as lifestyle-related diseases, orthopedic diseases, the presence or absence of treatment, medical history, and exercise habits, and discussed contents of physical activities that can be safely implemented according to the participant's situation (JASSO 2016).

10.14. Appendix 14: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

After approval by local ERBs, regulatory bodies and any other relevant authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

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

Considerations for making a change

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

Informed Consent
Additional consent from the participant will be obtained, as applicable, for

- participation in remote visits, as defined under "Remote Visits" below.
- 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

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

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

1. Remote visits

In source documents and the CRF, the study site should capture the visit location and method, with a specific explanation for the reason of conducting a remote visit instead of an onsite visit.

> **Telemedicine:** Telephone or technology-assisted virtual visits, or both are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, AEs and product complaints, concomitant medications, review of study participant diary (including study drug compliance), review diet and exercise goals, C-SSRS (Since Last Visit Version), Self-Harm Supplement Form, Self-Harm Follow-up Form (if applicable), and PHQ-9.
> **Mobile healthcare:** Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to, weight and waist measurements, physical assessments, vital signs, ECG, patient reported outcome questionnaires administration, collection of blood samples and health information.
> **Other alternative locations:** Laboratory draws may be done at an alternate location in exceptional circumstances.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

2. Local laboratory testing option

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

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

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

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

4. Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken prior to Visit 3 are valid for a maximum of 90 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If paused for less than 90 days from Visit 1 to Visit 3: the participant will proceed to the next study visit per the usual Schedule of Activities, provided that Visit 3 must be conducted within 90 days from Visit 1.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay in the CRF.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If paused for more than 90 days from Visit 1 to Visit 3: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen fail in the CRF with a reason of exceptional circumstance. This screen fail is allowed in addition to the main protocol screen fail. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual Schedule of Activities should be followed, starting at Visit 1 to ensure participant eligibility by Visit 3.

5. Adjustments to Visit Windows

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

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 4 through Visit 21 and Visit 801	Primary endpoint visit (Visit 21 or 99) and 4 weeks post end of treatment visit (Visit 801) should be completed as per original schedule whenever possible and safe to do so. However, the visit windows may be brought forward no sooner than 14 days or extended up to 28 days upon specific guidance from the sponsor.

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

Documentation

Changes to study conduct will be documented:

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

10.15. Appendix 15: Abbreviations

Term	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his 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/his 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 subjects are aware of the treatment received.
BMI	body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
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.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician and global safety physician or other medical officer.
CRS	clinical research scientist: Individual responsible for the medical conduct of the study as same as CRP
CT	computerized tomography
device deficiencies	Equivalent to product complaint
DM	diabetes mellitus
DNA	deoxyribonucleic acid
EAS	Efficacy Analysis Set
ECG	electrocardiogram

eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	EuroQol – 5 Dimension – 5 Level
ERB	ethical review board
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIPR	glucose-dependent insulinotropic polypeptide receptor
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
HbA1c	hemoglobin A1c
HFF	hepatic fat fraction
hsCRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGT	impaired glucose tolerance
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

investigational product (IP)	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
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.
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
IWRS	interactive web-response system
JASSO	Japan Society for the Study of Obesity
mITT	modified intention-to-treat
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
NAFLD	non-alcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
OGTT	oral glucose tolerance test
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
PDFF	proton density fat fraction
PGIS	Patient Global Impression of Status for Physical Activity
PHQ-9	Patient Health Questionnaire-9
PK/PD	pharmacokinetics/pharmacodynamics
QTc	corrected QT interval
QTL	quality tolerance limit
QW	once weekly
SAE	serious adverse event
SAP	statistical analysis plan

SAT	subcutaneous adipose tissue
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SF-36v2	Short-Form 36-item Health Survey Version 2
SS	Safety Analysis Set
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TE	treatment-emergent
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TG	triglyceride
ULN	upper limit of normal
VAS	visual analog scale
VAT	visceral adipose tissue

10.16. Appendix 16: Protocol Amendment History

Amendment [a]

Overall Rationale for the Amendment:

The correction of inclusion criteria is the primary driver for this amendment.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Inclusion criteria 2a has been updated from "…, and/or OGTT 2-hour glucose of ≥140 mg/dL…" to "…and OGTT 2-hour glucose of ≥140 mg/dL…."	This corrects an error in the original protocol.
8.1.2.9.5.1 Meal Intake	The object of vendor calculation has been changed from "percentage" to "volume."	This addition is made to clarify protocol procedure.
10.1.7 Data Quality Assurance	Languages about quality tolerance limits has been added.	This addition is made to clarify protocol procedure.
10.5 Contraceptive Guidance and Collection of Pregnancy Information	The definition of still birth has been changed from "at >20 weeks gestational age" to "at ≥20 weeks gestational age."	This corrects an error in the original protocol.
10.15 Abbreviations	Definition of QTL is added.	This addition is made to keep alignment with the change.
Protocol header	Study alias in the header has been changed from "I8F-MC-GPHZ" to "Protocol I8F-JE-GPHZ."	This corrects an error in the original protocol.

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