Title Page

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Investigational Tirzepatide Doses in Participants with Type 2 Diabetes and Obesity

Protocol Number: I8F-MC-GPIT (Tirzepatide High Dose)

Amendment Number: a

Compound: LY3298176

Brief Title: The Effect of Investigational Tirzepatide Doses in Participants with Type 2 Diabetes and Obesity

Study Phase: 2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:

IND: 139721

EU trial number: 2023-504561-24-00

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

Document ID: VV-CLIN-077179

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*20-Mar-2023*

Amendment (a)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update protocol wording to align with current regulatory requirements of the EU countries.

Section # and Name	Description of Change	Brief Rationale
1.3.1. Screening (Period I), Dose Escalation (Period II), and High Dose Treatment (Period III) 1.3.2. Extension Phase (Period IV) and Posttreatment Follow-up	Added a comment in urine pregnancy testing "For country-specific requirements, please see Section 10.8, Appendix 8" to refer to EU-specific requirements	To refer to the EU-specific requirements.
9.4. Interim Analyses	More details provided about interim analyses plan	To align with current regulatory requirements of the EU countries.
10.8. Appendix 8: Country-specific Requirements	Added requirement for more frequent (monthly) urine pregnancy tests in SoA	To align with current regulatory requirements of the EU countries.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Investigational Tirzepatide Doses in Participants with Type 2 Diabetes and Obesity.

Brief Title: The Effect of Investigational Tirzepatide Doses in Participants with Type 2 Diabetes and Obesity

Regulatory Agency Identifier Numbers:

IND: 139721

EU trial number: 2023-504561-24-00

Rationale:

No study to date has investigated the effects of tirzepatide at doses higher than 15 mg. This study is designed to provide initial safety, pharmacokinetic (PK), and efficacy data for tirzepatide 20 mg and 25 mg compared to placebo and investigate the potential additional clinical benefit of higher doses of tirzepatide compared to tirzepatide 15 mg in participants with type-2 diabetes (T2D) and obesity Class II (body mass index ≥35 kg/m^2).

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
Demonstrate whether pooled data from tirzepatide 15 mg, 20 mg and 25 mg is superior to placebo in reducing body weight from baseline at Week 44	• Percent change in body weight
Key Secondary (controlled for type I error)	
• Demonstrate whether pooled data from tirzepatide 15 mg, 20 mg and 25 mg is superior to placebo in glycemic control from baseline at Week 44	• Change in HbA1c
• Demonstrate whether tirzepatide 25 mg is superior to tirzepatide 15 mg in reducing body weight from Week 24 at Week 80 • Demonstrate whether tirzepatide 20 mg is superior to tirzepatide 15 mg in reducing body weight from Week 24 at Week 80	• Percent change in body weight

Objectives	Endpoints
Additional Secondary	
• Compare the glycemic control from Week 24 at Week 80 o tirzepatide 25 mg vs. 15 mg o tirzepatide 20 mg vs. 15 mg	• Change in HbA1c
• Compare tirzepatide to placebo in reducing body weight from baseline at Week 44 • Compare the change in body weight from Week 24 at Week 44 o tirzepatide 25 mg vs. 15 mg o tirzepatide 20 mg vs. 15 mg	• Percent change in body weight
• Compare tirzepatide to placebo in additional measures of reducing body weight from baseline at Week 44 • Compare additional measures of reducing body weight from Week 24 at Weeks 44 and 80 o tirzepatide 25 mg vs. 15 mg o tirzepatide 20 mg vs. 15 mg	• Absolute change in body weight • Change in BMI • Change in waist circumference
• Compare tirzepatide to placebo in additional measures of reducing body weight from baseline at Week 44 • Compare additional measures of reducing body weight from baseline at Weeks 44 and 80 o tirzepatide 25 mg vs. 15 mg o tirzepatide 20 mg vs. 15 mg	• Proportion of participants achieving: o ≥5% body weight reduction o ≥10% body weight reduction o ≥15% body weight reduction o ≥20% body weight reduction
• Compare tirzepatide to placebo in additional measures of glycemic control from baseline at Week 44 • Compare additional measures of glycemic control from Week 24 at Weeks 44 and 80 o tirzepatide 25 mg vs. 15 mg o tirzepatide 20 mg vs. 15 mg	• Change in fasting serum glucose • Mean change in 7-point SMBG profiles
• Compare tirzepatide to placebo in additional measures of glycemic control at Week 44 • Compare additional measures of glycemic control at Weeks 44 and 80 o tirzepatide 25 mg vs. 15 mg o tirzepatide 20 mg vs. 15 mg	• Proportion of participants achieving: o HbA1c <7.0% (53 mmol/mol) o HbA1c ≤6.5% (48 mmol/mol) o HbA1c <5.7% (39 mmol/mol)
• Compare tirzepatide to placebo for change in lipid parameters from baseline at Week 44 • Compare the change in lipid parameters from Week 24 at Weeks 44 and 80 o tirzepatide 25 mg vs. 15 mg	• Change in fasting: o Total cholesterol o LDL o HDL o VLDL

Objectives	Endpoints
○ tirzepatide 20 mg vs. 15 mg	○ Triglycerides
• To describe the safety and tolerability of each study intervention	• Summary of safety data, including number and incidence of ○ SAEs ○ TEAEs ○ discontinuations due to AEs ○ occurrence of hypoglycemic episodes • Mean change in systolic and diastolic blood pressure and pulse rate
To characterize the population PK of tirzepatide 20 mg and 25 mg	• Population PK parameters

Abbreviations: AE = adverse event; BMI = body mass index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PK = pharmacokinetics; SAE = serious adverse event; SMBG = self-monitoring of blood glucose; TEAE = treatment-emergent adverse event; VLDL = very-low-density lipoprotein.

Primary estimands:

There will be 2 estimands for the primary objective planned in the study. The estimands address intercurrent events (ICEs) using either the treatment policy strategy or the hypothetical strategy.

Treatment regimen estimand:

The primary clinical question of interest is:

What is the treatment difference in the percent change in body weight from baseline at Week 44 between tirzepatide and placebo in individuals who meet eligibility criteria regardless of adherence to study intervention or initiation of prohibited medications?

Efficacy estimand:

The clinical question of interest is:

What is the treatment difference in the percent change in body weight from baseline at Week 44 between tirzepatide and placebo in individuals who meet the eligibility criteria if they would remain on their randomized treatment for 44 weeks and would not initiate prohibited medications?

Overall Design

Study I8F-MC-GPIT (GPIT) is a Phase 2, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tirzepatide 20 mg and 25 mg in participants with T2D and obesity Class II.

The study includes a

- Screening/Lead-in period
- dose escalation period
- high dose treatment period
- extension phase, and
- posttreatment follow-up period

Brief Summary:

The main purpose of this study is to provide initial safety, PK, and efficacy data for tirzepatide 20 mg and 25 mg.

Study Population (Key Inclusion Criteria):

In general, an individual may take part in this study if they

- Are 18 to 75 years of age inclusive, at the time of signing the informed consent.
- Have a BMI ≥35 kg/m^2 at Visit 1.
- Have had stable body weight (±5%) during the 90 days preceding Visit 1.
- Have been diagnosed with T2D based on the World Health Organization classification or other locally applicable diagnostic standards.
- Have an HbA1c of ≥7% (≥53 mmol/mol) and ≤10% (≤86 mmol/mol) as determined by the central laboratory at Visit 1.
- Have been on a stable treatment of metformin only at least 90 days preceding Visit 1 and between Visits 1 and 3 with the minimum effective dose of ≥1500 mg/day.

Number of Participants:

The study will enroll approximately 350 participants.

Intervention Groups and Duration:

Participants will be randomly assigned in a 6:1 ratio to tirzepatide or placebo at Week 0. At Week 24, participants on tirzepatide will undergo a second randomization in a 1:1:1 ratio to receive tirzepatide 15 mg or 20 mg or 25 mg.

Participants randomly assigned to tirzepatide

The starting dose is 2.5 mg once weekly with a dose escalation every 4 weeks at 2.5 mg increments until the 15 mg dose is reached. Participants randomly assigned to higher doses of tirzepatide will have additional escalation every 4 weeks at 5 mg increments until the randomized dose of 20 mg or 25 mg is reached. To achieve the assigned dose, all participants will be required to receive 2 injections per week starting at Week 24.

Participants randomly assigned to placebo

To maintain blinding, participants randomly assigned to the placebo treatment group will also receive study intervention weekly and will follow a sham dose escalation schedule every 4 weeks matched with the tirzepatide treatment group. Additionally, starting at Week 24, all participants will be required to receive 2 injections per week to maintain the blind.

Study duration

The study duration will be approximately 89 weeks including screening and follow-up.

The primary treatment duration for all participants randomly assigned tirzepatide or placebo at Week 0 will be approximately 44 weeks. Participants randomly assigned a tirzepatide maintenance dose at Week 24 will continue in the extension phase and have a total treatment duration of approximately 80 weeks.

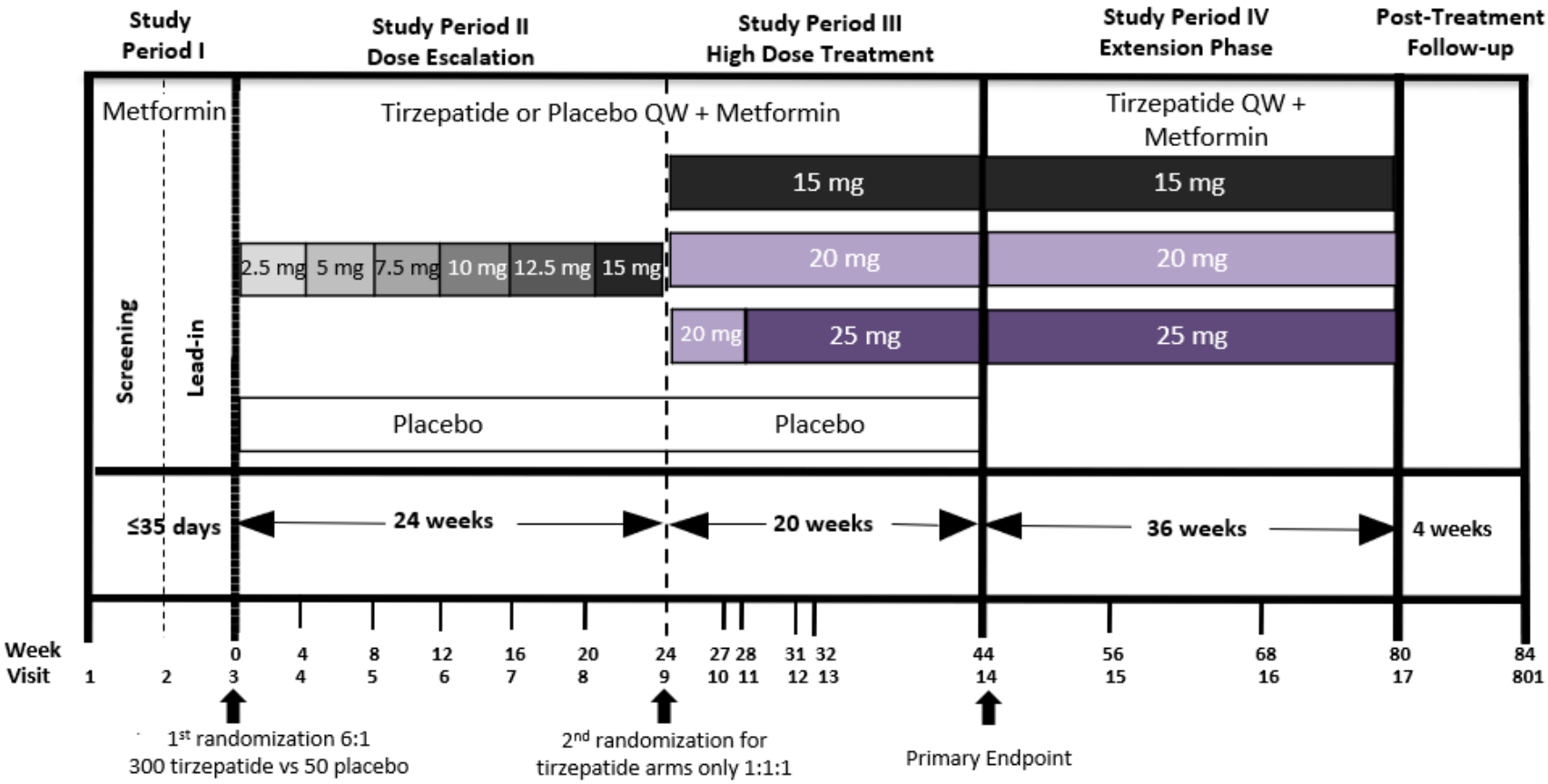
Ethical Considerations of Benefit/Risk:

The safety and efficacy profile seen to date for tirzepatide at doses up to 15 mg supports the overall benefit risk for participants in this study. Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with higher doses of tirzepatide are justified by the anticipated benefits that may be afforded to participants living with T2D and obesity Class II.

Data Monitoring Committee: No

There is no external Data Monitoring Committee for this study.

1.2. Schema



Abbreviation: QW = once weekly.

1.3. Schedule of Activities (SoA)

Two tables describe the SoA.

Section 1.3.1 describes procedures for Screening (Period I), Dose Escalation (Period II), and High Dose Treatment (Period III)

Section 1.3.2 describes Extension Phase (Period IV) and Posttreatment Follow-up

Fasting Visits
Participants should not eat or drink anything except water for approximately 8 hours before the visit.

PK only

The only procedure performed for these visits is PK sample collection.

