Protocol(c): I8F-MC-GPHJ

A Phase 3b, Randomized Controlled Study to Evaluate the Efficacy and Safety of Tirzepatide Compared to Semaglutide in Adults Who Have Obesity or Overweight with Weight-Related Comorbidities (SURMOUNT-5)

NCT05822830

Approval Date: 24-Aug-2023

Title Page

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A Phase 3b, Randomized Controlled Study to Evaluate the Efficacy and Safety of Tirzepatide Compared to Semaglutide in Adults Who Have Obesity or Overweight with Weight-Related Comorbidities (SURMOUNT-5)

Protocol Number: I8F-MC-GPHJ

Amendment Number: c

Compound: Tirzepatide (LY3298176)

Brief Title:

Efficacy and Safety of Tirzepatide Compared to Semaglutide in Adults Who Have Obesity or Overweight (SURMOUNT-5)

Study Phase: 3b

Acronym: SURMOUNT-5

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 139721

EU Number: 2022-501106-35-00

Document ID: VV-CLIN-116398

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

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	*20-Jun-2023*
Amendment (a)	*29-Jul-2022*
Original Protocol	*23-Jun-2022*

Amendment [c]

Overall Rationale for the Amendment:

This amendment reflects updates made in the most recent version of the US Semaglutide (Wegovy) package insert. Updates have also been made throughout the protocol to remove the safety-follow-up visit (Visit 801). The safety follow-up visit is no longer required given available safety information from similar duration of exposure to semaglutide or tirzepatide at all doses being studied. Corrections and clarifications have also been added where needed.

Section # and Name	Description of Change	Brief Rationale
Title Page and 1.1 Synopsis	Removed "2.4 mg" from semaglutide dose in protocol title	To reflect the most recent information in the US package insert.
1.1 Synopsis	Updated "Rationale", "Objectives, Endpoints, and Estimands", and "Overall Design" sections to reflect the maximum-tolerated dose of semaglutide (1.7 mg or 2.4 mg)	To reflect the most recent information in the US package insert.
	Updated "Overall Design", "Brief Summary", and "Ethical Considerations of Benefit/Risk" sections to reflect the change in study duration from 78 weeks to 74 weeks and removal of safety follow-up period	The safety follow-up visit (Visit 801) is no longer required.
	Updated "Ethical Considerations of Benefit/Risk" section to reflect change in duration of medical care from 76 weeks to 72 weeks	The safety follow-up visit (Visit 801) is no longer required.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Removed Visit 801	The safety follow-up visit (Visit 801) is no longer required.
	Updated the semaglutide dose to include 1.7 mg as a possible maintenance dose	To reflect the most recent information in the US package insert.
1.3 Schedule of Activities (SoA)	Removed Visit 801	The safety follow-up visit (Visit 801) is no longer required.
	"Site transmits study intervention prescription for central pharmacy study intervention dispensing" row: Added "as needed" to visit detail	Clarification
2.1 Study Rationale	Added information about the maximum-tolerated dose of semaglutide (1.7 mg or 2.4 mg)	To reflect the most recent information in the US package insert.
2.2 Background	Updated information about the semaglutide dose	To reflect the most recent information in the US package insert.
2.3.1 Risk Assessment	Updated 2.4 mg semaglutide to 1.7 mg semaglutide	To reflect the most recent information in the US package insert.
2.3.3 Overall Benefit Risk Conclusion	Updated the duration of medical care from 76 weeks to 72 weeks	The safety follow-up visit (Visit 801) is no longer required.
3. Objectives, Endpoints, and Estimands	Added information about the maximum-tolerated dose of semaglutide (1.7 mg or 2.4 mg)	To reflect the most recent information in the US package insert.
	Added an additional secondary objective for mean percent decrease in weight loss	To investigate a scientifically relevant question.
4.1 Overall Design	Added information about the maximum-tolerated dose of semaglutide (1.7 mg or 2.4 mg) and information about the	To reflect the most recent information and the safety follow-up visit (Visit 801) is no longer required.

Section # and Name	Description of Change	Brief Rationale
	safety-follow up period has been removed	
4.1.2.2 Treatment Period	**End of Visit 2 to Visit 8** Added information about the maximum-tolerated dose of semaglutide (1.7 mg or 2.4 mg)	To reflect the most recent information in the US package insert.
	End of Visit 8 to Visit 20 Added "as needed" to transmission of prescription for central pharmacy study intervention dispensing	Clarification
	Early discontinuation visit Removed "of treatment" from title of section and throughout section and added reference to Section 7.1	Clarification
4.1.2.3 Safety Follow-Up Period	This section has been removed	The safety follow-up visit (Visit 801) is no longer required.
4.2 Scientific Rationale for Study Design	Added information about the maximum-tolerated dose of semaglutide (1.7 mg or 2.4 mg) and removed information about the safety follow-up period	To reflect the most recent information in the US package insert and the safety follow-up visit (Visit 801) is no longer required.
4.3 Justification for Dose	Added the word "recommended" to semaglutide maintenance dose of 2.4 mg and added information about the maximum-tolerated dose of semaglutide (1.7 mg or 2.4 mg)	To reflect the most recent information in the US package insert.
5.2 Exclusion Criteria	EC 36: removed 2.4 mg from dose of Wegovy	To reflect the most recent information in the US package insert.

Section # and Name	Description of Change	Brief Rationale
5.3.1 Meals and Dietary Restrictions	Revised to allow either tirzepatide or semaglutide dose to be reduced in case a participant reaches BMI ≤22 kg/m^2	To reflect the most recent information in the US package insert.
6.1 Study Intervention(s) Administered	Updated semaglutide dosage level	To reflect the most recent information in the US package insert.
6.5 Dose Modification	Revised to allow either tirzepatide or semaglutide dose to be reduced in case a participant reaches BMI ≤22 kg/m2	To reflect the most recent information in the US package insert.
6.5.2 Semaglutide	Updated information regarding semaglutide dose escalation phase and maintenance dose phase	To reflect the most recent information in the US package insert.
	Removed "weight maintenance" from footnote [a] in "Tirzepatide and Semaglutide Temporary Dose Adjustment Schedule" table	To reflect the most recent information in the US package insert.
6.6 Continued Access to Study Intervention after the End of the Study	Removed semaglutide dose	To reflect the most recent information in the US package insert.
7.1 Discontinuation of Study Intervention	Removed information about the safety follow-up visit and added clarifying language regarding ED visit	The safety follow-up visit (Visit 801) is no longer required.
	Removed pregnancy from list of clinical considerations for permanent discontinuation from study intervention	Duplication
7.2 Participant Discontinuation/Withdrawal from the Study	Removed information about the safety follow-up visit	The safety follow-up visit (Visit 801) is no longer required.

Section # and Name	Description of Change	Brief Rationale
8.2.4 Clinical Safety Laboratory Tests	Removed "or within 4 weeks after the last dose of study intervention" from the requirement to repeat abnormal laboratory tests	The safety follow-up visit (Visit 801) is no longer required.
8.3.1 Timing and Mechanism for Collecting Events	Removed information about the safety follow-up visit	The safety follow-up visit (Visit 801) is no longer required.
8.3.3.7 Arrhythmias and Cardiac Conduction Disorders	Removed information about central reading center	Correction
9.1 Statistical Hypotheses	Added information about the maximum-tolerated dose of semaglutide (1.7 mg or 2.4 mg)	To reflect the most recent information in the US package insert.
9.2 Analyses Sets	Safety Analysis Set (SS) description: Updated "Treatment Period plus Safety Follow-up" to "study"	The safety follow-up visit (Visit 801) is no longer required.
9.3.2 Primary Endpoint Analysis	Added information about maximum-tolerated dose of semaglutide	To reflect the most recent information in the US package insert.
9.3.4 Safety Analyses	Updated "safety follow-up" to "study participation"	The safety follow-up visit (Visit 801) is no longer required.
9.5 Sample Size Determination	Added information about maximum-tolerated dose of semaglutide	To reflect the most recent information in the US package insert.
10.4.2 Contraception Guidance	Added clarification about adding second form of contraception in females who had bilateral tubal ligation	Clarification
10.10 Appendix 10: Provisions for Changes in Study Conduct During Exceptional Circumstances	***Adjustments to visit windows:*** Removed Visit 801	The safety follow-up visit (Visit 801) is no longer required.