1.3.1. Screening (Period I), Dose Escalation (Period II), and High Dose Treatment (Period III)

Study I8F-MC-GPIT	Prescreening	Period I Screening/ Lead-in		Period II Dose Escalation						Period III High Dose Treatment						Comments
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Prescreening Visit 601 is optional
Weeks from randomization		≤35 days		0	4	8	12	16	20	24	27	28	31	32	44	
Visit interval tolerance (days)					±3	±3	±3	±3	±3	±3		±3		±3	±7	
Fasting visit				X	X	X	X	X	X	X		X		X	X	
Visit detail											PK		PK			PK = visit only for PK sample collection
Abbreviated informed consent	X															The abbreviated informed consent grants consent only for procedures and assessments marked under Visit 601.
Abbreviated medical history and concomitant medication	X															Includes collection of history of T2D and current diabetes and weight loss medications.
Informed consent		X														Must be signed prior to conducting any protocol procedures.
Inclusion and exclusion criteria, review and confirm	X	X	X	X												Confirm prior to randomization and administration of first dose of study intervention.
Demographics	X	X														Includes ethnicity (where permissible), year of birth, sex and race.
Preexisting conditions and medical history, including relevant surgical history		X														Include assessment of relevant preexisting conditions and medical history (for example, history of T2D, gallbladder disease, CV disease,

Study I8F-MC-GPIT	Prescreening	Period I Screening/ Lead-in		Period II Dose Escalation						Period III High Dose Treatment						Comments
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Weeks from randomization		≤35 days		0	4	8	12	16	20	24	27	28	31	32	44	
Visit interval tolerance (days)					±3	±3	±3	±3	±3	±3		±3		±3	±7	
Fasting visit				X	X	X	X	X	X	X		X		X	X	
Visit detail											PK		PK			PK = visit only for PK sample collection
																medullary thyroid carcinoma, pancreatitis, and OSA) and substance usage (alcohol and tobacco).
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent. Collect additional data for AESIs and other safety topics. See Section 8.3.3.
Physical evaluation																
Height	X	X														
Weight	X	X		X	X	X	X	X	X	X		X		X	X	
Waist circumference				X	X	X	X	X	X	X		X		X	X	
Vital signs		X		X	X	X	X	X	X	X		X		X	X	Measure blood pressure and pulse rate 2 times, after participant has been sitting at least 5 min. Vital signs should be taken before ECG tracing and before collection of blood samples for laboratory testing. See Section 8.2.2.
Physical examination		X													X	
Symptom-direct physical assessment				X	X	X	X	X	X	X		X		X		Symptom-directed physical assessments may be conducted during the study at the

Study I8F-MC-GPIT	Prescreening	Period I Screening/ Lead-in		Period II Dose Escalation						Period III High Dose Treatment						Comments
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Prescreening Visit 601 is optional
Weeks from randomization		≤35 days		0	4	8	12	16	20	24	27	28	31	32	44	
Visit interval tolerance (days)					±3	±3	±3	±3	±3	±3		±3		±3	±7	
Fasting visit				X	X	X	X	X	X	X		X		X	X	
Visit detail											PK		PK			PK = visit only for PK sample collection
																discretion of the PI or qualified personnel per local regulations, as indicated based on participant status and standard of care. Qualified personnel per local regulations will perform the examination.
12-lead ECG				X						X		X		X	X	Collect ECG before blood sample collection for laboratory testing if these procedures occur at the same visit. ECG may be repeated at the investigator's discretion at any visit. See Section 8.2.3.
Dilated fundoscopic examination			X												X	An ophthalmologist (or optometrist if allowed per local regulations) will perform the examination between Visits 2 and 3. Documentation of a previous examination ≤90 days prior to screening is acceptable to confirm eligibility. Document the previous examination results in CRF. See Section 8.3.3.13.

Study I8F-MC-GPIT	Prescr eening	Period I Screening/ Lead-in		Period II Dose Escalation						Period III High Dose Treatment						Comments
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Prescreening Visit 601 is optional
Weeks from randomization		≤35 days		0	4	8	12	16	20	24	27	28	31	32	44	
Visit interval tolerance (days)					±3	±3	±3	±3	±3	±3		±3		±3	±7	
Fasting visit				X	X	X	X	X	X	X		X		X	X	
Visit detail											PK		PK			PK = visit only for PK sample collection
Participant diary (paper)																
Diary dispensed			X	X	X	X	X	X	X	X		X		X	X	Diary includes SMBG collection, information on dosing date/time, and hypoglycemia.
Diary return and review				X	X	X	X	X	X	X		X		X	X	
Mental health questionnaires (paper)																
C-SSRS screening/baseline		X														Collect C-SSRS after assessment of AEs.
C-SSRS since last assessment				X	X	X	X	X	X	X		X		X	X	Collect C-SSRS after assessment of AEs and capture information since most recent C-SSRS administration.
PHQ-9		X		X			X			X				X	X	PHQ-9 is self-administered and complete after assessment of AEs**.**
Participant education and supplies																
Diabetes and lifestyle management counseling				X	X	X	X	X	X	X		X		X	X	Includes counseling on diet and exercise, symptoms and management of hyperglycemia and hypoglycemia, etc. See Sections 5.3, 6.9.2 and 8.3.3.1.

Study I8F-MC-GPIT	Prescreening	Period I Screening/ Lead-in		Period II Dose Escalation						Period III High Dose Treatment						Comments
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Prescreening Visit 601 is optional
Weeks from randomization		≤35 days		0	4	8	12	16	20	24	27	28	31	32	44	
Visit interval tolerance (days)					±3	±3	±3	±3	±3	±3		±3		±3	±7	
Fasting visit				X	X	X	X	X	X	X		X		X	X	
Visit detail											PK		PK			PK = visit only for PK sample collection
																Provide additional training as needed.
Dispense BG meter and supplies			X													Includes training on the use of BG meter.
Blood glucose monitoring																
Review 7-point SMBG values collected in diary				X						X					X	Site staff will remind participants of collection times before visit. Participant will collect two 7-point SMBGs on 2 nonconsecutive days within 2 weeks of each visit specified.
Laboratory tests and sample collections																
Hematology		X		X			X			X				X	X	
Hemoglobin A1c (HbA1c)	X	X		X			X			X		X		X	X	
Clinical chemistry		X		X			X			X		X		X	X	
Lipid panel		X		X			X			X				X	X	
Serum pregnancy		X														Collect for WOCBP. See Section 10.4, Appendix 4.
Urine pregnancy (local)				X						X					X	The result must be available before the first dose of study intervention for WOCBP.

Study I8F-MC-GPIT	Prescreening	Period I Screening/ Lead-in		Period II Dose Escalation						Period III High Dose Treatment						Comments
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Prescreening Visit 601 is optional
Weeks from randomization		≤35 days		0	4	8	12	16	20	24	27	28	31	32	44	
Visit interval tolerance (days)					±3	±3	±3	±3	±3	±3		±3		±3	±7	
Fasting visit				X	X	X	X	X	X	X		X		X	X	
Visit detail											PK		PK			PK = visit only for PK sample collection
																For country-specific requirements, please see Section 10.8, Appendix 8 Perform additional pregnancy tests at any time during the study if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation. If the urine pregnancy test is positive or inconclusive at any visit, an additional serum pregnancy test should be collected.
Follicle Stimulating Hormone (FSH)		X														Perform as needed to confirm postmenopausal status. See Section 10.4.1.
Thyroid-Stimulating Hormone (TSH)		X														
Calcitonin		X					X			X				X	X	
Pancreatic amylase		X		X			X			X				X	X	
Lipase		X		X			X			X				X	X	
Cystatin-C		X		X			X			X		X		X	X	
Estimated glomerular filtration rate (eGFR)		X		X			X			X		X		X	X	Calculated using CKD-EPI creatinine-cystatin C equation.

Study I8F-MC-GPIT	Prescreening	Period I Screening/ Lead-in		Period II Dose Escalation						Period III High Dose Treatment						Comments
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Prescreening Visit 601 is optional
Weeks from randomization		≤35 days		0	4	8	12	16	20	24	27	28	31	32	44	
Visit interval tolerance (days)					±3	±3	±3	±3	±3	±3		±3		±3	±7	
Fasting visit				X	X	X	X	X	X	X		X		X	X	
Visit detail											PK		PK			PK = visit only for PK sample collection
Urinary albumin/creatinine ratio (UACR)		X		X						X					X	
PK samples (post-dose)											X		X			Collect at windows of 1 to 24 hr, 24 to 96 hr, or 120 to 168 hr post-dose, as assigned by IWRS. Dependent on the time windows to which a participant is assigned, they may be required to come to site for PK-specific visits.
Immunogenicity (ADA) samples				X	X		X			X					X	Collect predose sample.
PK sample for immunogenicity					X		X			X					X	Collect predose sample.
Stored samples																
Genetics sample				X												
Exploratory biomarker samples				X						X					X	
Randomization and dosing																
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X		X		X	X	
Randomization via IWRS				X						X						
Dispense study intervention via IWRS				X	X	X	X	X	X	X		X		X	X	

Study I8F-MC-GPIT	Prescreening	Period I Screening/ Lead-in		Period II Dose Escalation						Period III High Dose Treatment						Comments
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Prescreening Visit 601 is optional
Weeks from randomization		≤35 days		0	4	8	12	16	20	24	27	28	31	32	44	
Visit interval tolerance (days)					±3	±3	±3	±3	±3	±3		±3		±3	±7	
Fasting visit				X	X	X	X	X	X	X		X		X	X	
Visit detail											PK		PK			PK = visit only for PK sample collection
Review injection technique				X	X					X						
Observe participant administer study intervention				X	X					X						
Dispense ancillary supplies to participant				X	X	X	X	X	X	X		X		X	X	
Participant returns study intervention and ancillary supplies					X	X	X	X	X	X		X		X	X	
Assess study intervention compliance					X	X	X	X	X	X		X		X	X	

Abbreviations: ADA = antidrug antibody; AESI = adverse events of special interest; BG = blood glucose; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; CV = cardiovascular; ECG = electrocardiogram; IWRS = interactive web-response system; OSA = obstructive sleep apnea; PHQ-9 = Patient Health Questionnaire-9; PI = principal investigator; PK = pharmacokinetic; SMBG = self-monitoring of blood glucose; T2D = type-2 diabetes; WOCBP = women of childbearing potential.

1.3.2. Extension Phase (Period IV) and Posttreatment Follow-up

Study I8F-MC-GPIT	Period IV Extension Phase (Placebo Group Discontinued)				Posttreatment Follow-up	Comments
Visit number	15	16	17	ED	801	
Weeks from randomization	56	68	80	—	84 (or 48 for certain participants)	All participants assigned placebo or who discontinue study intervention prior to Visit 9 will complete Visit 801 at Week 48
Visit interval tolerance (days)	±7	±7	±7	—	±7	
Fasting visit	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	Any events that occur after signing the informed consent. Collect additional data for AESIs and other safety topics. See Section 8.3.3.
Physical evaluation						
Weight	X	X	X	X	X	
Waist circumference	X	X	X	X	X	
Vital signs	X	X	X	X	X	Includes pulse rate, blood pressure. Measure blood pressure and pulse rate 2 times, after participant has been sitting at least 5 min. See Section 8.2.2.
Physical examination			X	X		
Symptom-direct physical assessment	X	X			X	Symptom-directed physical assessments may be conducted during the study at the discretion of the PI or qualified personnel per local regulations, as indicated based on participant status and standard of care. Qualified personnel per local regulations will perform the examination.
12-lead ECG			X	X	X	Collect ECG before blood sample collection for laboratory testing if these procedures occur at the same

Study I8F-MC-GPIT	Period IV Extension Phase (Placebo Group Discontinued)				Posttreatment Follow-up	Comments
Visit number	15	16	17	ED	801	
Weeks from randomization	56	68	80	—	84 (or 48 for certain participants)	All participants assigned placebo or who discontinue study intervention prior to Visit 9 will complete Visit 801 at Week 48
Visit interval tolerance (days)	±7	±7	±7	—	±7	
Fasting visit	X	X	X	X	X	
						visit. ECG may be repeated at the investigator's discretion at any visit. See Section 8.2.3.
Dilated fundoscopic examination			X	X		An ophthalmologist (or optometrist if allowed per local regulations) will perform the examination. See Section 8.3.3.13.
Participant diary (paper)						
Diary dispensed	X	X	X	X		
Diary return and review	X	X	X	X	X	
Mental health questionnaires (paper)						
C-SSRS since last assessment	X	X	X	X	X	
PHQ-9	X	X	X	X	X	
Participant education						
Diabetes and lifestyle management counseling	X	X	X	X		Includes counseling on diet and exercise, symptoms and management of hyperglycemia and hypoglycemia, etc. See Sections 5.3, 6.9.2 and 8.3.3.1. Provide additional training as needed.
Blood glucose monitoring						
Review 7-point SMBG values collected in diary			X			Site staff will remind participants of collection times before visit. Participant will collect two 7-point SMBGs on 2 nonconsecutive days within 2 weeks of each visit specified.
Laboratory tests and sample collections						
Hematology	X	X	X	X	X	
Hemoglobin A1c (HbA1c)	X	X	X	X	X	

Study I8F-MC-GPIT	Period IV Extension Phase (Placebo Group Discontinued)				Posttreatment Follow-up	Comments
Visit number	15	16	17	ED	801	
Weeks from randomization	56	68	80	—	84 (or 48 for certain participants)	All participants assigned placebo or who discontinue study intervention prior to Visit 9 will complete Visit 801 at Week 48
Visit interval tolerance (days)	±7	±7	±7	—	±7	
Fasting visit	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	
Lipid panel	X	X	X	X	X	
Urine pregnancy (local)			X	X	X	For country-specific requirements, please see Section 10.8, Appendix 8 Perform additional pregnancy tests if there is clinical suspicion of pregnancy, or if required by local law or regulation. If the urine pregnancy test is positive or inconclusive at any visit, an additional serum pregnancy test should be collected.
Calcitonin	X	X	X	X	X	
Pancreatic amylase	X	X	X	X	X	
Lipase	X	X	X	X	X	
Cystatin-C	X	X	X	X	X	
Estimated glomerular filtration rate (eGFR)	X	X	X	X	X	Calculated using CKD-EPI creatinine-cystatin C equation.
Urinary albumin/creatinine ratio (UACR)			X	X	X	
Immunogenicity (ADA) samples		X	X	X	X	Pre dose if applicable.
PK samples for immunogenicity		X	X	X	X	Pre dose if applicable.
Stored samples						
Exploratory biomarker samples	X		X	X	X	
Randomization and dosing						
Register visit with IWRS	X	X	X	X	X	

Study I8F-MC-GPIT	Period IV Extension Phase (Placebo Group Discontinued)				Posttreatment Follow-up	Comments
Visit number	15	16	17	ED	801	
Weeks from randomization	56	68	80	—	84 (or 48 for certain participants)	All participants assigned placebo or who discontinue study intervention prior to Visit 9 will complete Visit 801 at Week 48
Visit interval tolerance (days)	±7	±7	±7	—	±7	
Fasting visit	X	X	X	X	X	
Dispense study intervention via IWRS	X	X				
Dispense ancillary supplies to participant	X	X				
Participant returns study interventions and ancillary supplies	X	X	X	X		
Assess study intervention compliance	X	X	X	X		

Abbreviations: ADA = antidrug antibody; AESI = adverse events of special interest; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; IWRS = interactive web-response system; PHQ-9 = Patient Health Questionnaire-9; PI = principal investigator; PK = pharmacokinetic; SMBG = self-monitoring of blood glucose; WOCBP = women of childbearing potential.