Section # and Name	Description of Change	Brief Rationale
11. References and throughout	Updated reference and citations for Wegovy package insert	To reflect the most recent information in the US package insert.
Throughout	Minor editorial changes	For clarity

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 3b, Randomized Controlled Study to Evaluate the Efficacy and Safety of Tirzepatide Compared to Semaglutide in Adults Who Have Obesity or Overweight with Weight-Related Comorbidities (SURMOUNT-5)

Brief Title:

Efficacy and Safety of Tirzepatide Compared to Semaglutide in Adults Who Have Obesity or Overweight (SURMOUNT-5)

Regulatory Agency Identifier Number(s):

IND: 139721

EU Number: 2022-501106-35-00

Rationale:

This Phase 3b study will evaluate the efficacy and safety of once-weekly treatment with tirzepatide 15 mg or the maximum-tolerated dose of tirzepatide (10 mg or 15 mg) compared with semaglutide 2.4 mg or the maximum-tolerated dose of semaglutide (1.7 mg or 2.4 mg) on change in body weight in adult participants who have obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with weight-related comorbidities.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary[a]	
To demonstrate that tirzepatide at 15 mg or MTD (10 mg or 15 mg) is superior to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) for the mean percent decrease in weight loss	Percent change from baseline in body weight at 72 weeks
Key Secondary[a]	
To demonstrate that tirzepatide at 15 mg or MTD (10 mg or 15 mg) is superior to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) at Week 72 for: • Body weight	Body weight reduction from baseline of: • ≥10% • ≥15% • ≥20%, and • ≥25%

• Waist circumference	Change from baseline in waist circumference (cm)
Additional Secondary	
To compare tirzepatide at 15 mg or MTD (10 mg or 15 mg) to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) at Week 72 for:	
• Body weight	Change from baseline in body weight (kg) Body weight reduction from baseline of ≥30%
• BMI	Change from baseline in BMI (kg/m^2)
To compare tirzepatide at 15 mg to semaglutide at 2.4 mg for the mean percent decrease in weight loss	Percent change from baseline in body weight at 72 weeks

Abbreviations: BMI = body mass index; MTD = maximum-tolerated dose.

[a] Primary and key secondary endpoints are controlled for multiplicity.

Overall Design:

This is a Phase 3b, parallel-design, open-label, randomized active-controlled study to evaluate the efficacy and safety of once-weekly treatment with 15 mg or the maximum-tolerated dose (MTD) of tirzepatide (10 mg or 15 mg) compared with semaglutide or MTD of semaglutide (1.7 mg or 2.4 mg) on change in body weight in adult participants who have obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with weight-related comorbidities.

The study includes a 2-week screening period and a 72-week treatment period.

Brief Summary:

This is a study to compare the weight loss efficacy of tirzepatide to semaglutide in people with obesity or overweight, without Type 2 diabetes. The trial will last 74 weeks, including 72 weeks on study intervention, and include 20 visits.

The primary outcome is the change in body weight at 72 weeks.

Study Population:

In general, participants may take part in the study if they

- are 18 years of age or older
- have a BMI ≥30 kg/m^2 or ≥27 kg/m^2 and previously diagnosed with at least 1 weight-related comorbidity (excluding Type 2 diabetes), and
- have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight.

In general, participants may not take part in the study if they

- have Type 1 diabetes or Type 2 diabetes or a history of ketoacidosis or hyperosmolar state or coma

- have a self-reported change in body weight >5 kg within 3 months prior to screening
- are women who are pregnant, lactating, or breastfeeding, or
- have a history or presence of an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with the interpretation of data.

Number of Participants:

Approximately 700 participants will be randomly assigned to tirzepatide and semaglutide in a 1:1 ratio. With the assumption of a 20% discontinuation rate of study intervention, approximately 280 participants will complete 72 weeks of treatment for each treatment group.

Intervention Groups and Duration:

Participants who meet entry criteria will be randomly assigned in a 1:1 ratio tirzepatide or semaglutide treatment. Tirzepatide and semaglutide will be administered once-weekly.

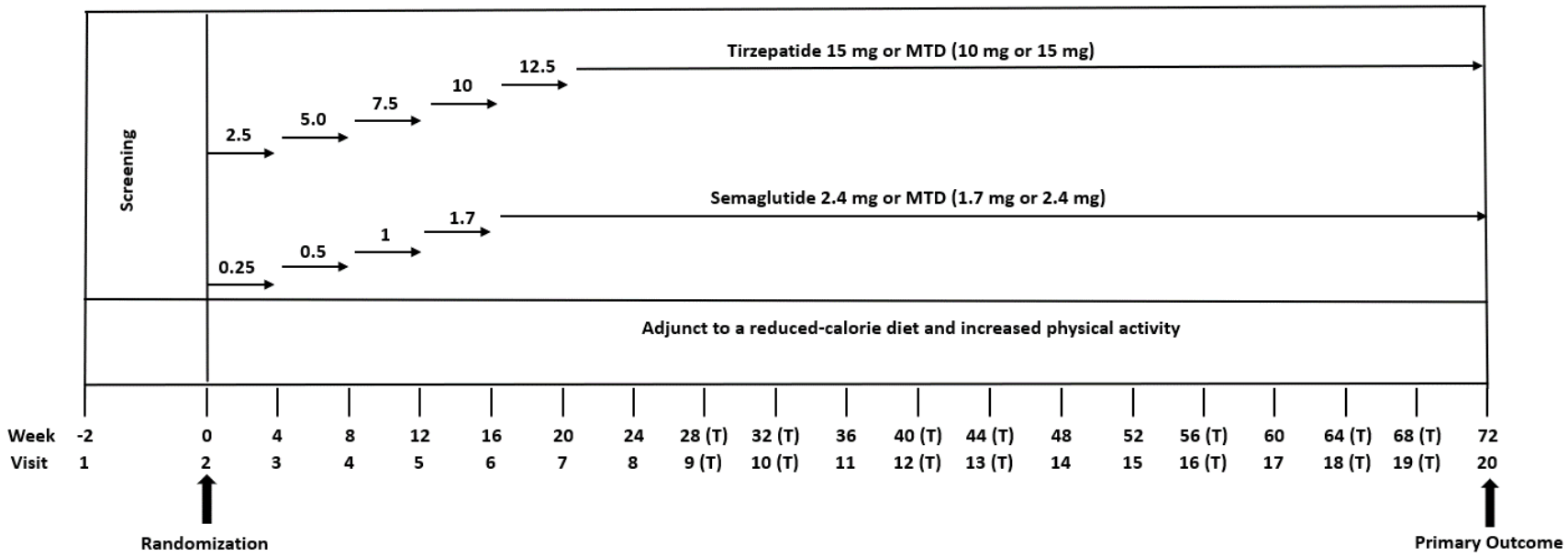
The study treatment period is 72 weeks.

Ethical Considerations of Benefit/Risk:

The potential benefits from participation in this study, which include frequent expert medical care for up to 72 weeks and the chance for achieving body weight reduction, are expected to outweigh the described risks, which will be closely monitored and managed through the established procedures.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: MTD = maximum-tolerated dose; (T) = Telephone Visit.

1.3. Schedule of Activities (SoA)

The SoA described below should be followed for all participants enrolled in Study I8F-MC-GPHJ (GPHJ). However, for those participants whose participation in this study is affected by exceptional circumstances, such as pandemics or natural disasters, please refer to Section 10.10 for additional guidance.

Period I – Screening (Visit 1): Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.

Period II – Treatment period (Visits 2-20): For early discontinuation that occurs before the last visit in treatment period, see the activities listed for ED in this table. Participants who are unable or unwilling to continue the study 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 (See Section 7.1).

Telephone visits

Telephone visits may be by telephone or other technology. Gray-shaded columns in the SoA tables represent telephone visits.

Fasting visits

On all office visits, study participants should be reminded to report to the site in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or any significant physical activity. If a participant attends a fasting visit in a non-fasting state, they will be offered to return in fasting state; if they are not able to return, then the samples should be collected as a non-fasting and this will not be considered a protocol deviation. However, if a participant attends Visits 2, 8, 11, 15, or 20 in the non-fasting state, these visits must be rescheduled.

If a participant is adversely affected by the fasting condition, they can be allowed to eat after specific study procedures that need to be completed while fasting. See Section 10.7 for a suggested order of activities that occurs at office visits.

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**ED**
Weeks from randomization	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**—**
Visit interval tolerance (days)	**-21 to -7**	**_**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**—**
Visit Detail	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**	**F**	**T**	**F**	**T**	**T**	**F**	**F**
	F = fasting visit; T = telephone visit (shaded columns)																				
Informed consent	X																				
	The informed consent form must be signed before any protocol-specific tests or procedures are performed. See Appendix 10.1, Section 10.1.3, for additional details.																				
Inclusion and exclusion criteria, review and confirm	X	X																			
	Inclusion/exclusion criteria should be confirmed prior to drug assignment and administration of first dose of study intervention.																				
Demographics	X																				
	Includes ethnicity (where permissible), year of birth, sex, and race.																				
Preexisting conditions and medical history, including relevant surgical history	X																				
	All conditions ongoing and relevant past surgical and medical history should be collected.																				
Prespecified medical history (indication and history of interest)	X																				
	Should include, but not limited to, collecting diagnosis of obesity, and obesity-related health problems.																				
Prior treatments for indication	X																				
	Include medications used for overweight or obesity.																				
Substance use (alcohol, tobacco use)	X																				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**ED**
Weeks from randomization	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**—**
Visit interval tolerance (days)	**-21 to -7**	**_**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**—**
Visit Detail	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**	**F**	**T**	**F**	**T**	**T**	**F**	**F**
	F = fasting visit; T = telephone visit (shaded columns)																				
	AE collection begins when the ICF is signed (Section 8.3.1). For AESIs, additional data could be collected (Section 8.3.3).																				
Evaluation of antihypertensive or lipid-lowering treatment											X									X	X
	For participants receiving antihypertensive or lipid-lowering treatment, the investigator should evaluate changes in the participant's treatment intensity within each therapeutic area. The evaluation should be based on whether an overall change from randomization until the time of evaluation has occurred.																				
Physical Evaluation																					
Height	X																				
Weight	X	X	X	X	X	X	X	X			X			X	X		X			X	X
Waist circumference		X	X	X	X	X	X	X			X			X	X		X			X	X
Vital signs	X	X	X	X	X	X	X	X			X			X	X		X			X	X
	Include pulse rate and blood pressure. Measure after participant has been sitting for at least 5 min and before obtaining an ECG tracing and before collection of blood samples for laboratory testing. See Section 8.2.2.																				
Physical examination	X																				
	See Section 8.2.1																				
Symptom-direct physical assessment		X (refer to comment below)																			
	Will be conducted at the discretion of the PI or qualified personnel per local regulations, as indicated based on participant status and standard of care for Visits 2-8, 11, 14-15, 17, and 20, ED. If Visits 9, 10, 12, 13, 16, 18, and 19 are performed as telephone visits, then the symptom-directed physical assessment will not be done at these visits.																				
First day of last menstrual cycle in	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**ED**
Weeks from randomization	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**—**
Visit interval tolerance (days)	**-21 to -7**	**_**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**—**
Visit Detail	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**	**F**	**T**	**F**	**T**	**T**	**F**	**F**
	F = fasting visit; T = telephone visit (shaded columns)																				
WOCBP with menstrual cycles																					
12-lead ECG (local)		X						X												X	X
	Perform prior to collection of blood samples for laboratory testing. Participants should be supine for approximately 5 to 10 min before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit. See Section 8.2.3.																				
Participant Electronic Diary																					
Dispense electronic diary, instruct to use		X																			
	Diary contains the following assessments: exposures and self-reported hypoglycemia.																				
Electronic diary review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Review of diary (electronic)																				
Electronic diary return																				X	X
Participant Paper 3-day Diet and Exercise Log																					
Dispense paper log		X	X	X	X	X	X	X			X			X	X		X				
Paper log review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient-Reported Outcomes (Electronic) *Complete prior to any Clinician Administered Assessments*																					
Short Form Health Survey Version 2 (SF-36 v2)		X									X									X	X
Patient Global Impression of Status for Physical		X									X									X	X

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**ED**
Weeks from randomization	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**—**
Visit interval tolerance (days)	**-21 to -7**	**_**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**—**
Visit Detail	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**	**F**	**T**	**F**	**T**	**T**	**F**	**F**
	F = fasting visit; T = telephone visit (shaded columns)																				
Activity (PGIS Physical Activity)																					
Patient Health Questionnaire (PHQ-9)	X	X	X	X	X	X	X	X			X			X	X		X			X	X
Clinician-Administered Assessments (Paper)																					
C-SSRS screening/baseline	X																				
	AE collection should occur prior to the collection of the C-SSRS.																				
C-SSRS since last visit		X	X	X	X	X	X	X			X			X	X		X			X	X
	AE collection should occur prior to the collection of the C-SSRS.																				
Weight history questionnaire		X																			
Participant Education																					
Lifestyle (diet and exercise goals) program instruction		X	X	X	X			X			X			X			X			X	X
Review diet and exercise goals		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of contraceptive measures as applicable for WOCBP and males		X			X			X			X			X			X			X	
Laboratory Tests and Sample Collection																					
HbA1c	X							X							X					X	X

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**ED**
Weeks from randomization	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**—**
Visit interval tolerance (days)	**-21 to -7**	**_**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**—**
Visit Detail	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**	**F**	**T**	**F**	**T**	**T**	**F**	**F**
	F = fasting visit; T = telephone visit (shaded columns)																				
Hematology	X				X			X			X				X					X	X
Clinical chemistry	X				X			X			X				X					X	X
Lipid panel		X			X			X			X									X	
Serum pregnancy	X																				
	For all WOCBP and females with a history of tubal ligation. See Section 8.3.2.																				
Urine pregnancy (local)		X			X			X			X			X			X			X	X
	A urine pregnancy test must be performed at Visit 2 with the result available prior to first dose or injection of study intervention for all women of childbearing potential only. Additional pregnancy tests (beyond those required per the SoA) should be performed at any time during the trial if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation.																				
Follicle-stimulating hormone (FSH)	X																				
	Optional; performed as needed to confirm postmenopausal status. See Section 10.2.																				
Thyroid-stimulating hormone (TSH)	X																				
Insulin	X										X									X	
Cystatin-c	X							X							X					X	X
Calcitonin	X							X							X					X	X
Pancreatic amylase	X							X							X					X	X
Lipase	X							X							X					X	X
eGFR	X							X							X					X	X

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**ED**
Weeks from randomization	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**—**
Visit interval tolerance (days)	**-21 to -7**	**_**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**—**
Visit Detail	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**	**F**	**T**	**F**	**T**	**T**	**F**	**F**
	F = fasting visit; T = telephone visit (shaded columns)																				
	Calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.																				
Stored Samples																					
Epigenetics sample		X									X									X	
Exploratory biomarker samples		X			X			X			X									X	
Genetics											X										
	Optional, confirm informed consent before collection. See Section 8.6.																				
Randomization and Dosing																					
Register visit with IWRS	X	X																			
Assign treatment via IWRS		X																			
	For Visit 2 - Baseline assessments must be completed before processing in the IWRS.																				
Dispense study intervention		X																			
Site transmits study intervention prescription for central pharmacy study intervention dispensing as needed			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study intervention injection training		X																			
Observe participant administer first dose of study intervention		X																			

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**ED**
Weeks from randomization	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**—**
Visit interval tolerance (days)	**-21 to -7**	**_**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**—**
Visit Detail	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**	**F**	**T**	**F**	**T**	**T**	**F**	**F**
	F = fasting visit; T = telephone visit (shaded columns)																				
Dispense ancillary supplies to participant		X																			
	Ancillary Supplies may be resupplied as needed from central pharmacy per participant requirements.																				
Participant returns study intervention			X	X	X	X	X	X			X			X	X		X			X	X
Assess study intervention compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse events, AESI = adverse event of special interest; C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram; eGFR = estimated glomerular filtration rate, ICF = informed consent form; IWRS = Interactive Web-Response System; PI = principal investigator.

2. Introduction

Tirzepatide is once-weekly GIP and GLP-1R agonist that integrates the actions of both incretins into a single molecule being developed for the once-weekly treatment of T2D and weight management.

2.1. Study Rationale

This Phase 3b study will evaluate the efficacy and safety of once-weekly treatment with tirzepatide 15 mg or the maximum-tolerated dose of tirzepatide (10 mg or 15 mg) compared with semaglutide 2.4 mg or the maximum-tolerated dose of semaglutide (1.7 mg or 2.4 mg) on change in body weight in adult participants who have obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with weight-related comorbidities.

2.2. Background

Obesity is a chronic disease, and its increasing prevalence is a public health concern associated with rising incidence of T2D, increased risk for premature death, and increased risk for some cancers (Allison et al. 2008; AMA 2013; Council on Science, and Public Health 2013). Although loss of 5% to 10% body weight has been shown to reduce complications related to obesity and improve quality of life (Mertens and Van Gaal 2000, Knowler et al. 2002; Jensen et al. 2014; Warkentin et al. 2014), lifestyle therapies fail to achieve sustainable weight loss in the majority of patients with obesity (Dombrowski et al. 2014). Restricted energy intake and voluntary efforts to increase energy expenditure through physical activity have been shown to be counteracted by adaptive physiological responses that make continued weight loss difficult and predispose to weight regain (Pasman et al. 1999; Rosenbaum et al. 2005; Sumithran et al. 2011). Therefore, there is increasing recognition that adjunctive therapies are required in addition to lifestyle modification for patients with obesity to achieve and maintain sufficient weight loss to improve health outcomes.