2. Introduction

Tirzepatide

Tirzepatide is approved as an adjunct to diet and exercise to improve glycemic control in adults with T2D. It is a single molecule with agonist activity at both the GIP and GLP-1 receptors and has demonstrated significant and clinically meaningful HbA1c and body weight reductions in adults with T2D at doses ranging from 5 mg to 15 mg (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022).

Tirzepatide is in clinical development for

- T2D in the pediatric population
- Chronic Weight Management (CWM)
- Non-alcoholic Steatohepatitis (NASH)
- Heart Failure with preserved Ejection Fraction (HFpEF) in people with obesity, and
- Obstructive Sleep Apnea (OSA) in people with obesity.

2.1. Study Rationale

No study to date has investigated the effects of tirzepatide at doses higher than 15 mg. This study is designed to provide initial safety, PK, and efficacy data for tirzepatide 20 mg and 25 mg compared to placebo and investigate the potential additional clinical benefit of higher doses of tirzepatide compared to tirzepatide 15 mg in participants with T2D and obesity Class II (BMI $\geq$35 kg/m^2). These participants could be eligible for bariatric surgery and may benefit from higher doses of tirzepatide.

2.2. Background

Phase 3 clinical studies

Clinical reductions in body weight and HbA1c

In 5 global Phase 3 studies in participants with T2D, tirzepatide demonstrated clinically meaningful reductions in HbA1c and improvements in body weight, which were greater than placebo and active comparators including semaglutide 1 mg QW (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022). These treatment effects were sustained up to 104 weeks (Del Prato et al. 2021). The mean body weight reduction achieved with tirzepatide in participants with T2D was up to 13.9% (Ludvik et al. 2021).

The chronic weight management program consists of 4 global Phase 3 trials assessing adults with overweight or obesity with and without T2D. Results from the SURMOUNT-1 study, in participants without T2D who have obesity or are overweight with weight-related comorbidities, showed mean percent weight reductions up to 22.5% (Jastreboff et al. 2022).

Improvements in metabolic endpoints

Tirzepatide also significantly improved fasting serum glucose, 2-hour post meal glucose, continuous glucose monitoring-assessed time in euglycemic range, waist circumference, volume of abdominal visceral and SC adipose tissue, and fasting lipid profile in participants with T2D

(Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Battelino et al. 2021; Dahl et al. 2022; Gastaldelli et al. 2022).

Common adverse events

Overall, the safety and tolerability profile is similar to GLP-1 RAs. GI AEs, such as nausea, diarrhea, and vomiting, were the most common AEs seen in tirzepatide-treated participants.

Hypoglycemia events

In line with the ability of tirzepatide to lower BG in a glucose-dependent manner, the overall incidence of clinically significant (<54 mg/dL) or severe hypoglycemia attributable to tirzepatide was low. The risk of clinically significant or severe hypoglycemia was higher when tirzepatide was used in combination with insulin glargine or sulfonylurea, as has been observed with GLP-1 RAs (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tirzepatide may be found in the IB.

2.3.1. Risk Assessment

Potential risks for this study

The potential risks associated with higher doses of tirzepatide are anticipated to be similar to that of currently marketed doses of tirzepatide (Mounjaro® 5 – 15 mg) and that of marketed GLP-1 RAs. The most commonly reported TEAEs observed in tirzepatide clinical studies were GI related, including nausea, diarrhea, and vomiting. Most were mild to moderate in intensity and tended to occur during the dose escalation period and decreased over time.

Identified and potential risks associated with tirzepatide include

- acute pancreatitis
- increases in heart rate
- hypoglycemia
- acute gallbladder disease
- diabetic retinopathy complications
- hypersensitivity reactions, and
- thyroid C-cell effects (only observed in rodents).

Management of risks

Sections 5.1, 5.2, and 8.3 address known and potential risks associated with tirzepatide.

2.3.2. Benefit Assessment

The potential benefits from participation in this study include improved glycemic control, weight loss, and continued expert medical care for the study duration.

Participants may benefit by receiving personal health information, routine safety assessments, lifestyle management counseling, and frequent engagement with health care providers during the study, which provide opportunities for coaching and support.

2.3.3. Overall Benefit Risk Conclusion

The safety and efficacy profile seen to date for tirzepatide at doses up to 15 mg supports the overall benefit risk for participants in this study. Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with higher doses of tirzepatide are justified by the anticipated benefits that may be afforded to participants living with T2D and obesity Class II.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
Demonstrate whether pooled data from tirzepatide 15 mg, 20 mg and 25 mg is superior to placebo in reducing body weight from baseline at Week 44	• Percent change in body weight
Key Secondary (controlled for Type I error)	
• Demonstrate whether pooled data from tirzepatide 15 mg, 20 mg and 25 mg is superior to placebo in glycemic control from baseline at Week 44	• Change in HbA1c
• Demonstrate whether tirzepatide 25 mg is superior to tirzepatide 15 mg in reducing body weight from Week 24 at Week 80 • Demonstrate whether tirzepatide 20 mg is superior to tirzepatide 15 mg in reducing body weight from Week 24 at Week 80	• Percent change in body weight
Additional Secondary	
• Compare the glycemic control from Week 24 at Week 80 o tirzepatide 25 mg vs. 15 mg o tirzepatide 20 mg vs. 15 mg	• Change in HbA1c
• Compare tirzepatide to placebo in reducing body weight from baseline at Week 44 • Compare the change in body weight from Week 24 at Week 44 o tirzepatide 25 mg vs. 15 mg o tirzepatide 20 mg vs. 15 mg	• Percent change in body weight
• Compare tirzepatide to placebo in additional measures of reducing body weight from baseline at Week 44 • Compare additional measures of reducing body weight from Week 24 at Weeks 44 and 80 o tirzepatide 25 mg vs. 15 mg o tirzepatide 20 mg vs. 15 mg	• Absolute change in body weight • Change in BMI • Change in waist circumference
• Compare tirzepatide to placebo in additional measures of reducing body weight from baseline at Week 44 • Compare additional measures of reducing body weight from baseline at Weeks 44 and 80 o tirzepatide 25 mg vs. 15 mg	• Proportion of participants achieving: o ≥5% body weight reduction o ≥10% body weight reduction o ≥15% body weight reduction o ≥20% body weight reduction

Objectives	Endpoints
○ tirzepatide 20 mg vs. 15 mg	
• Compare tirzepatide to placebo in additional measures of glycemic control from baseline at Week 44 • Compare additional measures of glycemic control from Week 24 at Weeks 44 and 80 ○ tirzepatide 25 mg vs. 15 mg ○ tirzepatide 20 mg vs. 15 mg	• Change in fasting serum glucose • Mean change in 7-point SMBG profiles
• Compare tirzepatide to placebo in additional measures of glycemic control at Week 44 • Compare additional measures of glycemic control at Weeks 44 and 80 ○ tirzepatide 25 mg vs. 15 mg ○ tirzepatide 20 mg vs. 15 mg	• Proportion of participants achieving: ○ HbA1c <7.0% (53 mmol/mol) ○ HbA1c ≤6.5% (48 mmol/mol) ○ HbA1c <5.7% (39 mmol/mol)
• Compare tirzepatide to placebo for change in lipid parameters from baseline at Week 44 • Compare the change in lipid parameters from Week 24 at Weeks 44 and 80 ○ tirzepatide 25 mg vs. 15 mg ○ tirzepatide 20 mg vs. 15 mg	• Change in fasting: ○ Total cholesterol ○ LDL ○ HDL ○ VLDL ○ Triglycerides
• To describe the safety and tolerability of each study intervention	• Summary of safety data, including number and incidence of ○ SAEs ○ TEAEs ○ discontinuations due to AEs ○ occurrence of hypoglycemic episodes • Mean change in systolic and diastolic blood pressure and pulse rate
To characterize the population PK of tirzepatide 20 mg and 25 mg	• Population PK parameters

Abbreviations: AE = adverse event; BMI = body mass index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PK = pharmacokinetics; SAE = serious adverse event; SMBG = self-monitoring of blood glucose; TEAE = treatment-emergent adverse event; VLDL = very-low-density lipoprotein.

Primary estimands:

There will be 2 estimands for the primary objective planned in the study. The estimands address ICEs using either the treatment policy strategy or the hypothetical strategy.

Treatment policy strategy

The occurrence of the ICE is considered irrelevant in defining the treatment effect of interest; the values for the variable of interest are used regardless of whether the ICE occurs. ***Hypothetical strategy***

A scenario is envisaged in which the ICE would not occur. The value of the variable to reflect the clinical question of interest is the value that the variable would have taken in the hypothetical scenario defined.

Treatment regimen estimand:

The primary clinical question of interest is:

What is the treatment difference in the percent change in body weight from baseline at Week 44 between tirzepatide and placebo in individuals who meet eligibility criteria regardless of adherence to study intervention or initiation of prohibited medications?

The "treatment regimen" estimand is described by the following attributes:

- ***Population:*** Participants who meet the eligibility criteria. Further details can be found in Sections 5 and 9.
- ***Primary endpoint:*** Percent change from baseline in body weight at Week 44.
- ***Treatment condition:*** The randomized study intervention with allowance for potential dose interruptions and modifications, regardless of adherence to study intervention or initiation of prohibited medications.
- ***Remaining intercurrent events:*** No ICEs are defined since treatment adherence and the initiation of prohibited medications are a part of the treatment condition.
- ***Population-level summary:*** Difference in mean percent change from baseline in body weight at Week 44 between tirzepatide and placebo.

Rationale for the estimand: This estimand aims to evaluate the efficacy of tirzepatide that reflects the real-life behavior of the target population.

Efficacy estimand:

The clinical question of interest is:

What is the treatment difference in the percent change in body weight from baseline at Week 44 between tirzepatide and placebo in individuals who meet the eligibility criteria if they would remain on their randomized treatment for 44 weeks and would not initiate prohibited medications?

The "efficacy" estimand is described by the following attributes:

- ***Population:*** Participants who meet the eligibility criteria. Further details can be found in Sections 5 and 9.
- ***Endpoint:*** Percent change from baseline in body weight at Week 44.
- ***Treatment condition:*** The randomized study intervention with allowance for potential dose interruptions and modifications.
- ***Intercurrent events:*** ICEs include permanent discontinuation of study intervention and initiation of prohibited medications, which is handled by the hypothetical strategy. The

potential outcome of interest is the response in the efficacy measurement if participants would remain on their randomized treatment for 44 weeks and would not initiate prohibited medications. Dose modification and interruption will not be considered an ICE since they are part of the treatment condition.

- ***Population-level summary and treatment effect of interest:*** Difference in mean percent changes in body weight from baseline at Week 44 between tirzepatide and placebo.

Rationale for the estimand: This estimand aims to evaluate the efficacy of tirzepatide under the ideal condition that all participants would adhere to the randomized study intervention without being confounded by the initiation of prohibited medications.

There will be 2 estimands for the key secondary objectives planned in the study similar to that for the primary objective. The estimands address ICEs using either the treatment policy strategy or the hypothetical strategy.

4. Study Design

4.1. Overall Design

Study I8F-MC-GPIT (GPIT) is a Phase 2, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tirzepatide 20 mg and 25 mg in participants with T2D and obesity Class II.

The study includes a

- Screening/Lead-in period
- dose escalation period
- high dose treatment period
- extension phase, and
- posttreatment follow-up period

See the SoA (Section 1.3) for additional details about the study periods and visit-specific assessments, including assessments needed at an ED visit.

4.1.1. Overview of Study

Prescreening

An optional prescreening visit which includes assessment of abbreviated eligibility criteria as outlined in the SoA may be conducted at a traditional investigator site or other location associated with the investigator. HbA1c measurement may be performed through the central laboratory or at a local laboratory or via point-of-care testing, if permissible by local regulations and requirements. Local laboratories performing testing must be qualified in accordance with applicable local regulations. Registration of the visit with IWRS is required to obtain a participant identifier. The prescreening visit must be recorded in the CRF with the associated participant identifier.

Confirm the participant meets applicable eligibility criteria before proceeding to Visit 1. It is recommended that the prescreening visit be performed within 8 weeks of Visit 1. Certain activities will be repeated at Visit 1 for confirmation of study eligibility, including collection of height and weight to calculate BMI and HbA1c measurement via the central laboratory.

Period I – screening/lead-in

All screening activities must take place within the 35-day window prior to randomization.

Visit 1

The purpose of screening procedures at Visit 1 is to establish eligibility and to obtain blood samples for laboratory assessments needed to confirm eligibility. The participant must sign the ICF before study procedures are performed, as outlined in SoA, Section 1.3. Participants who meet all applicable eligibility criteria (Section 5) at Visit 1 will continue on their prestudy dose and formulation of metformin between Visits 1 and 3.

Visit 2

Visit 2 should not occur until Visit 1 results are received and initial assessments of eligibility are completed. At Visit 2, screening laboratory results will be reviewed to confirm eligibility. Once

eligibility is confirmed, a dilated fundoscopic examination will be performed between Visits 2 and 3 by an ophthalmologist (or optometrist if allowed per local regulations) to identify and exclude participants with diabetic retinopathy or macular edema requiring treatment. Documentation of a previous examination ≤90 days prior to screening is acceptable to confirm eligibility.