The incretin hormones, GIP and GLP-1, are secreted after meal ingestion and mediate the incretin effect. Both hormones have effects on endocrine cells in the pancreas, increasing insulin biosynthesis and secretion, and modifying glucagon secretion (Skow et al. 2016). Based on these properties, several GLP-1R agonists have been approved for pharmacological treatment of T2D (Baggio and Drucker 2007).

In addition to its pancreatic effects, GLP-1R activation decreases gut motility, slows gastric emptying, and promotes satiety (presumably through a combination of GLP-1R activation in the central and peripheral nervous system), thereby regulating food intake and body weight (Shah and Vella, 2014). The US Food and Drug Administration and the European Medicines Agency approved the GLP-1R agonists liraglutide (SAXENDA® package insert, 2014; SAXENDA® summary of product characteristics, 2015) and more recently, semaglutide (Wegovy® package insert, 2023) for the treatment of overweight and obesity. Semaglutide is a GLP-1R agonist that has been shown to achieve a clinically relevant reduction in body weight compared to placebo in participants who have obesity or overweight. Once-weekly semaglutide demonstrated significantly greater body weight loss compared to once-daily liraglutide at 68 weeks in adults with overweight or obesity without diabetes (Rubino et al. 2022).

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

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

As a GIP/GLP-1R agonist, tirzepatide could exceed the efficacy of currently available selective GLP-1R analogs by recruiting metabolically active tissues not targeted by selective GLP-1R analogs, for example, adipose tissue as indicated by the observation in preclinical models of increased energy utilization (Baggio and Drucker 2007). Tirzepatide also has the potential to reach higher efficacy in target tissues, such as insulin-producing pancreatic beta-cells that express both GIPR and GLP-1R, before reaching its therapeutic limitation. Results from the SURPASS program for T2D provide strong evidence that tirzepatide has the potential to be a highly efficacious treatment option for both glycemic control in T2D and as a medication for chronic weight management. Tirzepatide resulted in clinically important reductions in body weight across the T2D disease continuum and showed superiority in weight loss versus all comparators (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al., 2022). SURPASS 2, which compared tirzepatide 5 mg, 10 mg, and 15 mg to semaglutide 1 mg, demonstrated superior weight loss with tirzepatide with mean weight loss of 7.6 kg, 9.3 kg, 11.2 kg compared to 5.7 kg after 40 weeks of study intervention (Frías et al. 2021). Tirzepatide has been approved in the US for treatment of T2D (Mounjaro® package insert, 2022).

Study GPHJ is a Phase 3b, multicenter, randomized, parallel-arm, open-label, active comparator-controlled, 72-week study that will investigate the effects of treatment with tirzepatide 15 mg or the MTD of tirzepatide (10 mg or 15 mg) compared with semaglutide 2.4 mg or the MTD of semaglutide (1.7 mg or 2.4 mg) on change in body weight in adult participants and who have obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with weight related comorbidities.

2.3. Benefit/Risk Assessment

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

In addition, detailed information about the known and expected benefits and risks of semaglutide may be found in the semaglutide package insert (Wegovy® package insert, 2023).

2.3.1. Risk Assessment

The data from global tirzepatide Phase 3 studies (SURPASS) indicate that the safety and tolerability profile of tirzepatide is consistent with the safety profile of other GLP-1R agonists (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al., 2021; Rosenstock et al., 2021).

The most common AEs observed in the tirzepatide clinical trials in healthy participants and participants with T2D have been GI effects (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al., 2021; Rosenstock et al., 2021). Similar GI-related effects have been observed with semaglutide (Rubino et al. 2022). For both interventions, GI-related effects will be closely monitored and managed through titration to target dose and dose de-escalation (for duration of study if needed). If still unable to tolerate the intervention (at least 10 mg tirzepatide or 1.7 mg semaglutide), participants will continue to receive a benefit of continued safety monitoring visits for the duration of the study.

Participation in the study may impact mental health status, for example due to changes in body weight. Each participant will be regularly monitored for this risk.

Other safety topics of interest for both interventions include pancreatic safety, cardiovascular events, hypoglycemia, hypersensitivity reactions, and thyroid C-cell effects; refer to Section 8.3.3 for further details. Please refer to the tirzepatide IB Section 6 and the semaglutide package insert for more details. These risks are managed through proposed monitoring and exclusion of those with relevant risk history.

Overall, the potential risks to participating in this study are deemed to be monitorable and manageable.

2.3.2. Benefit Assessment

All participants, regardless of intervention, will be monitored and treated at more frequent intervals than regular standard of care by experts in the field. Additionally, all participants in this study will receive diet and physical activity counseling.

In global Phase 3 studies, tirzepatide demonstrated superior efficacy on body weight reductions and glycemic control as well as an improvement in different measures, which are associated with increased risk of longer-term cardiometabolic complications in participants with T2D (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al., 2021; Rosenstock et al., 2021). The results indicate that clinically meaningful improvements in body weight reduction are anticipated for those randomized to and remaining on tirzepatide in this study.

For those randomized to and remaining on semaglutide, body weight reductions are an anticipated benefit as this intervention has been approved for the treatment of overweight and obesity (Wegovy® package insert, 2023).

2.3.3. Overall Benefit Risk Conclusion

The potential benefits from participation in this study, which include frequent expert medical care for up to 72 weeks and the chance for achieving body weight reduction, are expected to outweigh the described risks, which will be closely monitored and managed through established procedures.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary[a]	
To demonstrate that tirzepatide at 15 mg or MTD (10 mg or 15 mg) is superior to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) for the mean percent decrease in weight loss	Percent change from baseline in body weight at 72 weeks
Key Secondary[a]	
To demonstrate that tirzepatide at 15 mg or MTD (10 mg or 15 mg) is superior to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) at Week 72 for:	
• Body weight	Body weight reduction from baseline of • ≥10% • ≥15% • ≥20%, and • ≥25%
• Waist circumference	Change from baseline in waist circumference (cm)
Additional Secondary	
To compare tirzepatide at 15 mg or MTD (10 mg or 15 mg) to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) at Week 72 for:	
• Body weight	Change from baseline in body weight (kg) Body weight reduction from baseline of ≥30%
• BMI	Change from baseline in BMI (kg/m^2)
To compare tirzepatide at 15 mg to semaglutide at 2.4 mg for the mean percent decrease in weight loss	Percent change from baseline in body weight at 72 weeks
Tertiary	
To compare tirzepatide at 15 mg or MTD (10 mg or 15 mg) to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) at Week 72 for	
• Lipid parameters	Change from baseline in

	• triglycerides (mg/dL) • VLDL (mg/dL) • non-HDL cholesterol (mg/dL)
• Insulin	Change from baseline in fasting insulin (pmol/L)
• HbA1c	Change from baseline in HbA1c (%)

Abbreviations: BMI = body mass index; HDL = high-density lipoprotein; MTD = maximum-tolerated dose; SF36 physical function = Short Form 36 physical function; VLDL = very low-density lipoprotein.

[a] Primary and key secondary endpoints are controlled for multiplicity.

Primary estimand

The primary estimand evaluated in this study is a modified treatment-regimen estimand. This estimand aims at reflecting how participants with obesity or overweight with at least 1 weight-related comorbid condition are treated in clinical practice and takes into account both tolerability and efficacy.

This modified treatment-regimen estimand answers the following question of interest for the primary objective: What is the treatment difference in mean percent change from baseline in body weight after 72 weeks of treatment as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity or overweight with at least 1 weight-related comorbid condition. Under this estimand framework, participants will be included regardless of treatment discontinuation for any reason and regardless of initiation of other anti-obesity medication (except for non-study tirzepatide or semaglutide). This estimand also assumes that participants who had bariatric surgery or another weight loss procedure did not get any benefit or might have worsened from their randomized study treatment.

The modified treatment-regimen estimand is described by the following attributes:

- *Population:* Participants who have obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with at least 1 weight-related comorbid condition, but without Type 2 diabetes. Further details can be found in Section 5.
- *Endpoint*: Percent change from baseline to Week 72 in body weight.
- *Treatment condition*: The randomized treatment as an adjunct to a reduced-calorie diet and increased physical activity regardless of adherence to treatment with or without other anti-obesity medications, except for non-study tirzepatide, or semaglutide. Further details on study treatment and concomitant therapy can be found in Section 6.
- *Intercurrent events*: Intercurrent events of interest: “treatment discontinuation for any reason” and “initiation of other anti-obesity medication except for non-study tirzepatide or semaglutide” are addressed by the treatment condition. Bariatric surgery or other weight loss procedures will be addressed by the hypothetical strategy. It will be assumed that patients who undergo any of these procedures did not get any benefits or might have worsened from their randomized study treatment.
- *Population-level summary*: Difference in mean percent change between treatment conditions.

Secondary estimand

The secondary estimand evaluated in this study is the efficacy estimand. This estimand focuses on the treatment effect if participants who underwent randomization continued to receive the study treatment without taking other anti-obesity therapies *such as* weight management drugs, bariatric surgery, or weight loss procedure. This estimand will be used in publications to inform prescribers or physicians and may be submitted to other regulatory agencies outside the United States.

The efficacy estimand answers the following question of interest for the primary objective: What is the treatment difference in percent change in body weight from baseline after Week 72 of treatment as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity or overweight with at least 1 weight-related comorbid condition assuming that participants had stayed on treatment and not taken other anti-obesity therapies (that is, other weight management drugs, bariatric surgery, or other weight management procedures)?

The efficacy estimand is described by the following attributes.

- *Population*: Participants who have obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with at least 1 weight-related comorbid condition, but without Type 2 diabetes. Further details can be found in Section 5.
- *Endpoint*: Percent change from baseline to Week 72 in body weight.
- *Treatment condition*: The randomized treatment as an adjunct to a reduced-calorie diet and increased physical activity. Further details on study treatment can be found in Section 6.
- *Intercurrent events*: "Treatment discontinuation for any reason" and "Initiation of other anti-obesity therapies such as weight management drugs, bariatric surgery or other weight management procedures" will be addressed using the hypothetical strategy:
    - Had participants stayed on treatment.
    - Had participants not taken other weight management drugs or bariatric surgery or weight loss procedure.
- *Population-level summary*: Difference in mean changes between treatment conditions.

Both the efficacy and treatment-regimen estimands will be evaluated for the primary and all key secondary objectives. The population, treatment condition, intercurrent events, and population-level summary specified above for each estimand for the primary objective will also apply to the key secondary objectives. The endpoint for each key secondary objective is defined in the table above.

4. Study Design

4.1. Overall Design

Study GPHJ is a Phase 3b, multicenter, randomized, parallel-arm, open-label, comparator-controlled, 72-week trial that will investigate the efficacy and safety of 15 mg or MTD tirzepatide (10 mg or 15 mg) compared with 2.4 mg or MTD semaglutide (1.7 mg or 2.4 mg) in study participants who have obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2).

Study GPHJ will consist of 2 periods: a 2-week screening period and a 72-week open-label tirzepatide and semaglutide treatment period (including a 20-week dose escalation period for tirzepatide and a 16-week dose escalation period for semaglutide). The study participants will be randomly assigned in a 1:1 ratio to tirzepatide 15 mg or MTD (10 mg or 15 mg) or semaglutide 2.4 mg or MTD (1.7 mg or 2.4 mg) at the end of the screening period. An upper limit of 70% enrollment of women will be used to ensure a sufficient enrollment of men.

4.1.1. Overview of Study Periods

Visit structure for fasting office visits

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

4.1.2. Main Study Period

4.1.2.1. Screening Period

Visit 1

The purpose of screening procedures at Visit 1 is to establish initial eligibility and to obtain blood samples for laboratory assessments needed to confirm eligibility. The participant must sign the ICF before the study procedures are performed, as outlined in the SoA, Section 1.3. Since some screening procedures need to be completed in the fasting state (at least 8 hours without eating, drinking [except water], or any significant physical activity), Visit 1 may be conducted over more than 1 day to ensure necessary conditions are met. The Mental Health Questionnaires should be completed after the assessment for AEs. The preferred administration order is

1. Patient Health Questionnaires
2. C-SSRS screening/baseline

4.1.2.2. Treatment Period

Visit 2

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

Patient-reported outcomes questionnaires should be administered as early as possible. Preferred administration order is

1. SF-36 v2 acute form
2. PGIS Physical Activity

The Mental Health Questionnaires (PHQ-9 and C-SSRS Since Last Visit) should be completed after the assessment for AEs.

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

End of Visit 2 to Visit 8

At the end of Visit 2, for participants that meet all the entry criteria are enrolled in this study and randomized, study site personnel will demonstrate use of molecule-specific device using the provided instructions for use and observe the study participant inject the first dose of study intervention. The date and time of the first dose of study intervention will be recorded in the e-diary.

After study enrollment, participants will undergo either a 20-week tirzepatide or a 16-week semaglutide dose escalation as indicated in the SoA.

Patient-reported outcomes questionnaires should be administered as early as possible. Preferred administration order is the same as described for Visit 2. Mental Health Questionnaires should be completed after the assessment of AEs.

Study intervention and injection supplies will be returned per the SoA and according to local requirements. New supplies will be dispensed as needed.

The starting dose of tirzepatide is 2.5 mg for 4 weeks, then the dose is increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 to 12.5 to 15 mg) up to 15 mg or MTD (10 mg or 15 mg) (see Section 6.5.1).

The starting dose of semaglutide is 0.25 mg for 4 weeks, then the dose is increased every 4 weeks (0.25 to 0.5 to 1.0 to 1.7 to 2.4 mg) up to the 2.4 mg dose but with the dosing flexibility for 1.7 mg if unable to tolerate 2.4 mg (see Section 6.5.2).

End of Visit 8 to Visit 20

Office and telephone visits should occur as indicated in the SoA (Section 1.3).

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

- weight, waist circumference, and vital signs measurements
- laboratory testing
- administration of PRO questionnaires, collection of AEs, product complaints, and concomitant medications
- Mental Health Questionnaires
- review of participant electronic diary information and diet and exercise log (to include reinforcement and compliance assessments for study intervention administration and lifestyle goals), and

- transmission of prescription for central pharmacy study intervention dispensing, as needed.

Patient-reported outcomes questionnaires should be administered as early as possible. Preferred administration order is the same as Visit 2.

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

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

At each of the 7 scheduled telephone visits, procedures will include

- collection of AEs, product complaints, and concomitant medications
- review first day of last menstrual cycle in applicable WOCBP
- review of electronic diary and diet and exercise log
- reinforcement and compliance assessments for study intervention administration and lifestyle goals, and
- transmission of prescription for central pharmacy study intervention dispensing, as needed.

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

Early discontinuation visit

Participants unable or unwilling to continue the study for any reason will perform an early discontinuation visit. Procedures should be completed according to the SoA. Patient-reported outcomes questionnaires should be administered as early as possible. Administration of Mental Health Questionnaires should be after the assessment for AEs (see Section 7.1).

4.1.3. Study Procedures

Participants will perform study procedures listed in the SoA (Section 1.3). Study participants will be permitted to use concomitant medications that they require during the study, except certain excluded medications (Section 5.2) that may interfere with the assessment of efficacy and safety characteristics of the study treatments.

Study governance considerations are described in detail in Section 10.1.

4.1.3.1. Management of Participants with Gastrointestinal Symptoms

Participants who report significant GI symptoms (for example, nausea, vomiting, or diarrhea) at any time during the study should follow the steps outlined in the table below (see also Section 5.3.2).

Step 1	Be counseled on dietary behaviors that may help mitigate nausea and vomiting, for example, eating smaller meals, splitting 3 daily meals into 4 or more smaller ones, and stopping eating when they feel full
Step 2	If symptoms persist, the participant should be prescribed, at the investigator's discretion, symptomatic medication, for example, antiemetic or antidiarrheal medication
Step 3	A temporary interruption of study intervention for 1 dose is permitted. Study intervention should be resumed immediately, either alone, or in combination with symptomatic medication, which can also be utilized to manage symptoms. A single-dose interruption is not recommended in participants that have missed any of the last 3 weekly doses
Step 4	If significant GI symptoms develop after randomization and persist despite the above measures, for example, dietary counseling, symptomatic medication, and interruption of study intervention for 1 dose, the investigator should contact Lilly medical monitor to consider dose de-escalation with subsequent re-escalation

4.1.3.2. Management of Incident Diabetes

Participants who develop diabetes (Section 10.9) during the study will be

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

Participants will be referred to their usual care provider and provided with a letter showing the study results indicative of diabetes. The decision to further evaluate, to initiate antihyperglycemic therapy, and the choice of antihyperglycemic medication will be at the discretion of the participant's usual care provider, with the exception of use of DPP-4 inhibitors and GLP-1R agonists, which are prohibited in the study. Monitoring for hypoglycemia includes capture of events as defined in Section 8.3.3.1. Diagnosis date of diabetes will be captured in the AE CRF.