Participants will be provided paper diaries and will start recording SMBG measurements and any hypoglycemic events. Participants will be trained on how to utilize BG meters and how to collect SMBG, including 7-point measurements. Participants will collect at least 3 fasting SMBG measurements per week during the study and two 7-point SMBGs on 2 nonconsecutive days within 2 weeks of each visit specified in the SoA. A 7-point SMBG consists of measurements before and 2 hours after each of 3 main meals within the same day and at bedtime. BG meters and supplies will be provided to measure SMBG.

Period II – dose escalation

Visit 3 – randomization

At Visit 3, participants who meet all applicable eligibility criteria will perform all required study procedures prior to randomization (Section 1.3).

Following randomization, participants will be trained by site personnel on self-injection of investigational product. Site personnel will observe participant administration of first dose of study intervention. Date and time of first dose of study intervention will be recorded on the CRF.

At this visit participants will receive diabetes and lifestyle management counseling according to Section 5.3.

Beginning at randomization, all participants will receive study intervention according to their randomization arm (either tirzepatide or placebo) for the duration of the 24-week escalation period, as specified in Section 6.1.

Period III – high dose treatment

Visit 9 – second randomization

Participants randomly assigned to tirzepatide at Visit 3 who have not discontinued study intervention will be randomly reassigned to a tirzepatide maintenance dose (15 mg, 20 mg, or 25 mg). From Visit 9, these participants will receive study intervention according to their randomization arm for the duration of the 20-week high dose treatment period, as specified in Section 6.1.

Participants randomly assigned to placebo at Visit 3 will undergo a mock re-randomization at Visit 9 and will continue to receive placebo for the duration of Period III (until Week 44).

Participants who have permanently discontinued study intervention prior to this visit will not be re-randomized and will continue in the study for the duration of Period III (until Week 44).

Visit 14 - primary endpoint

Participants randomly assigned to placebo at Visit 3 will not have study intervention assigned by IWRS and will complete the treatment period at this visit. These participants will complete all Visit 14 procedures and proceed to the posttreatment follow-up visit at Week 48.

Participants who discontinued study intervention prior to Visit 9 (second randomization**)** will complete the treatment period at this visit. These participants will complete all Visit 14 procedures and proceed to the posttreatment follow-up visit at Week 48.

All other participants randomized to tirzepatide will complete Visit 14 procedures and continue in the study for the duration of the 36-week extension phase.

Period IV – extension phase

All participants randomly assigned to a tirzepatide maintenance dose at Visit 9 (second randomization) will complete all visits in the extension phase according to the SoA and complete the posttreatment follow-up visit at Week 84.

Early discontinuation

Participants unable or unwilling to continue the study for the duration of the treatment period for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as an ED visit. Procedures should be completed according to the SoA.

Posttreatment follow-up - Visit 801

A posttreatment follow-up visit will occur approximately 4 weeks following the last treatment period visit or final treatment visit. All participants are required to complete a posttreatment follow-up visit.

4.2. Scientific Rationale for Study Design

Primary endpoint

The primary efficacy measure, mean percent change in body weight, is an accepted Phase 2 endpoint for investigational interventions being developed for weight management (FDA 2007).

The primary objective will be evaluated at 44 weeks because this period is considered adequate for evaluation of the efficacy, safety, and tolerability of tirzepatide compared to placebo.

Blinding and control treatment

The double-blind design minimizes bias on safety and efficacy assessments and allows a more robust comparison among tirzepatide and placebo.

Currently, there is no data available for tirzepatide treatment at doses higher than 15 mg in comparison with placebo. Inclusion of a placebo-control treatment will allow for a direct assessment of whether any observed effects are treatment-related or simply reflect the study conditions. A placebo comparator was selected for this study in accordance with regulatory guidance (FDA 2007; EMA 2016). In addition, all participants, regardless of treatment assignment, will receive lifestyle management counseling and diabetes education consistent with current guidelines for weight management (Jensen et al. 2014) and T2D management (ADA 2023). Specifically, participants will consult with a dietician, or equivalent qualified delegate, to establish healthy diet and physical activity goals and the importance of adherence to the lifestyle component of the study will be reinforced at each visit by site staff.

In addition, assessment of safety and tolerability of tirzepatide 20 mg and 25 mg versus tirzepatide 15 mg enables robust benefit risk characterizations of higher doses of tirzepatide in participants with T2D and obesity Class II.

Concomitant therapy

Metformin was chosen as the required concomitant antihyperglycemic medication because it is commonly used in clinical practice as first-line therapy for T2D and when used in combination, the risk of hypoglycemia is low. The minimum dose (at least 1500 mg/day) was chosen to ensure maximizing efficacy of metformin prior to adding additional therapy (Nathan et al. 2009). To minimize the potential confounding effect of changes to concomitant metformin, participants will be expected to maintain metformin throughout the treatment period until the last dose of randomized treatment, other than for the situations described in Section 6.1.2.

Study duration

The planned study duration including extension to 80 weeks allows for 52 weeks of treatment at the highest dose achieved following dose escalation and is considered adequate to assess the full effects of each maintenance dose of tirzepatide. The 80-week treatment period should be sufficient to capture the maximal or near-maximal weight loss effects of tirzepatide.

Collection of race and ethnicity data

In this study, collection of demographic information includes race and ethnicity (where permissible). The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

4.3. Justification for Dose

Tirzepatide doses of 15 mg, 20 mg, and 25 mg administered SC QW will be evaluated in this study. These doses were selected based on the following criteria:

- Efficacy, safety, and tolerability of tirzepatide up to doses of 15 mg in participants with T2D have been well established based on the SURPASS Phase 3 submission program that supported the approval of tirzepatide in T2D
- The 15 mg dose of tirzepatide has also demonstrated robust weight reduction in the SURMOUNT-1 program in people who are overweight or living with obesity (Jastreboff et al. 2022)
- Exposure response modeling of data-to-date estimates that tirzepatide doses of 20 mg and 25 mg may provide additional weight reduction benefits in participants who are living with obesity and T2D.

In summary, we expect the doses being investigated in this study to enable a robust dose-exposure response analysis of multiple safety and efficacy measures to support further clinical development of tirzepatide.

The 15 mg dose will be attained in the same manner as with completed Phase 3 trials of tirzepatide completed to date with a starting dose of 2.5 mg QW for 4 weeks, followed by dose escalation of 2.5 mg increments every 4 weeks to attain a dose of 15 mg. Doses of 20 mg and 25 mg will be attained by following 5 mg dose increments every 4 weeks after the 15 mg dose is

attained. The dose escalation scheme is designed to minimize the development of intolerable GI symptoms.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit or last scheduled procedure shown in the SoA (Section 1.3) for the last active participant.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

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 applies:

Age

1. Participant must be 18 to 75 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Have a BMI ≥35 kg/m^2 at Visit 1.
3. Have had stable body weight (±5%) during the 90 days preceding Visit 1.
4. Have been diagnosed with T2D based on the World Health Organization classification or other locally applicable diagnostic standards.
5. Have an HbA1c of ≥7% (≥53 mmol/mol) and ≤10% (≤86 mmol/mol) as determined by the central laboratory at Visit 1.
6. Have been on a stable treatment of metformin only at least 90 days preceding Visit 1 and between Visits 1 and 3 with the minimum effective dose of ≥1500 mg/day.

Contraceptive and barrier requirements

7. Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   - Male and female participants: For the contraception requirements of this protocol, see Section 10.4, Appendix 4.

Informed consent

8. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusion criteria

9. Are reliable and willing to make themselves available for the duration of the study, attend required study visits, and are willing and able to follow study procedures as required.

5.2. Exclusion Criteria

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

Medical conditions

Diabetes-related

10. Have T1D, history of ketoacidosis or hyperosmolar state/coma, or any other types of diabetes except T2D

11. Have had 1 or more episode of severe hypoglycemia and/or 1 or more episode of hypoglycemia unawareness within the 6 months prior to Visit 1
12. Have at least 2 confirmed fasting SMBG values >255 mg/dL (14.2 mmol/L) (on 2 nonconsecutive days) between Visit 1 to Visit 3
13. Are currently receiving or planning to receive treatment for diabetic retinopathy and/or macular edema (for example, laser photocoagulation or intravitreal injections of anti–vascular endothelial growth factor inhibitors)
    Note: A dilated fundoscopic examination performed by an ophthalmologist (or optometrist if allowed per local regulations) between Visits 2 and 3, or a previous examination ≤90 days of Visit 1 meeting study requirements, is required to confirm eligibility.

Obesity-related

14. Have a prior or planned surgical treatment for obesity
    Exception: liposuction or abdominoplasty if performed >1 year prior to screening
15. Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months prior to screening, including:
    - mucosal ablation
    - lap band
    - gastric artery embolization
    - intragastric balloon
    - duodenal-jejunal endoluminal liner
16. Have obesity induced by other endocrinologic disorders (for example Cushing syndrome) or diagnosed monogenetic or syndromic forms of obesity, for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome

CV related

17. Have any of the following CV conditions within 2 months prior to screening
    - acute myocardial infarction
    - cerebrovascular accident (stroke)
    - unstable angina
    - hospitalization due to congestive heart failure, or
    - coronary artery revascularization
18. Have uncontrolled hypertension at Visit 3
    - systolic blood pressure ≥160 mmHg, or
    - diastolic blood pressure ≥ 100 mmHg)
19. Have elevated resting pulse rate (>100 bpm) at Visit 3
20. Have NYHA Functional Classification class IV congestive heart failure

Other medical

21. Have renal impairment measured as eGFR <45 mL/min/1.73 m^2 (or lower than the country-specific threshold for discontinuing metformin therapy per local label), calculated by CKD-EPI creatinine-cystatin C equation as determined by central laboratory during screening
22. Have a known clinically significant gastric emptying abnormality such as severe gastroparesis or gastric outlet obstruction or chronically take drugs that directly affect GI motility
23. Have a history of chronic or acute pancreatitis
24. Have a TSH outside of 0.4 to 6.0 mIU/L at the screening visit
    Note: Participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 3 months and their TSH at screening falls within the range indicated above.
    Note: Participants with a history of subclinical hypothyroidism but a TSH at screening within the range indicated above, may be included if, in the investigator's opinion, the participant is unlikely to require initiation of thyroid hormone replacement during the course of the study.
25. Have a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder within the last 2 years prior to Visit 1 in the opinion of the investigator. Examples include schizophrenia, bipolar disorder, or other serious mood or anxiety disorder.
26. Have any lifetime history of a suicide attempt.
27. Are, in the judgment of the investigator, actively suicidal, and therefore deemed to be at significant risk for suicide.
28. Have a PHQ-9 score of 15 or more on or before Visit 3.
29. Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS **and** the ideation occurred within the past month
    OR
    have answered "yes" to any of the suicide-related behaviors on the "Suicidal Behavior" portion of the C-SSRS **and** the behavior occurred within the past month.
30. Have acute or chronic hepatitis, or clinical signs or symptoms of any liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the central laboratory at screening
    - ALT or AST levels >3 times the upper limit of the reference range,
    - ALP level >1.5 times the upper limit of the reference range, or
    - TBL ≥1.2 times the upper limit of the reference range, except for participants previously diagnosed with Gilbert's syndrome.

    People with nonalcoholic fatty liver disease/non-alcoholic steatohepatitis are eligible for participation if, at screening, their ALT and AST levels are ≤3 times the upper limit of the reference range, and TBL is <1.2 times the upper limit of the reference range.
31. Have a serum calcitonin level (at Visit 1) ≥35 pg/mL, as determined by central laboratory.

32. Have a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia (MEN) syndrome Type 2.
33. Have a presence or history of malignant neoplasms within the past 5 years prior to Visit 1.
    Exceptions:
    basal or squamous cell skin cancer,
    Stage 0 non-invasive carcinoma of the cervix, or
    in situ or Grade 1 (for example, Gleason 6 or lower) prostate cancer.
34. 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
35. Have had a transplanted organ or awaiting an organ transplant
    Exception: corneal transplants (keratoplasty) allowed
36. Have any hematological condition that may interfere with HbA1c measurement, such as hemolytic anemias or sickle cell disease.
37. Are women who are pregnant, planning to become pregnant or breastfeeding.
38. Have a history of hypersensitivity or any contraindication to tirzepatide, GLP-1 RAs, or any related compound.
39. Have a history of intolerability to tirzepatide, GLP-1 RAs or any related compound.

Prior/concomitant therapy

40. Are receiving or have received within 3 months prior to screening chronic (>14 days) systemic glucocorticoid therapy or have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids during the course of the study

    Exception: topical, intraocular, intranasal, interphalangeal, or inhaled preparations.

41. Have a current or history of (within 6 months prior to screening) treatment with medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotics, and mood stabilizers
    Examples:
    - imipramine
    - mirtazapine
    - phenelzine
    - thioridazine
    - olanzapine
    - lithium
    - amitriptyline
    - paroxetine
    - chlorpromazine
    - clozapine
    - valproic acid (and its derivatives)

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

42. Use products intended for weight loss including prescription drugs, over the counter (OTC) drugs, and herbal preparations, within 3 months prior to screening.

Examples include, but are not limited to:

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

43. Have been treated with any antihyperglycemic medication (other than metformin) within the 3 months prior to Visit 1 or between Visits 1 and 3. An exception is for short-term use (<14 days) of insulin for acute conditions such as acute illness, hospitalization, or elective surgery
44. Have started implantable or injectable contraceptives (such as Depo Provera®, Nexplanon®) within 18 months prior to screening

Prior/concurrent clinical study experience

45. Are currently enrolled in any other clinical study involving an investigational medicinal product or any other type of medical research judged not to be scientifically or medically compatible with this study
46. Have participated in a clinical study involving an investigational medicinal product within the last 30 days. If the previous intervention is scientifically or medically incompatible with this study and has a long half-life, then 3 months or 5 half-lives, whichever is longer, should have passed before screening.
    Exception: Participation in observational studies may be permitted upon review of the observational study protocol and approval by the sponsor.
47. Have previously completed or withdrawn from this study or any other study investigating tirzepatide after receiving at least 1 dose.