4.2. Scientific Rationale for Study Design

Tirzepatide is an agonist at both the GIPR and GLP-1R. Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety (Coskun et al. 2018). It is administered once-weekly by injection.

As a GIP/GLP-1R agonist, tirzepatide could exceed the efficacy of selective GLP-1R agonists by recruiting metabolically active tissues not targeted by selective GLP-1R agonists such as semaglutide, which is approved for chronic weight management (Wegovy® package insert, 2023). Tirzepatide demonstrated superior weight loss in SURPASS 2, which evaluated efficacy and safety of tirzepatide compared to semaglutide 1 mg in people with T2D (Frías et al. 2021). Tirzepatide has been approved in the US for treatment of T2D (Mounjaro® package insert, 2022). Semaglutide 2.4 mg or MTD (1.7 mg or 2.4 mg) will be provided consistent with FDA-approved

USPI (Wegovy® package insert, 2023), while tirzepatide intended dose will be 15 mg or MTD (10 mg or 15 mg).

Higher weight loss efficacy with next generation anti-obesity medications is expected to be paradigm shifting for obesity care. It has been proposed that higher efficacy anti-obesity medications will allow individualized treat-to-target approach in weight management that was not achievable with historical anti-obesity medications (Garvey 2022). Defining characteristics of individual anti-obesity medications will support shared decision making with the treat-to-target approach. The current trial will determine the differences in weight loss efficacy for what are expected to be the 2 leading next generation anti-obesity medications. The weight loss efficacy, the primary objective, is essential to the individualized treat-to-target approach. The study will also determine if cardiovascular risk factors are differently impacted by tirzepatide and semaglutide. Also, of relevance is the additional secondary outcome to determine physical function, an important predictor of long-term outcomes including mortality (Tice et al. 2006; St. John et al. 2016).

All participants, regardless of treatment assignment, will receive lifestyle modification counseling consistent with current guidelines for weight management (Jensen et al. 2013). Specifically, participants will consult with a dietitian, or equivalent qualified delegate, throughout the study to achieve at least a 500 kcal/day energy deficit through a combination of caloric restriction and increased physical activity (Section 5.3.1). The planned duration of treatment for the primary endpoint at 72 weeks allows for at least a 52-week treatment period at the dose achieved following dose escalation to 15 mg or MTD (10 mg or 15 mg).

An upper limit of 70% enrollment of women will be used to ensure a sufficiently large sample of men.

In this study, collection of demographic information includes race and ethnicity. 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 dose of 15 mg administered SC is the intended dose to be evaluated in this study with the option of lower maintenance dose of 10 mg if participant does not tolerate 15 mg.

These doses and associated escalation scheme for tirzepatide were consistent with the design of the ongoing studies (GPHM, GPHN) for chronic weight management indication.

Dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5 mg increments every 4 weeks should permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns.

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

Tirzepatide doses 15 mg or MTD (10 mg or 15 mg) were selected based principally on the following criteria

- each dose provides robust weight loss relative to placebo

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

Semaglutide recommended maintenance dose of 2.4 mg or MTD (1.7 mg or 2.4 mg) and associated escalation scheme were selected in accordance with the approved Wegovy® label (Wegovy® package insert, 2023).

The proposed tirzepatide maintenance dose of 15 mg or MTD (10 mg or 15 mg) using a dose escalation regimen is expected to safely maximize the potential for weight loss with tolerable GI profile.

4.4. End of Study Definition

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

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 apply:

Age

1. Participants must be ≥18 years of age or of an acceptable age to provide informed consent according to local regulations, whichever is older

Weight

2. Have a BMI of
    - ≥30 kg/m^2 or
    - ≥27 kg/m^2 and previously diagnosed with at least 1 of the following weight-related comorbidities:
        - hypertension: treated or with systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg
        - dyslipidemia: treated or with LDL ≥160 mg/dL (4.1 mmol/L) or triglycerides ≥150 mg/dL (1.7 mmol/L), or HDL <40 mg/dL (1.0 mmol/L) for men or HDL <50 mg/dL (1.3 mmol/L) for women
        - obstructive sleep apnea, and
        - cardiovascular disease, for example, ischemic cardiovascular disease, New York Heart Association Functional Classification Class I-III heart failure
3. Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight
4. In the investigator's opinion, are well motivated, capable, and willing to
    - learn how to self-inject study intervention, as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study intervention; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study intervention)
    - inject study intervention (or receive an injection from a trained individual if visually impaired or with physical limitations), and
    - follow study procedures for the duration of the study, including, but not limited to, following lifestyle advice (for example, dietary restrictions and exercise plan), maintaining a study diary, and completing required questionnaires

- for visual impaired participants, they must have the assistance of a sighted individual for maintaining 3-day diet and exercise log be completed prior to each counseling visit

Sex and contraceptive/barrier requirements

5. Male and/or female

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Section 10.4.

- Male participants
  - Male participants with partners of childbearing potential should be willing to use reliable contraceptive methods throughout the study and for 5 half-lives of study intervention plus 90 days, corresponding to 4 months after the last injection.
- Female participants
  - Female participants not of childbearing potential may participate and include those who are
    - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy), congenital anomaly such as Mullerian agenesis; or
    - postmenopausal – defined as either:
      - A woman at least 40 years of age up to 55 years with an intact uterus, not on hormone therapy, who has cessation of menses for at least 12 consecutive months without an alternative medical cause, AND an FSH ≥ 40 mIU/mL; women in this category must test negative in pregnancy test prior to study entry

    or

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

    or

      - A woman at least 55 years of age with a diagnosis of menopause prior to starting HRT
  - Female participants of childbearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) and 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:
    - test negative for pregnancy at Visit 1 based on a serum pregnancy test
    - agree to use 2 forms of effective contraception, where at least 1 form is highly effective (less than 1% failure rate) for the duration of the trial plus 30 days thereafter, and
    - not be breastfeeding

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

Diabetes Related

7. Have T1D or T2D, history of ketoacidosis, or hyperosmolar state or coma
8. Have at least 1 laboratory value suggestive of diabetes during screening including 1 or more of HbA1c ≥6.5% (≥48 mmol/mol), fasting glucose ≥126 mg/dL (≥7.0 mmol/L), or random glucose ≥200 mg/dL (≥11.1 mmol/L)

Obesity Related

9. Have a self-reported change in body weight >5 kg within 3 months prior to screening
10. Have a prior or planned surgical treatment for obesity, excluding liposuction or abdominoplasty if performed >1 year prior to screening
11. Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months prior to screening

    Examples:

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

Other Medical

12. Have renal impairment measured as eGFR <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease Epidemiology as determined by central laboratory during screening
13. Have a known clinically significant gastric emptying abnormality (for example, severe gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect GI motility
14. Have a history of chronic or acute pancreatitis

15. Have TSH outside of the range of 0.4 to 6.0 mIU/L at the screening visit

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

    Note: Participants with a history of subclinical hypothyroidism but a TSH at screening within the range indicated above may be included if, in the investigator's opinion, the participant is unlikely to require initiation of thyroid hormone replacement during the course of the study.

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

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

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

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

19. Are, in the judgment of the investigator, actively suicidal, and therefore deemed to be at significant risk for suicide

20. On the C-SSRS on or before Visit 2

    - have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS or
    - have answered "yes" to any of the suicide-related behaviors on the "Suicidal Behavior" portion of the C-SSRS, and
    - the ideation or behavior occurred within the past month.