Other exclusion criteria

48. Are investigator site personnel directly affiliated with this study and/or their immediate family. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
49. Are Lilly employees or employees of third-party organizations involved with the study.

5.3. Lifestyle Considerations

Diabetes and lifestyle management counseling

Per the SoA (Section 1.3), participants will have access to personnel who have experience in providing diabetes and lifestyle management counseling at baseline and throughout the study duration, according to local standards.

Diabetes education will be performed by personnel who are qualified to educate participants on symptoms and management of hyperglycemia and hypoglycemia, SMBG, self-injection and diabetes management. SMBG training will be provided at Visit 2 and all other training at Visit 3

according to American Diabetes Association Standards of Medical Care in Diabetes or local standards. Additional trainings may be provided during the study as needed.

At Visit 3 participants will be advised to increase their current physical activity levels. Recommendation should consider current activity level and any chronic condition that can affect mobility. The objective is to increase amount and intensity of physical activity over time to achieve 150 minutes or more of moderate to vigorous intensity aerobic activity per week, spread over at least 3 days a week, with no more than 2 consecutive days without activity (ADA 2023) or other local recommendation.

Diet and exercise goals established during the lifestyle consultation and the importance of adherence to the lifestyle component of the study will be reviewed by study staff at every visit during the study.

Blood product donation

Study participants should be instructed not to donate blood or blood products during the study.

5.3.1. Meals and Dietary Restrictions

At Visit 3 and subsequent visits study participants will receive dietary counseling by a dietician, or equivalent qualified delegate, according to local standard. Dietary counseling will consist of advice on healthy food choices and focus on calorie restriction using a hypocaloric diet with an energy deficit of approximately 500 kcal/day compared to the participant's estimated total energy expenditure. To encourage adherence, study staff may use tools like diet logs and fitness trackers to be reviewed during each visit.

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

Total energy expenditure (TEE) is calculated by multiplying the estimated BMR (see table below) with a Physical Activity Level value of 1.3 (FAO/WHO/UNU 2004), which reflects an inactive lifestyle. This calculation provides a conservative estimate of caloric requirements:

TEE (kcal/day) = BMR X 1.3

Equations for estimating BMR in kcal/day[a] **Sex**	**Age**	**BMR (kcal/day)**
Men	18 to 30 years	15.057 X actual weight in kg + 692.2
	31 to 60 years	11.472 X actual weight in kg + 873.1
	>60 years	11.711 X actual weight in kg + 587.7
Women	18 to 30 years	14.818 X actual weight in kg + 486.6
	31 to 60 years	8.126 X actual weight in kg + 845.6

>60 years	9.082 X actual weight in kg + 658.5

Abbreviation: BMR = basal metabolic rate; WHO = World Health Organization.
[a] Revised WHO equations (adapted from: FAO/WHO/UNU 2004).

5.4. Screen Failures

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

Visit 1 labs that do not meet inclusion criteria will be considered a screen failure.

Retests are not allowed, except for cases when results are not available from the original sample.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened only once at the discretion of the investigator. Before rescreening is performed, the participant must sign a new ICF and receive a new identification number.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable to this study. All entry criteria must be met within the specified visit intervals in the SoA (Section 1.3).

See Section 10.10, Appendix 10 for changes in study conduct during exceptional circumstance.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

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

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

This table lists the interventions used in this clinical study.

Intervention Name	Tirzepatide	Placebo	Metformin as background therapy
Dosage Level(s)	2.5 mg 5 mg 7.5 mg 10 mg 12.5 mg 15 mg 20 mg, and 25 mg	Matched	Refer to prescribing information as appropriate
Number of Injections to Achieve Dose Level	Week 0-24: 1 injection Week 24 to end of treatment: 2 injections	Week 0-24: 1 injection Week 24 to end of treatment: 2 injections	Not applicable
Route of Administration	Subcutaneous using a single-dose pen	Subcutaneous using a single-dose pen	Oral. Refer to prescribing information as appropriate
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU	Authorized and used according to EU authorization

Participants randomly assigned to tirzepatide

For participants randomized to tirzepatide, the starting dose will be 2.5 mg QW with a dose escalation every 4 weeks at 2.5 mg increments until the 15 mg dose is reached. Participants randomized to higher doses of tirzepatide will have additional escalation every 4 weeks at 5 mg increments until the randomized dose of 20 mg or 25 mg is reached.

To achieve the assigned dose, all participants will be required to receive 2 injections per week starting at Week 24.

Participants randomly assigned to placebo

To maintain blinding, participants randomized to the placebo treatment group will also receive study intervention weekly and follow a sham dose escalation schedule every 4 weeks matched with the tirzepatide treatment group. Additionally, starting at Week 24, all participants will be required to receive 2 injections per week to maintain the blind.

Timing of dose administration

Participants should try to administer the SC injections on the same day of the week and similar time of day, but there are no restrictions on the time of day for each weekly dose.

The participant may administer the injection without regard to the timing of meals.

For information on restarting study intervention after missed doses, see Section 6.6.

Anatomical location of injections

Acceptable locations for injection include the abdomen and thigh, as well as upper arm if administered by another person.

Participants should rotate injection sites from 1 injection to the next, even when injecting within the same region.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.1.1. Medical Devices

Tirzepatide will be provided as a drug/device combination product in a prefilled single-dose pen for the administration of study intervention. A new single-dose pen will be used for each injection.

Medical devices for tirzepatide used in this study are manufactured by the sponsor or manufactured for the sponsor by a third-party.

Instructions for the medical device use for tirzepatide are provided in the Instructions for Use.

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

6.1.2. Background Therapy with Metformin

Participants in this study must be treated with metformin for at least 3 months prior to Visit 1 and between Visits 1 to 3; the minimum required dose during this time will be 1500 mg/day. The prescreening dose and formulation (short-acting or long-acting) should be maintained during the screening and lead-in periods, through randomization at Visit 3.

After randomization, discontinuation of metformin or change in dosage and formulation is not permitted, except in the following situations:

1. In the event of a hypoglycemic episode(s) (clinical symptoms of hypoglycemia and/or BG-confirmed symptomatic hypoglycemia: glucose concentration <3.0 mmol/L [54 mg/dL]): Participants may reduce/discontinue the dose of metformin.
2. In certain situations that require short-term discontinuation in line with the product(s) labeling for each respective country (for example: severe dehydration, elective surgery, or need for radiologic examination involving IV iodinated contrast dye). Once the situation that led to temporary discontinuation of the intervention is resolved, treatment should be restarted at investigator discretion.
3. If a participant develops contraindications to metformin such that the use of the drug is contraindicated according to the country-specific label.
4. If participant meets the criteria for severe, persistent hyperglycemia (Section 6.9.2) or discontinues study intervention, then metformin dose may be increased according to country-specific label.

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

Dose reduction/discontinuation of metformin during the study should be properly documented and recorded on the appropriate CRF.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention.

Only authorized study personnel may supply, prepare, or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy manual.

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

Participant responsibilities

Study participants will be trained on the proper storage and handling of the study intervention and should follow in-use storage conditions according to the Instructions for Use provided by the sponsor.

6.3. Assignment to Study Intervention

This is a double-blind, randomized, controlled study.

Randomization and stratification

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

Participants will be randomly assigned in a 6:1 ratio to tirzepatide or placebo at Week 0.

At Week 24, participants on tirzepatide will undergo a second randomization in a 1:1:1 ratio to receive tirzepatide 15 mg, or 20 mg, or 25 mg.

Participants will be stratified based on

- at Week 0:
  - Country of enrollment, and
  - Sex (F/M)
- at Week 24:
  - Country of enrollment
  - Sex (F/M), and
  - Occurrence of GI AE (that is, nausea, vomiting, or diarrhea) from baseline (Week 0) to Week 24 (Yes/No)

6.4. Blinding, Masking

This is a double-blind study in which participants and study personnel are blinded to study intervention through the primary endpoint at Week 44. Participants assigned placebo will complete the treatment period at Week 44 and proceed to the posttreatment follow-up visit at Week 48. Participants and study personnel will remain blinded only to tirzepatide dose during the extension phase from Week 44 to Week 80. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant.

If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. 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 study intervention. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician for the participant to continue in the study.

6.5. Study Intervention Compliance

Participant compliance with study intervention will be assessed at visits summarized in the SoA.

The investigator site personnel will review the amount of unused study intervention returned in addition to injection information provided by the participant. Study intervention compliance will be recorded on the CRF for each visit interval after randomization when study intervention is dispensed.

If a participant is considered poorly compliant with their study procedures, for example, missed visits or specific diagnostic tests, they will be retrained as needed by designated study personnel.

6.6. Dose Modification

No adjustment in doses will be allowed unless for safety reasons. Dose de-escalation is not permitted. Details about dose administration of study intervention are described in Section 6.1.

6.6.1. Management of Participants with GI Symptoms

The dose escalation scheme is designed to minimize the development of intolerable GI symptoms. Every effort should be made by the investigator to escalate participants to the assigned maintenance dose.

This table describes steps the investigator should follow to mitigate GI symptoms and manage participants with intolerable GI AEs during the escalation period through Week 32.

STEP 1	Advise participants to eat smaller meals, for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full.
STEP 2	Continue STEP 1 + Prescribe symptomatic medication, for example, anti-emetic or antidiarrheal medication, per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the CRF.
STEP 3	Continue STEP 1 + STEP 2 + Temporarily interrupt tirzepatide; omit 1 dose, the participant will take 3 of 4 doses at that dose level. After the interruption, the investigator should restart the dose as required, with the participant taking medication to alleviate their GI symptoms. A maximum of 1 dose may be omitted at each escalation step every 4 weeks. The data related to temporary interruption of study treatment should be documented in source documents and in the CRF.
STEP 4	If intolerable GI symptoms or events persist despite the above measures, the investigator may decide to discontinue study intervention. De-escalation of study intervention will not be allowed.

Abbreviations: CRF = case report form; GI = gastrointestinal.

In the event of intolerable persistent GI symptoms that occur after the escalation period (after Week 32), the investigator can advise on behavioral changes and consider prescribing symptomatic medication to keep the participant on study treatment before stopping the study intervention permanently.

6.6.2. Temporary Interruption of Study Intervention

In certain situations, the investigator may need to temporarily interrupt study intervention, for example, if the participant experiences an acute illness, has surgery, or requires hospitalization.

Guidance when temporary interruption of study intervention occurs

Every effort should be made by the investigator to maintain participants on tirzepatide and to restart after any temporary interruption, as soon as it is safe to do so.

If study intervention interruption is…	then…
2 consecutive doses or less	participant resumes study intervention at the same dose, as per dosing schedule.
3 consecutive doses or more	participant restarts study intervention (at 5 mg, managed by IWRS) and repeats dose escalation scheme.
due to an AE	the event is to be documented and followed according to the procedures in Section 8.3 of this protocol.
due to intolerable persistent GI AE	participants should be treated as suggested in Section 6.6.1.

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

6.7. Continued Access to Study Intervention After the End of the Study

The sponsor will not provide participants with any ongoing supplies or study intervention after they have completed the study treatment period or permanently discontinued the study intervention.

6.8. Treatment of Overdose

Tirzepatide overdose is defined as administration of any amount of tirzepatide over the intended dose in less than 72 hours.

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

- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.

- Closely monitor the participant for any AE or SAE and laboratory abnormalities as medically appropriate.
- Initiate appropriate supportive treatment according to the participant's clinical signs and symptoms.

6.9. Prior and Concomitant Therapy

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

Allowed concomitant therapy

Participants are allowed to use concomitant medications that they require during the study, except certain medications (for example, other medications for diabetes or weight management, see below) that may interfere with the assessment of efficacy and safety characteristics of the study intervention.

Prohibited surgical treatments, procedures, or medications for weight management

- Any planned elective major surgery during the study should be discussed with the sponsor.
- Prohibited bariatric surgical treatments include gastric bypass or sleeve gastrectomy.
- Prohibited procedures for weight management include liposuction, abdominoplasty, or cryolipolysis.
- Endoscopic or device-based therapy for obesity are prohibited. Examples include
    - mucosal ablation
    - lap band
    - gastric artery embolization
    - intragastric balloon, or
    - duodenal-jejunal endoluminal liner.
- Prohibited medications include those intended to promote weight loss or may cause significant weight gain, including prescribed, over-the-counter, or alternative remedies as outlined in Section 5.2.

Prohibited antihyperglycemic medications

Amylin analogues/agonists, GLP-1 RAs and DPP-4 inhibitors are not allowed at any time during the study.

Concomitant therapy data collection

Any concomitant medication or vaccine, including over-the-counter or prescription medicines, vitamins, 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, and
- additional data for a subset of concomitant therapies.

Contact the medical monitor if there are any questions regarding concomitant or prior therapy.

6.9.1. Rescue Medicine

Initiation of new antihyperglycemic medication

The introduction of new antihyperglycemic medication is expected during the study only in the following situations:

- As an antihyperglycemic intervention for severe, persistent hyperglycemia ("rescue therapy"), as defined in Section 6.9.2.
- In those participants who require permanent discontinuation of study intervention, but remain in the study (Section 7.1)
- During the posttreatment follow-up period

Amylin analogues/agonists, GLP-1 RAs and DPP-4 inhibitors are not allowed at any time during the study, including the situations described above.

6.9.2. Management of Severe, Persistent Hyperglycemia

Severe, persistent hyperglycemia will be collected during the study to assess the risk of extreme imbalance in glycemic control. Participants who develop severe, persistent hyperglycemia during the treatment period may be candidates for glycemic rescue and should be considered for dose increase in metformin (if applicable) or addition of a new antihyperglycemic medication. The choice of new antihyperglycemic medication (with the exception of amylin analogues/agonists, GLP-1 RAs, or DPP-4 inhibitors) or amount of dose increase will be at the discretion of the investigator or the participant's usual diabetes care physician, according to local and international guidelines for individualized treatment of participants with T2D. Addition of a sodium-glucose cotransporter-2 inhibitor is recommended first, unless a contraindication is present. The use of rescue therapy must be recorded in the CRF.

Investigators will be trained on the application of criteria for deciding when and how to intervene with participants who do not reach glycemic targets. Participants will collect at least 3 fasting SMBG measurements per week. If any of the fasting BG values within 1 week for 2 consecutive weeks exceed the limits outlined below and no intercurrent cause of the hyperglycemia could be identified (investigators should first confirm that the participant is fully compliant with the assigned therapeutic regimen and that he or she does not have an acute condition causing severe hyperglycemia), rescue medication may be prescribed as an add-on to randomized treatment.

- >255 mg/dL (>14.2 mmol/L) from baseline to Week 8
- >240 mg/dL (>13.3 mmol/L) from Week 8 to Week 16
- >200 mg/dL (>11.1 mmol/L) from Week 16 to end of study, OR
- HbA1c ≥8% (≥64 mmol/mol) by and after Week 24 AND inadequate response to the existing regimen defined as improvement in HbA1c over the last 3 months (for example, Week 12 to Week 24) that is <0.3%.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9, Appendix 1.

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. Participants who discontinue study intervention before Visit 9 (Week 24) will remain in the study and follow procedures until Visit 14 (Week 44). Participants assigned to placebo who discontinue study intervention after Visit 9 (Week 24) will continue procedures for all remaining study visits until Visit 14 (Week 44) and participants assigned to tirzepatide who discontinue study intervention after Visit 9 will continue procedures for all remaining study visits until Visit 17 (Week 80), as shown in the SoA.

A participant should be permanently discontinued from study intervention if:

- the participant becomes pregnant during the study
- BMI ≤19 kg/m^2 is reached at any time during the treatment period
- the participant is diagnosed with T1D
- the participant undergoes bariatric surgery or other weight loss procedure
- the participant requests to discontinue intervention
- the participant develops confirmed pancreatitis
- the participant is diagnosed with medullary thyroid carcinoma, C-cell hyperplasia, or multiple endocrine neoplasia syndrome Type 2
- significant elevation of serum calcitonin (Section 8.3.3.5)
- the participant is diagnosed with an active malignancy or if a previously treated malignancy becomes known after enrollment
- the participant experiences a significant study intervention-related hypersensitivity reaction after administration of study intervention
- any other AE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons
- PHQ-9 score ≥15
    - Participants should be referred to a mental health professional to assist in deciding whether the participant should be discontinued from study intervention. If a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the participant, at the discretion of the investigator (in agreement with the mental health professional), may be continued in the study on randomized therapy.
- In addition, study intervention may be discontinued if participants
    - answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or**

- answered "yes" to any of the suicide-related behaviors on the "Suicidal Behavior" portion of the C-SSRS.

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

7.1.1. Liver Chemistry Stopping Criteria

Interrupting study intervention based on liver test elevations in participants with normal or near normal baseline liver tests

In study participants with normal or near normal baseline liver tests (ALT, AST, ALP <1.5x ULN), the study intervention should be **interrupted** and close hepatic monitoring initiate (see Section 8.2.6) if 1 or more of these conditions occur:

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications	

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

Interrupting study intervention based on elevated liver tests in participants with abnormal baseline liver tests

In study participants with abnormal baseline liver tests (ALT, AST, ALP ≥1.5x ULN), the study intervention should be **interrupted** if 1 or more of these conditions occur:

Elevation	Exception
ALT or AST >4x baseline	
ALT or AST >3x baseline for more than 2 weeks	

ALT or AST >2x baseline and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >2.5x baseline, when the source of increased ALP is the liver	
ALP >2x baseline and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications	

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

Resuming study intervention after elevated liver tests

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

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee, for example, legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

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

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

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3).

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

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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

See Section 3 for specific efficacy endpoints.

The primary efficacy measurement in this study is body weight. Body weight measurements will be collected at specific clinic visits as summarized in the SoA. Methods for measuring body weight are described in Section 10.9, Appendix 9.

8.2. Safety Assessments

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

Adjudicated endpoint reporting is described in Sections 8.3.3.2 and 8.3.3.6.

8.2.1. Physical Examinations

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

- CV system
- respiratory system
- GI system
- neurological system, and
- thyroid examination

Height, weight, and waist circumference will be measured and recorded, per Section 10.9, Appendix 9. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Symptom-directed physical assessments after screening

These assessments are performed based on participant status and standard of care.

8.2.2. Vital Signs

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

Measurement of blood pressure and pulse rate

- Vital sign measurements, measured by pulse, should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing.
- An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of blood pressure measurements.
- Blood pressure should be taken with an automated blood pressure instrument.
- If blood pressure and pulse measurements are taken separately, pulse should be taken prior to blood pressure.

Step 1. The participant should sit quietly for approximately 5 minutes before vital signs measurements are taken.

Step 2. For each parameter, 2 measurements will be taken using the same arm, preferably the nondominant arm.

Step 3. The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and blood pressure needs to be recorded in the CRF.

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.

8.2.3. Electrocardiograms

For each participant, single tracing 12-lead ECGs should be collected according to the SoA (see Section 1.3). Participants should be supine for approximately 5 to 10 minutes before ECG collections and remain supine but awake during the ECG collection.

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

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

8.2.4. Clinical Safety Laboratory Tests

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

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE.

The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

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

8.2.5. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA (Section 1.3).

Serum pregnancy test must be performed at screening only for WOCBP including females with a history of tubal ligation.

A local urine pregnancy test must be performed for WOCBP only, prior to administering study intervention and the result must be available prior to first dose or injection of study intervention.

Additional pregnancy tests, beyond those required per the SoA, should be performed at any time during the study if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation. If the urine pregnancy test is positive or inconclusive at any visit, an additional serum pregnancy test should be collected. If the participant is pregnant, she must be permanently discontinued from study intervention and the study (Sections 7 and 8.3.2).

8.2.6. Hepatic Monitoring

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

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

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

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

What to do if the abnormal condition persists or worsens

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including

- symptoms
- recent illnesses, for example, heart failure, systemic infection, hypotension, or seizures
- recent travel
- history of concomitant medications, including over-the-counter, herbal and dietary supplements, and
- history of alcohol drinking and other substance abuse.

Frequency of monitoring

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.

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

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

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

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

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

What a comprehensive evaluation should include

At a minimum, this evaluation should include

- physical examination and a thorough medical history, as outlined above
- tests for
  - PT-INR
  - viral hepatitis A, B, C, or E, and
  - autoimmune hepatitis, and
- an abdominal imaging study, for example, ultrasound or computed tomography scan.

Based on the participant's history and initial results, further testing should be considered in consultation with the medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and
- blood phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

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

Collect additional hepatic safety data in the hepatic safety CRFs if a participant

- develops a hepatic event considered to be an SAE
- discontinues study intervention due to a hepatic event, or
- has changes in laboratory results described in this table.

If a participant with baseline results of...	develops the following elevations…	Then…
ALT <1.5x ULN	ALT to ≥5x ULN on 2 or more consecutive blood tests	Collect additional hepatic safety data in the hepatic safety CRF.
ALT ≥1.5x ULN	ALT ≥3x baseline on 2 or more consecutive blood tests	
TBL <1.5x ULN	TBL ≥2x ULN, except for participants with Gilbert's syndrome	
TBL ≥1.5x ULN	TBL ≥2x baseline	
ALP <1.5x ULN	ALP ≥2x ULN on 2 or more consecutive blood tests	
ALP ≥1.5x ULN	ALP to ≥2x baseline on 2 or more consecutive blood tests	

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

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

See Section 10.6, Appendix 6 for hepatic laboratory tests.

8.2.7. Suicidal Ideation and Behavior Risk Monitoring

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

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

Baseline assessment of SIB/intervention emergent SIB will be monitored during the study using C-SSRS and PHQ-9.

Columbia-Suicide-Severity Rating Scale (C-SSRS)

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

Patient Health Questionnaire-9 (PHQ-9)

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

Timing of collection and AE monitoring

Nonleading AE collection should occur prior to the collection of the C-SSRS and PHQ-9.

If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form. However, if an AE elicited through the C-SSRS or PHQ-9 is serious or leads to discontinuation, it needs to be included on the AE form. For SAEs, the process for reporting SAEs is followed.

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

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

- AEs
- SAEs, and
- PCs

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest as defined in Section 8.3.3. will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.3, Appendix 3.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the ICF	The safety follow-up visit OR participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hr of awareness	SAE CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hr of awareness	SAE CRF	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	4 months after the last injection for female partners of male participants and 2 months after the last injection for female participants	Within 24 hr (see Section 8.3.2)	Pregnancy paper form	Pregnancy 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 hr of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

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

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

After learning of a pregnancy in the female partner of a study participant, the investigator will

- obtain a consent to release information from the pregnant female partner directly, and
- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

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

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Events of Special Interest and Other Safety Topics

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

If these events are reported, investigators may be prompted to collect additional data about the event.

8.3.3.1. Hypoglycemia

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia in the study according to the SoA (Section 1.3). Site personnel will enter this information into the CRF at each visit.

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

Hypoglycemia classification and definitions

Level 1

Glucose <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L)

Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

Level 2

Glucose <54 mg/dL (<3.0 mmol/L)

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

Level 3 Severe

A severe hypoglycemic event is characterized by altered mental or physical status requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions for the treatment of hypoglycemia.

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

Examples of severe hypoglycemia in adults are

- altered mental status and the inability to assist in their own care
- semiconscious or unconscious, or
- coma with or without seizures.

Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

Nocturnal hypoglycemia

Nocturnal hypoglycemia is a hypoglycemia event, including severe hypoglycemia, which **occurs at night** and presumably during sleep.

Reporting of severe hypoglycemic events

If a hypoglycemic event meets the criteria of severe, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

The investigator should also determine if repeated or prolonged episodes of hypoglycemia occurred prior to the severe event.

8.3.3.2. Acute Pancreatitis (Adjudicated)

Diagnosis of acute pancreatitis

The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks et al. 2006; Koizumi et al. 2006)

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

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase
- perform imaging studies, such as abdominal computed tomography scan with or without contrast, or abdominal MRI, and
- evaluate for possible causes of acute pancreatitis including
    - alcohol use
    - gallstone or gall bladder disease
    - hypertriglyceridemia, and
    - concomitant medications.

Case adjudication and reporting

An independent CEC will adjudicate all suspected cases of acute pancreatitis (see Section 10.1.5.1). 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.

If typical signs or symptoms of pancreatitis are present and confirmed by laboratory values of total or pancreatic amylase, and imaging studies, report the event as an AE.

If the event meets SAE criteria (see Section 10.3.2) report it as an SAE.

The investigator is responsible for determining the seriousness and relatedness of the event to study intervention.

See Section 10.3 for further information on AE and SAE definitions and reporting.

Asymptomatic elevation of serum amylase and/or lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic participants (Nauck 2016; Steinberg et al. 2017a, 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes (lipase and/or p-amylase ≥3x ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition. 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.

8.3.3.3. Severe GI 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 CRF. See Section 6.6.1 for detailed information concerning the management of GI AEs.

8.3.3.4. Biliary Disorders and Hepatic Events

All events of treatment-emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. Biliary disorders will include acute cholecystitis and acute cholelithiasis.

Hepatic events will include drug-induced liver injury. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 10.6, Appendix 6.

8.3.3.5. Thyroid Malignancies and C-Cell Hyperplasia

The assessment of thyroid safety during the study will include reporting of any case of thyroid malignancy including medullary thyroid carcinoma, papillary carcinoma, and measurements of calcitonin. These data will be captured in specific CRFs.

The purpose of calcitonin measurements is to assess the potential of study intervention to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Definition of significant increase in calcitonin measurements in participants with eGFR ≥60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR ≥60 mL/min/1.73 m^2 is defined as a calcitonin value of

≥35 pg/mL AND ≥50% over the screening value.

If a participant's labs meet these criteria, these clinically significant labs should be recorded as an AE.

Definition of significant increase in calcitonin measurement in participants with eGFR <60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR <60 mL/min/1.73 m^2 is defined as a calcitonin value of

≥50 pg/mL AND ≥50% over the screening value.

If a participant's labs meet these criteria, these clinically significant labs should be recorded as an AE.

Guidance when clinically significant laboratory results occur

The investigator should first confirm the value as soon as possible, and if confirmed, temporarily interrupt study intervention and recommend that the participant immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist to exclude any SAE on the thyroid.

When the possibility of thyroid diseases such as C-cell hyperplasia, medullary thyroid carcinoma, and papillary carcinoma is excluded as background of an elevated calcitonin concentration and no further increase in calcitonin concentration occurs, study intervention can be restarted at the discretion of the investigator.

8.3.3.6. Major Adverse CV Events (Adjudicated)

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

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

8.3.3.7. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. Examples of systemic hypersensitivity reactions are intervention-related symptomatic bronchospasm, allergy-related edema or angioedema.

If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

A clinically significant systemic hypersensitivity reaction is one that occurs after administration of the study intervention and includes any of the following:

- does not respond to symptomatic medication

- results in clinical sequelae
- requires parenteral medication, or
- is an anaphylactic reaction.

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

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

8.3.3.8. Injection Site Reactions

Symptoms and signs of a local injection site reaction may include erythema, induration, pain, pruritus, and edema.

If an injection site reaction is reported by a participant or site staff, the injection site reaction CRF will be used to capture additional information about this reaction. At the time of injection site reaction occurrence, samples will be collected for measurement of tirzepatide ADAs and tirzepatide concentration.

8.3.3.9. Antidrug Antibodies

The occurrence of ADA formation will be assessed as outlined in Section 8.8.

8.3.3.10. Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent arrhythmias and cardiac conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG, which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 10.3 must be reported as SAEs.