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

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

    - acute myocardial infarction
    - cerebrovascular accident (stroke)
    - unstable angina, and
    - hospitalization due to CHF

23. Have New York Heart Association Functional Classification Class IV CHF

24. Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than NAFLD, or any of the following, as determined by the central laboratory during screening:
    - ALT level >3.0x ULN for the reference range
    - ALP level >1.5x ULN for the reference range, or
    - TBL level >1.5x ULN for the reference range (except for cases of known Gilbert's Syndrome)

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

25. Have a serum calcitonin level (at Visit 1) of
    - ≥20 ng/L, if eGFR ≥60 mL/min/1.73 m^2, and
    - ≥35 ng/L, if eGFR <60 mL/min/1.73 m^2

26. Have a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome Type 2

27. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years

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

29. 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

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

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

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

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

Prior/concomitant therapy

33. Have used a GLP-1R agonist within 3 months of screening

34. Are receiving or have received within 3 months prior to screening chronic (>2 weeks or >14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) or have evidence of a significant, active

autoimmune abnormality (for example, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) during the course of the study

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

    Examples:

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

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

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

    Examples include, but are not limited to

    - Saxenda® (liraglutide injection 3.0 mg)
    - Xenical®/Alli® (orlistat)
    - Meridia® (sibutramine)
    - Acutrim® (phenylpropanolamine)
    - Sanorex® (mazindol)
    - Apidex® (phentermine)
    - Belviq® (lorcaserin)
    - Bontril® (phendimetrazine)
    - Qsymia® (phentermine/topiramate combination)
    - Contrave® (naltrexone/bupropion)
    - Wegovy® (semaglutide injection), and
    - Plenity® (Oral Superabsorbent Hydrogel)

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

Prior/concurrent clinical study experience

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

38. Within the last 30 days of Visit 2, have participated in a clinical study and received treatment, whether active, or placebo. If the study involved an IP, 5 half-lives or 30 days, whichever is longer, should have passed

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

Other exclusions

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

41. Are Eli Lilly and Company employees

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), participants will consult with a dietitian, or equivalent qualified delegate, according to local standards, to receive lifestyle management counseling at Weeks 0, 4, 8, and 12 during dose escalation and then at Week 24 and every 12 weeks thereafter through 72 weeks.

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

5.3.1. Meals and Dietary Restrictions

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

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

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

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

Additionally, if a BMI $\leq$22 kg/m^2 is reached in participants receiving study intervention, the site physician should contact Lilly medical monitor for consideration of a single dose reduction for remainder of trial (for example, 15 mg to 10 mg or 10 mg to 5 mg for tirzepatide or 2.4 mg to 1.7 mg for semaglutide).

Total energy expenditure 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	18-30 years	15.057 × actual weight in kg + 692.2
	31-60 years	11.472 × actual weight in kg + 873.1
	>60 years	11.711 × actual weight in kg + 587.7
Women	18-30 years	14.818 × actual weight in kg + 486.6
	31-60 years	8.126 × actual weight in kg + 845.6
	>60 years	9.082 × actual weight in kg + 658.5

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

5.3.2. Monitoring nutritional needs

Tirzepatide and semaglutide are next generation anti-obesity medications with potential for superior weight loss compared to established anti-obesity medications. Caloric restriction is a standard component of weight loss interventions, and there is potential that a small portion of participants will have significantly reduced caloric intake.

Medical staff should consider clinical monitoring (via history and physical and laboratory assessment as needed) of the participant's nutritional and hydration status if report of significantly reduced caloric intake (for example, below 800-1200 kcal). By recognizing early signs of poor intake and dehydration, preventive actions can be taken to reduce the risk of potential complications.

5.3.3. Activity

Participants will abstain from strenuous exercise for 8 hours before each blood collection for clinical laboratory tests.

At Visit 2 and all subsequent visits, participants will be advised to increase their physical activity to at least 150 minutes per week.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

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 intervals in the SoA.

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 or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study

Intervention Name	Tirzepatide	Semaglutide
Dosage Level(s)	15 mg or the MTD (10 mg or 15 mg)	2.4 mg or the MTD (1.7 mg or 2.4 mg)
Route of Administration	Subcutaneous injection	Subcutaneous injection

Abbreviation: MTD = maximum-tolerated dose.

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

The products provided for use in the study are tirzepatide locally marketed autoinjector or investigational autoinjector pending the marketing status of tirzepatide and semaglutide locally marketed pen, for example, prefilled and single-dose pen. Any medical device-related AEs, including those resulting from malfunctions of the devices, must be detected, documented, and reported by the investigator throughout the study.

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Investigator Site Responsibilities

Lilly or its designee is supplying study intervention to the investigator for Visit 2 dispensing.

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 study training materials.

6.2.2. Direct-to-Participant Study Intervention Access

Lilly or its designee is supplying study intervention to a central licensed pharmacy that will dispense study intervention direct-to-participant beginning at Visit 3 for at-home dosing.

Investigator responsibilities

Upon receipt, the investigator must confirm that appropriate storage conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.

Investigators are responsible for accountability of study intervention that they store and dispense at the site.

The investigator is responsible for ensuring the study intervention is used in accordance with the approved protocol and that each participant follows the instructions for use properly.

Investigators are responsible for dose adjustment decisions and documentation that they report within the case report form, as applicable.

Treatment compliance of trial participants falls under the investigator's responsibility and does not change with the direct-to-participant supply method. If needed, the central licensed pharmacy will supply records to support any investigator determinations related to treatment compliance or PCs.

Licensed pharmacy responsibilities

Upon receipt, the licensed pharmacy must confirm that appropriate storage conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before dispensing the study intervention.

Proper storage, handling, and disposition of study intervention stored and dispensed by the central licensed pharmacy shall be the responsibility of the central licensed pharmacy contracted by Lilly.

To ensure appropriate preparation, handling, and storage for at-home dosing, participants will be provided instructions for receipt, storage, and handling when study intervention is supplied by the central licensed pharmacy.

Participants will return any unused study intervention as instructed for the purpose of dosing compliance.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study.

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

to each site. The site will record the intervention assignment if required. Potential bias will be reduced by central randomization, and the randomization will be stratified by prediabetes status (yes, no), baseline BMI (<35 kg/m^2, ≥35 kg/m^2), and sex (female, male).

6.4. Study Intervention Compliance

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

Study intervention compliance will be determined by the following:

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

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

In addition to the assessment of a participant's compliance with the study intervention administration, other aspects of compliance with the study treatments will be assessed at each visit based on the participant's adherence to the visit schedule, completion of study diaries, and any other parameters the investigator considers necessary.

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

6.5. Dose Modification

Dose modification is permitted for management of intolerable GI symptoms only (Section 4.1.3.1). The only additional modification of dose is if a BMI ≤22 kg/m^2 is reached in participants receiving study intervention (Section 5.3.1).

Interventions to optimize study intervention tolerance and adherence may be employed throughout the study and include, but are not limited to, brief temporary interruptions (Section 7.1.3) and use of additional medications to manage GI symptoms, for example, nausea, vomiting, and diarrhea. If study intervention is interrupted, the participant will continue to follow the lifestyle program (see Section 5.3).

6.5.1. Tirzepatide

Tirzepatide is administered once-weekly by SC injection. There are no restrictions on the time of day each weekly dose of tirzepatide is given, but it is advisable to administer the SC injections on the same day of the week and similar time each week.

Dose escalation phase

The starting dose of tirzepatide is 2.5 mg for 4 weeks, then the dose is increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 to 12.5 to 15 mg) to intended maintenance dose of 15 mg but with dosing flexibility for 10 mg if unable to tolerate 15 mg.

During dose escalation of tirzepatide, participants unable to tolerate 2.5 mg despite measures taken as described in Section 4.1.3.1 will be discontinued from the study intervention but remain in the study for continued follow-up. For participants unable to tolerate any dose escalation between 5 mg and 15 mg inclusive, despite measures taken as described in Section 4.1.3.1, the investigator should contact Lilly medical monitor to consider dose de-escalation to next lower dose with subsequent re-escalation in an open-label fashion to reach the 15 mg or 10 mg dose as described below:

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

A maximum of 2 cycles of temporary dose adjustment to mitigate gastrointestinal intolerance are permitted during the study, with only 1 attempt at a dose less than the maintenance dose, 15 mg or 10 mg. Consecutive attempts with temporary dose adjustment from the same dose will not be allowed.

If a dose adjustment occurs, then additional visits at 4-week intervals will be scheduled to allow for the dose escalation.

This table below provides guidance if a participant does not tolerate a tirzepatide dose.

Tirzepatide Dose Adjustment

If a participant tolerates…	but after the de-escalation/re-escalation attempt(s) does not tolerate	then participant continues with their MTD/maintenance dose as…
15 mg	-	15 mg
12.5 mg	15 mg	10 mg
10 mg	12.5 or 15 mg	10 mg
5 mg	7.5 or 10 mg	Participant will be discontinued from study intervention but remains in the study for continued follow-up

Abbreviation: MTD = maximum-tolerated dose.

Maintenance dose phase

It is expected most temporary dose adjustments to mitigate gastrointestinal intolerance will occur during dose escalation to reach maintenance dose, tirzepatide MTD (10 mg or 15 mg). After this

time, if the participant has experienced 1 or no temporary dose adjustments, 1 additional de-escalation from maintenance dose for 4 weeks, with subsequent re-escalation to maintenance dose, can occur to mitigate gastrointestinal intolerance if the participant has received at least 4 consecutive doses of maintenance dose weekly.