8.3.3.11. Acute Renal Events

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

8.3.3.12. Depression, Suicidal Ideation and Behavior Risk 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 Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS

    or

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

    or

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

8.3.3.13. Diabetic Retinopathy Complications

A dilated retinal fundoscopic examination will be performed for all participants by a qualified eye care professional (ophthalmologist or optometrist) between Visits 2 and 3 or at a previous examination ≤90 days of screening meeting study requirements to confirm eligibility. Participants currently receiving or planning to receive treatment for diabetic retinopathy and/or macular edema (e.g., laser photocoagulation or intravitreal injections of anti– vascular endothelial growth factor [VEGF] inhibitors) will be excluded. The results from this examination will be recorded on a specific retinopathy CRF as a baseline measure of retinopathy. An adequate examination performed ≤90 days prior to screening can replace the study examination; results should be similarly recorded.

Additional dilated fundoscopic examination should be performed when clinically indicated by any AE suspected of worsening retinopathy, and the findings should be recorded on the retinopathy CRF.

A follow-up dilated fundoscopic examination will occur for all randomized participants at Visit 14 (Week 44) and Visit 17 (Week 80).

8.4. Pharmacokinetics

Blood samples for PK analyses will be collected from all randomized participants at the specified visits in accordance with SoA.

Each participant will be assigned via IWRS to one of the sampling PK time windows of 1 to 24 hours, 24 to 96 hours, or 120 to 168 hours post-dose at Weeks 27 and 31 of study intervention treatment per the study schedule or at ED (see Section 1.3).

Efforts should be taken to align clinical visits with PK sampling windows specified in the PK schedule of events (Section 1.3). Otherwise, participants may need to return to the clinical site for additional PK-specific visits to provide PK samples. Only samples from participants assigned to treatment with tirzepatide will be analyzed for drug concentration.

Date and time of each sample and the most recent tirzepatide dose prior to PK blood draw must be recorded.

Drug concentration information that would unblind the study will not be reported to study sites or blinded personnel while the study is blinded.

Sample retention is described in Section 10.1.12.

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry method. Samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, and/or bioanalytical method cross-validation.

8.5. Pharmacodynamics

Samples to assess the PD properties of tirzepatide are included in the efficacy measures listed in Section 8.1 and will be collected in accordance with the SoA.

8.6. Genetics

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

See Section 10.5, Appendix 5 for information regarding genetic research and Section 10.1.12 for details about sample retention and custody.

8.7. Biomarkers

Plasma and serum samples will be used for exploratory biomarker research, where local regulations allow.

See Section 3 for prespecified biomarkers. See clinical laboratory tests in Section 10.2, Appendix 2 and the SoA for sample collection information.

Samples will be used for

- research on the drug targets
- disease process
- variable response to tirzepatide
- pathways associated with diabetes, obesity, and metabolism
- mechanism of action of tirzepatide, and
- research method or in validating diagnostic tools or assay(s) related to diabetes.

Sample retention is described in Section 10.1.12.

8.8. Immunogenicity Assessments

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

In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional unscheduled samples should be collected as detailed in Section 10.2.1. Instructions for the

collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded. Sample collected at Visit 801 will assess immunogenicity at washout of tirzepatide (5 half-lives post end of treatment).

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

Treatment-emergent ADA are defined in Section 9.3.6.2.

Sample retention is described in Section 10.1.12.

8.9. Health Economics

Health economics parameters are not evaluated in this study

9. Statistical Considerations

The SAP will be finalized prior to unblinding for the primary analysis, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including the primary and key secondary endpoints.

9.1. Statistical Hypotheses

The primary objective is to demonstrate that tirzepatide is superior to placebo in percent change from baseline in body weight at Week 44. Thus, the null hypothesis to be tested in relation to the primary estimand is as follows:

Null hypothesis: Tirzepatide (pooled 15 mg, 20 mg, and 25 mg) is not different from placebo with respect to percent change from baseline in body weight at Week 44.

The null hypotheses corresponding to the secondary estimands are as follows:

1. Tirzepatide (pooled 15 mg, 20 mg, and 25 mg) is not different from placebo with respect to the change from baseline in HbA1c at Week 44
2. Tirzepatide 25 mg is not different from tirzepatide 15 mg with respect to percent change from Week 24 in body weight at Week 80
3. Tirzepatide 20 mg is not different from tirzepatide 15 mg with respect to percent change from Week 24 in body weight at Week 80

9.1.1. Multiplicity Adjustment

A closed testing procedure that controls the family wise error rate in the strong sense at the overall 2-sided 5% level will be applied. The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints will be carried out in the hierarchical order as indicated in Section 9.1. This means that the statistical hypotheses are tested in the prespecified order at the same significance level of $\alpha = 0.05$ as long as all preceding hypotheses are rejected. Once a hypothesis is not rejected, subsequent hypotheses will not be formally tested. Unless otherwise specified, there will be no adjustment for multiple comparisons for any other analyses outside of the primary and key secondary endpoints.

9.2. Analyses Sets

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

Participant Analysis Set / Population	Description
FAS	All randomized participants who meet the eligibility criteria.
FAS-W24	All participants in tirzepatide treatment group who meet the eligibility criteria that are re-randomized at Week 24.
Safety analysis set	All participants who are exposed to study intervention.

Abbreviation: FAS = full analysis set; W = week.

Unless otherwise noted, the FAS is used to analyze endpoints related to the efficacy objectives comparing to placebo and FAS-W24 is used comparing to tirzepatide 15 mg. The safety analysis set is used to analyze the endpoints and assessments related to safety.

The following data points sets are defined:

Data Points Sets	Description
Treatment regimen estimand data points set	All data points obtained during the treatment period defined as after baseline and up to the last visit within the treatment period, regardless of study intervention discontinuation or initiation of prohibited/rescue medications.
Efficacy estimand data points set	All data points obtained during the treatment period defined as after baseline and up to the earliest date of initiation of prohibited/rescue medications or 7 days after study intervention discontinuation.
Safety data points set	All data points obtained during the intervention period and the follow-up period defined as after baseline and up to the date of study withdrawal including the follow-up period and regardless of study intervention discontinuation or initiation of prohibited/rescue medications.

9.3. Statistical Analyses

9.3.1. General Considerations

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

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the statistical methods described in the protocol will require a protocol amendment only if it changes a principal feature of the protocol. Any other changes to the statistical analyses and the justification for the changes will be documented in the SAP and/or CSR. Some analyses and summaries described in this section may not be conducted if not warranted by data. Additional

secondary analyses of data may be conducted as deemed appropriate without further changes made to the protocol or SAP. Analyses will be fully detailed in the SAP.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the 2-sided 95% confidence interval will be calculated.

Unless otherwise noted, in statistical summaries and analyses, the statistical treatment comparisons will only be performed between

- pooled tirzepatide doses of 15 mg, 20 mg and 25 mg versus placebo from baseline to Week 44, or
- tirzepatide doses of 20 mg and 25 mg versus tirzepatide 15 mg from Week 24 to Week 80.

Unless specified otherwise, treatment effects will be assessed using the FAS (comparing to placebo) or FAS-Week 24 (comparing to tirzepatide 15 mg) population per intended treatment. Baseline will be defined as the last available non-missing measurement prior to taking the first dose. Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses with placebo irrespective of adherence to study intervention or initiation of prohibited/rescue medications. Thus, safety analysis will be conducted using safety analysis set.

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 will include an analysis of covariance (ANCOVA), with terms of treatment and stratification factor of sex, and baseline measurement as a covariate. For measures assessed over time, mixed model for repeated measures (MMRM) with terms for treatment, visit, treatment-by-visit interaction, and stratification factor of sex, and baseline measurement as a covariate will be used for comparisons between treatment groups.

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

9.3.2. Treatment Group Comparability

9.3.2.1. Participant Disposition

A detailed description of participant disposition will be provided.

Frequency counts and percentages of all safety participants will be presented. A listing of randomized participants not receiving study treatment will be provided, if applicable. All participants who discontinue the study intervention and/or study will be identified and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized.

9.3.2.2. Participant Characteristics

Demographics and other baseline characteristics will be summarized by treatment groups for all randomized participants.

9.3.2.3. Concomitant Therapy

Concomitant medications, including prior therapy, will be summarized by treatment groups for the safety analysis set participants during the treatment period.

9.3.2.4. Treatment Compliance

Treatment compliance is defined as taking at least 75% and no more than 125% of required study intervention during the treatment period. Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment groups using the safety analysis set during the treatment period.

9.3.3. Primary Endpoint(s)/Estimand(s) Analysis

The null hypotheses corresponding to the primary objective is specified in Section 9.1.

There will be 2 estimands of interest in comparing efficacy of tirzepatide (pooled 15 mg, 20 mg, and 25 mg) with placebo. No multiplicity adjustment is planned between estimands.

The efficacy analysis will be guided by the "treatment regimen" estimand using the FAS and the treatment regimen estimand data points sets as described in Section 3. The "treatment regimen" estimand, defined as the average treatment effect of tirzepatide 15 mg, 20 mg, and 25 mg doses relative to placebo from baseline at Week 44 in individuals who meet the eligibility criteria, regardless of the adherence to study intervention or initiation of prohibited medications.

Percent change in body weight at Week 44 will be analyzed using an analysis of covariance (ANCOVA) model that includes treatment (tirzepatide vs placebo) and stratification factor of sex, and baseline measurement as a covariate.

Missing data should be minimized for estimating the treatment regimen estimand. If there are occurrences of missing data despite the best precautions, missing data should be imputed in a manner consistent with what the values would likely have been had they been collected. Details regarding the imputation for missing values will be described in the SAP.

Analyses guided by the "efficacy" estimand will be conducted for the primary efficacy analysis. The assessments will be conducted using the FAS and the efficacy estimand data points set (Section 9.2) at Week 44. Mixed model for repeated measures (MMRM) with terms for treatment, visit, treatment-by-visit interaction, and stratification factor of sex, and baseline measurement as a covariate will be used. Additional details of the statistical modeling will be provided in the SAP.

9.3.4. Key Secondary Endpoint(s)/Estimand(s) Analysis

Secondary analyses specified in Section 9.1 will be conducted similarly to the primary analysis using 2 estimands of interest. For the comparisons of tirzepatide 25 mg or 20 mg with 15 mg, the "treatment regimen" estimand is defined as the treatment effect of tirzepatide 25 mg or 20 mg relative to tirzepatide 15 mg from Week 24 at Week 80 in individuals randomized at Week 24, regardless of the adherence to study intervention or initiation of rescue (for glycemic control endpoint) or prohibited (for body weight endpoint) medications.

The "efficacy" estimand is defined as the treatment effect of tirzepatide 25 mg or 20 mg relative to tirzepatide 15 mg from Week 24 at Week 80 in individuals randomized at Week 24 if they would remain on their randomized treatment until Week 80 and would not initiate rescue (for glycemic control endpoint) or prohibited (for body weight endpoint) medications for these 2 comparisons. More details will be provided in the SAP.

9.3.5. Additional Secondary Endpoint(s)/Estimand(s) Analysis

Details of additional secondary analyses will be provided in the SAP.

9.3.6. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of below comparisons irrespective of adherence to study intervention or initiation of prohibited or rescue medications

- pooled tirzepatide doses of 15 mg, 20 mg and 25 mg versus placebo, or
- tirzepatide doses of 20 mg and 25 mg versus tirzepatide 15 mg.

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

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

AEs will be coded from the actual term using the Medical Dictionary for Regulatory Activities and reported with preferred terms and system organ class. Counts and proportions of participants experiencing events will be reported.

The proportion of participants experiencing TEAE, SAE, and discontinuation due to AE will be summarized.

This section 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. The list of AESI and other safety topics in this study is provided in Section 8.3.3. Summaries and analyses for incidence of AESIs will be provided. The details of analysis of AESI will be provided in the SAP.

9.3.6.1. Central Laboratory Measures, Vital Signs, and Electrocardiograms

Actual values and change from baseline to postbaseline values of central laboratory measures, vital signs, and selected ECG parameters will be summarized at each scheduled visit. Change from baseline to postbaseline value will be summarized for participants who have both a baseline and at least 1 postbaseline result.

The percentages of participants with treatment-emergent abnormal, high, or low measures (including laboratory, vital, and ECG parameters) will be summarized.

The analysis details will be provided in the SAP.

9.3.6.2. Evaluation of Immunogenicity

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

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

9.3.7. Other Analyses

Subgroup analyses of the primary endpoint and key secondary endpoints comparisons will be made to assess consistency of the study intervention effect across the following subgroups:

- Age group: < 65 vs ≥ 65 years
- Sex: female vs male
- Race: white vs black vs other
- Ethnicity: Hispanic vs non-Hispanic

If the number of participants is too small within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. Further statistical analysis details will be provided in the SAP.

Analysis of C-SSRS and PHQ-9 Data

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (C-SSRS WWW). Depression-related symptoms will be assessed using PHQ-9. The analysis details will be provided in the SAP.

9.4. Interim Analyses

An interim safety analysis will occur after approximately 60 participants have completed 32 weeks of treatment. The purpose of this analysis will be to monitor the safety and tolerability of the 2 investigational tirzepatide doses. An IAC will be formed to review the interim analyses in an unblinded fashion. Only the IAC and Statistical Analysis Center will be authorized to evaluate unblinded interim data. Study sites will receive information about interim results only if they need to know for the safety of their participants. Additional details will be specified in the SAP.

Additional interim safety/efficacy analyses may be conducted for Lilly's planning purposes. If additional interim analyses are to be conducted the details will be included in the SAP and approved before any unblinding of data.

9.5. Sample Size Determination

A sample size of 350 participants (100 participants per tirzepatide treatment group, 300 in tirzepatide combined, and 50 participants in placebo group) provides more than 95% power to demonstrate superiority of tirzepatide (pooled 15 mg, 20 mg, and 25 mg) to placebo with regards to mean percent change from baseline in body weight at Week 44. The sample size determination assumes that evaluation of superiority of 15 mg, 20 mg, and 25 mg tirzepatide to placebo will be conducted at a 2-sided significance level of 0.05 using a 2-sample t-test. Additionally, a difference of at least 10% mean body weight reduction from baseline at Week 44 for tirzepatide compared with placebo and a common SD of 12% are assumed for statistical power calculations.

Assuming 15% attrition rate by Week 24, the sample size (85 participants randomized to each tirzepatide treatment group at Week 24) also provides roughly 80% power to demonstrate

superiority of 25 mg or 20 mg tirzepatide to 15 mg tirzepatide in mean percent change from Week 24 in body weight at Week 80. The sample size determination assumes each comparison at a 2-sided significance level of 0.05, a difference of at least 3% mean body weight reduction from Week 24 at Week 80 for tirzepatide 20 or 25 mg compared with tirzepatide 15 mg, and a common SD of 7%.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- International Organization for Standardization (ISO) 14155, andapplicable laws and regulations

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

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

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

The investigator will be responsible for the following:

- providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

Participants who are rescreened are required to sign a new ICF and receive a new identification number.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

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

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration, or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws, relevant legislations including the General Data Protection Regulation (GDPR) and the European Clinical Trial Regulation (Articles 56, 57, 58).

10.1.5. Committees Structure

10.1.5.1. Clinical Endpoint Committee

An independent CEC with membership external to the sponsor will be responsible for event adjudication in a blinded fashion. The independent CEC will adjudicate all suspected cases of acute pancreatitis (see Section 8.3.3.2). The CEC charter will contain the final detailed event definitions used for adjudication.

10.1.5.2. Internal Assessment Committee

An IAC will review the interim efficacy and safety data in an unblinded fashion.

The IAC will consist of a limited number of prespecified members not part of the blinded study team who do not have direct site contact or data entry or validation responsibilities. Details about IAC membership, purpose, responsibilities, and operation will be described in an IAC charter, which will be approved prior to the first unblinding.

Participant safety will be continuously monitored by the sponsor's blinded internal safety review team, which includes safety signal detection at any time during the study.

All safety data collected will be summarized and reviewed by the sponsor's internal safety review committee for agreement of next steps.

10.1.6. Dissemination of Clinical Study Data

Reports

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

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

Data

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

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

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

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

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

10.1.7. Data Quality Assurance

Investigator responsibilities

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

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

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

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

Data monitoring and management

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

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

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

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

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

Records retention and audits

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.

Electronic data capture system

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

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

Data storage and access

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

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor’s database system and reports 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 the sponsor will be encoded and stored in the global PC management system.

10.1.8. Source Documents

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

Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

10.1.9. Study and Site Start and Closure

First act of recruitment

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

The first act of recruitment is the first signed ICF.

Study or site termination

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

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

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

For study termination:

- discontinuation of further study intervention development

For site termination:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- total number of participants included earlier than expected.

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

10.1.10. Publication Policy

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

10.1.11. Investigator Information

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

10.1.12. Sample Retention

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

Sample Type	Custodian	Maximum Retention Period after Last Participant Visit[a]
Genetics	Sponsor or designee	7 years
Exploratory biomarker	Sponsor or designee	7 years
Pharmacokinetic	Sponsor or designee	1 year
Tirzepatide antidrug antibodies (ADA)	Sponsor or designee	15 years

[a] Sample retention periods may differ dependent upon local regulations.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the Lilly-designated laboratory or by the local laboratory.

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

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

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

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

Investigators must document their review of the laboratory safety results.

The table below identifies laboratory or analyte results that could unblind the study and will not be reported to investigative sites or other blinded personnel.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - Red Blood Cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - White Blood Cells)	
Differential	
Absolutes Count of:	
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Clinical chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Amylase	
Lipase	
Lipid panel	
High-density lipoprotein (HDL)	Assayed by Lilly-designated laboratory.
Low-density lipoprotein cholesterol (LDL-C)	Calculated by Lilly-designated laboratory. If triglycerides are >400 mg/dL, the direct LDL will be assayed.

Very-Low-density lipoprotein cholesterol (VLDL-C)	Generated by Lilly-designated laboratory.
Cholesterol	
Triglycerides	
Hormones (female)	
Serum pregnancy	Assayed by Lilly-designated laboratory.
Urine pregnancy	Assayed and evaluated locally.
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory.
Urine chemistry	
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI creatinine-cystatin C)	
Urinary albumin/creatinine ratio (UACR)	
Pharmacokinetic samples – LY3298176 concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Additional testing	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
HbA1c	
Cystatin-C	
Calcitonin	-
Pancreatic amylase	-
Lipase	
Thyroid stimulating hormone (TSH)	
Stored samples	
Genetics sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory biomarker storage samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
Plasma (EDTA)	
Plasma (P800)	
Immunogenicity (ADA) samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3298176 antibodies	
Anti-LY3298176 antibodies neutralization	

Abbreviations: ADA = antidrug antibodies; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; EDTA = Ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c.

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

Purpose of collecting samples after a systemic hypersensitivity event

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

When to collect samples after a systemic hypersensitivity event occurs

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

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

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

Abbreviations: IL = interleukin.

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

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

10.3.1. Definition of AE

AE definition

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

Events meeting the AE definition

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

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

Events NOT meeting the AE definition

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

10.3.2. Definition of SAE

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

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

interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

10.3.3. Definition of Product Complaints

Product complaint

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

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

AE, SAE, and PC recording

- When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

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

Assessment of intensity

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

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

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

Assessment of causality

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

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 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 postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via an electronic data collection tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) 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 SAE paper form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting can be found in SAE paper form.

SAE reporting via paper form

- Facsimile transmission of the SAE paper form 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 on the SAE paper form.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

Abbreviation: SERMs = selective estrogen receptor modulators.

10.4.2. Contraception Guidance

10.4.2.1. Females

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

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to treatment exposure. See the protocol SoA for subsequent pregnancy testing requirements.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective. These forms of contraception must be used during the study and after the study for at least 2 months after the last dose of the study intervention.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  o condom with spermicide
	  o diaphragm with spermicide, or
	  o female condom with spermicide

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

10.4.2.2. Males

The table below describes contraception guidance for all men.

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

10.5. Appendix 5: Genetics

Use/analysis of DNA

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

DNA samples may be used for research related to tirzepatide or diabetes, obesity and related diseases. They may also be used to develop tests/assays including diagnostic tests related to tirzepatide and diabetes or obesity and related diseases. 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.

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

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

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

The samples will be retained while research on tirzepatide or diabetes, obesity, and related diseases, continues but no longer than 15 years or other period as per local requirements.

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

Hepatic evaluation testing

See Section 8.2.6 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

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

The local laboratory must be qualified in accordance with applicable local regulations.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatitis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA [a]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA [a]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	HDV IgM antibody
Direct bilirubin	**Hepatitis E virus (HEV) testing:**
Alkaline phosphatase (ALP)	HEV IgG antibody
Alanine aminotransferase (ALT)	HEV IgM antibody
Aspartate aminotransferase (AST)	HEV RNA [a]
Gamma-glutamyl transferase (GGT)	**Anti-nuclear antibody (ANA)**
Creatine kinase (CK)	**Anti-smooth muscle antibody (ASMA)** [b]
Hepatic Coagulation Panel	**Anti-actin antibody** [c]
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgA (quantitative)**
Urine Chemistry	**Immunoglobulin IgG (quantitative)**
Drug screen	**Immunoglobulin IgM (quantitative)**
Haptoglobin	

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA [a]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA [a]
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology Culture:**
Ethyl glucuronide (EtG)	Blood
Epstein-Barr virus (EBV) testing:	Urine
EBV antibody	
EBV DNA [a]	

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

b Not required if anti-actin antibody is tested.

c Not required if anti-smooth muscle antibody (ASMA) is tested.

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

Refer to Section 10.3, Appendix 3 for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.8. Appendix 8: Country-specific Requirements

For sites in EU Member States

Section 1.3.1. Screening (Period I), Dose Escalation (Period II), and High Dose Treatment (Period III)

Study I8F-MC-GPIT	Prescr eening	Period I Screening/ Lead-in		Period II Dose Escalation						Period III High Dose Treatment						Comments
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Prescreening Visit 601 is optional
Weeks from randomization		≤35 days		0	4	8	12	16	20	24	27	28	31	32	44	
Visit interval tolerance (days)					±3	±3	±3	±3	±3	±3		±3		±3	±7	
Fasting visit				X	X	X	X	X	X	X		X		X	X	
Visit detail											PK		PK			PK = visit only for PK sample collection
Laboratory tests and sample collections																
Urine pregnancy (local)				X	X	X	X	X	X	X		X		X	X	The result must be available before the first dose of study intervention for WOCBP. After randomization, monthly pregnancy tests are required for WOCBP and may be performed at clinic visits or at home, as applicable. Perform additional pregnancy tests at any time during the study if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation. If the urine pregnancy test is positive or inconclusive at any visit, an additional serum

Study I8F-MC-GPIT	Prescreening	Period I Screening/ Lead-in		Period II Dose Escalation						Period III High Dose Treatment						Comments
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Prescreening Visit 601 is optional
Weeks from randomization		≤35 days		0	4	8	12	16	20	24	27	28	31	32	44	
Visit interval tolerance (days)					±3	±3	±3	±3	±3	±3		±3		±3	±7	
Fasting visit				X	X	X	X	X	X	X		X		X	X	
Visit detail											PK		PK			PK = visit only for PK sample collection
																pregnancy test should be collected.

Abbreviations: WOCBP = women of childbearing potential.

Section 1.3.2. Extension Phase (Period IV) and Posttreatment Follow-up

Study I8F-MC-GPIT	Period IV Extension Phase (Placebo Group Discontinued)				Posttreatment Follow-up	Comments
Visit number	15	16	17	ED	801	
Weeks from randomization	56	68	80	—	84 (or 48 for certain participants)	All participants assigned placebo or who discontinue study intervention prior to Visit 9 will complete Visit 801 at Week 48
Visit interval tolerance (days)	±7	±7	±7	—	±7	
Fasting visit	X	X	X	X	X	
Laboratory tests and sample collections						
Urine pregnancy (local)	X	X	X	X	X	Monthly pregnancy tests are required for WOCBP and may be performed at clinic visits or at home, as applicable. Perform additional pregnancy tests if there is clinical suspicion of pregnancy, or if required by local law or regulation. If the urine pregnancy test is positive or inconclusive at any

Study I8F-MC-GPIT	Period IV Extension Phase (Placebo Group Discontinued)				Posttreatment Follow-up	Comments
Visit number	15	16	17	ED	801	
Weeks from randomization	56	68	80	—	84 (or 48 for certain participants)	All participants assigned placebo or who discontinue study intervention prior to Visit 9 will complete Visit 801 at Week 48
Visit interval tolerance (days)	±7	±7	±7	—	±7	
Fasting visit	X	X	X	X	X	
						visit, an additional serum pregnancy test should be collected.

Abbreviations: ED = early discontinuation; WOCBP = women of childbearing potential.

For sites outside of EU Member States

Country-specific requirements, if any, will be described in a separate protocol addendum.

10.9. Appendix 9: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and BMI

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEP wise approach to Surveillance Manual.

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. If using a stadiometer or fixed measuring device, move the device's measurement arm gently down onto the top of the participant's head. Record the participant's height in centimeter (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 kilogram.
- 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.
- Participants should be lightly clothed but not wearing shoes while their weight is 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 kilogram (kg) to the nearest one-tenth kg.

Measuring waist circumference

- Use non-stretchy tape

- Waist circumference should be measured at midpoint, between lower margin of last palpable rib and top of iliac crest (approximately 1 inch [2.54 cm] above the navel)
- Participants should be lightly clothed, and
- Measure to the nearest 0.5 cm.

Step 1. Ask the participant to stand with their feet close together, and arms at their side with their body weight evenly distributed.

Step 2. Ask participant to relax.

Step 3. Measurements should be recorded at the end of a normal expiration.

Calculation of BMI

Height and weight measurements will be used to calculate BMI.

- BMI = weight (kg) / [height (m)]^2.

Calculation of BMI with amputation or limb loss

In participants with limb amputation or limb loss, use the formula given in the following link: Amputee Coalition – https://www.amputee-coalition.org/limb-loss-resource-center/resources-filtered/resources-by-topic/healthy-living/about-bmi/.

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

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific 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 and notifications must be retained in the study records.

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

Considerations for making a change

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

Informed consent

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

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

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, concomitant medications, review of study participant diary (including study intervention compliance), review diet and exercise goals, C-SSRS (Since Last Visit Version), 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, collection of blood samples, and health information.

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

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

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

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken:

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

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken prior to Visit 3 are valid for a maximum of 60 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 60 days from Visit 1 to Visit 3: the participant will proceed to the next study visit per the usual SoA, provided that Visit 3 must be conducted within 60 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 screening is paused for more than 60 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 failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at Visit 1 to ensure participant eligibility by Visit 3.

Adjustments to visit windows

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

Primary endpoint visit (Visit 12) should be completed as per original schedule whenever possible and safe to do so. However, the visit windows may be brought forward no sooner than 14 days or extended up to 28 days relative to the target visit date.

For 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, 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 at alternate locations

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

10.11. Appendix 11: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADA	antidrug antibodies
AE	Adverse event
AESI	Adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	Blood glucose
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BMR	basal metabolic rate
C-SSRS	Columbia-Suicide Severity Rating Scale
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CKD-EPI	chronic kidney disease - epidemiology collaboration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.

CSR	clinical study report
CV	cardiovascular
Device deficiencies	Equivalent to product complaint
DPP-4	dipeptidyl peptidase
ECG	Electrocardiogram
EDC	electronic data capture
ED	early discontinuation
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FAS	full analysis set
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
IAC	Internal Assessment Committee
IB	Investigator's Brochure
ICE	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.

informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MRI	magnetic resonance imaging
NYHA	New York Heart Association
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control

PC	product complaint
PHQ-9	Patient Health Questionnaire-9
PK/PD	pharmacokinetics/pharmacodynamics
QW	once weekly
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SIB	suicidal ideation and behavior
SMBG	self-monitoring of blood glucose
SoA	schedule of activities
T1D	Type-1 diabetes
T2D	Type-2 diabetes
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TSH	thyroid stimulating hormone
ULN	upper limit of normal
WOCBP	woman of childbearing potential
WNOCBP	Women not of childbearing potential

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