Participants unable to tolerate the 10 mg or 15 mg despite 2 attempts with temporary dose adjustment will be discontinued from the study intervention but remain in the study for continued follow-up.

6.5.2. Semaglutide

Semaglutide is administered once-weekly by SC injection. There are no restrictions on the time of day each weekly dose of semaglutide is given, but it is advisable to administer the SC injections on the same day of the week.

Dose escalation phase

The starting dose of semaglutide is 0.25 mg for 4 weeks, then the dose is increased every 4 weeks (0.25 mg to 0.5 mg to 1.0 mg to 1.7 mg to 2.4 mg) to recommended maintenance dose of 2.4 mg. If after attempting 2.4 mg and unable to tolerate 2.4 mg, there is dosing flexibility for 1.7 mg as the maintenance dose (Section 1.2). For participants unable to tolerate any dose escalation, despite the recommended measures described in Section 4.1.3.1, the investigator should contact Lilly medical monitor to consider temporary dose adjustment to mitigate gastrointestinal intolerance in an open-label fashion to reach 2.4 mg.

If difficulty tolerating the dose despite the recommended measures described in Section 4.1.3.1

- for the initial dose, 0.25 mg, a delay in dose escalation for 4 weeks before escalation (a total of 8 weeks with 0.25 mg), and
- for doses 0.5 mg to 2.4 mg, a de-escalation to next lower dose for 4 weeks with re-escalation can occur.

A maximum of 2 cycles of temporary dose adjustment to mitigate gastrointestinal intolerance are permitted during the study, with only 1 attempt at a dose less than the recommended maintenance dose, 2.4 mg (see the Tirzepatide and Semaglutide Temporary Dose Adjustment Schedule table below). Consecutive attempts with temporary dose adjustment from the same dose will not be allowed.

If a dose adjustment occurs, then additional visits at 4-week intervals will be scheduled to allow for the dose escalation

Maintenance dose phase

It is expected most temporary dose adjustments to mitigate gastrointestinal intolerance will occur during dose escalation to reach the recommended maintenance dose, 2.4 mg. After this time, if the participant has experienced 1 or no temporary dose adjustments, 1 additional de-escalation from 2.4 mg to 1.7 mg for 4 weeks with subsequent re-escalation to 2.4 mg can occur to mitigate

gastrointestinal intolerance if the participant has received at least 4 consecutive doses of semaglutide 2.4 mg weekly.

Participants unable to tolerate the 2.4 mg despite 2 attempts with temporary dose adjustment will be allowed to remain on 1.7 mg in consultation with Lilly medical monitor. Any participant who is unable to tolerate at least 1.7 mg despite above measures will be discontinued from the study intervention but remain in the study for continued follow-up.

The table below provides a summary to timing for temporary dose adjustment to mitigate gastrointestinal intolerance, which can occur after mitigation strategies and discussion with Lilly medical monitor.

Tirzepatide and Semaglutide Temporary Dose Adjustment Schedule

Maximum 2 attempts allowed during trial	Tirzepatide	Semaglutide
Dose escalation phase (initial dose)	If unable to tolerate 2.5 mg despite mitigation will discontinue study intervention, remain in study	If unable to tolerate 0.25 mg despite mitigation, delay dose escalation by 4 weeks
Dose escalation phase (de-escalation to next lower dose for 4 weeks then re-escalation)	One attempt when dose 5 mg to 15 mg	One attempt when dose 0.5 mg to 2.4 mg
Dose maintenance phase[a] (de-escalation to next lower dose for 4 weeks then re-escalation)	One-time attempt to maintain 15 mg/10 mg (see previous table)	One-time attempt to maintain the recommended maintenance dose 2.4 mg

[a] After receiving 4 consecutive weeks of dose.

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

Tirzepatide will not be made available to participants after conclusion of the study. Semaglutide is a marketed drug for chronic weight management in adults with obesity or overweight and is currently available with a prescription.

6.7. Treatment of Overdose

Study intervention overdose, defined as taking more than the assigned dose of tirzepatide in less than 72 hours or semaglutide in less than 48 hours, will be reported as an AE. In the event of an overdose, refer to the IB for tirzepatide or the semaglutide label (Wegovy® package insert, 2023).

In the event of an overdose, the investigator should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced, and
- closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention no longer has a clinical effect or can no longer be detected systemically (at least 35 days).

6.8. Concomitant Therapy

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

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.

Study participants will be permitted to use concomitant medications that they require during the study, except certain excluded medications (see Section 5.2) that may interfere with the assessment of efficacy and safety characteristics of the study treatments. If newly initiated concomitant medication could impact efficacy and safety, clinical site staff should discuss with participant and non-study prescribing physician possible alternative options.

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

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

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

- reason for use, and
- dates of administration, including start and end dates.

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

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 Appendix 1.

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study to complete procedures for the remaining study visits, as shown in the SoA. If study intervention is discontinued, the participant will continue to follow the lifestyle program (see Section 5.3).

If a participant who discontinues study treatment prematurely declines to complete the remaining scheduled study visits, efforts should be made to have the visits converted to telephone visits. Participants should be encouraged to come back for the "last treatment visit" (Visit 20) for final collection of primary and key secondary efficacy endpoints and to complete the end-of-treatment phase procedures.

If a participant who discontinues the treatment prematurely declines to complete the remaining scheduled study visits (onsite or by telephone), then the participant should be scheduled for the early discontinuation (ED) procedures indicated in the SoA.

A participant should be permanently discontinued from study intervention if

- **participant decision**
  - the participant requests to discontinue study intervention
- **clinical considerations**
  - initiation of open-label GLP-1R agonist or DPP-4 inhibitor, if participants will not, or cannot discontinue them
  - initiation of additional approved prescription anti-obesity medication, if participants will not, or cannot discontinue them
  - has bariatric surgery or weight loss procedure
  - any female participant who becomes pregnant while participating in the study (see Section 8.3.2)
  - BMI $\leq$18.5 kg/m^2 is reached at any time during the treatment period

    Note: The investigator should contact the Sponsor CRP to discuss whether it is medically appropriate for the participant to continue study treatment.
  - significant GI symptoms despite management (Section 4.1.3.1)

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

- occurrence of any other TEAE, SAE, or clinically significant finding for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken
- diagnosis of
  - T1D
  - thyroid C-cell hyperplasia, MTC, or MEN-2 after randomization, and
  - acute or chronic pancreatitis
- an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons

- **Suicidal ideation and behavior**
  - PHQ-9 score ≥15

    Participants should be referred to a Mental Health Professional to assist in deciding whether the subject should be discontinued from study intervention. If a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the subject, at the discretion of the Investigator (in agreement with the Mental Health Professional), may be continued in the trial on randomized therapy
  - 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.
- **Hypersensitivity reactions**
  - If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

7.1.1. Liver Chemistry Stopping Criteria

Interrupting study drug based on elevated liver tests

The study drug should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.7) 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	

Resuming study drug after elevated liver tests

Resumption of the study drug 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 drug should be discontinued.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Temporary Discontinuation

In certain situations, the investigator may need to temporarily interrupt study intervention. If study intervention is interrupted, the participant will continue to follow the lifestyle program (see Section 5.3).Every effort should be made by the investigator to maintain participants on study intervention and to restart study intervention after any temporary interruption, as soon as it is

safe to do so. This may require an additional unscheduled visit to address in a timely manner. Distribution of study intervention at the correct dose will be per protocol as detailed below.

If study intervention interruption is…	then…
2 consecutive doses or less	participant restarts study intervention at last administered dose, as per escalation schedule.
3 consecutive doses or more	participant restarts study intervention (at 5 mg for tirzepatide and 0.25 mg for semaglutide) and repeats dose escalation scheme.
due to an AE	the event is to be documented and followed according to the procedures in Section 10.3 of this protocol.
due to intolerable persistent GI AE	participants should be treated as suggested in Section 4.1.3.1.

Investigators should inform Lilly medical monitor that study intervention has been temporarily interrupted. The data related to temporary interruption of study treatment will be documented.

Missed dose

If a dose of tirzepatide is missed, the participant should take it as soon as possible unless it is within 72 hours of the next dose, in which case, that dose should be skipped and the next dose should be taken at the appropriate time.

If a dose of semaglutide is missed, the participant should take it as soon as possible unless it is within 48 hours of the next dose, in which case, that dose should be skipped and the next dose should be taken at the appropriate time.

7.2. Participant Discontinuation/Withdrawal from the Study

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

- adherence to or discontinuation from study intervention
- start of another anti-obesity medication
- adherence to visit schedule
- missing assessments
- study intervention discontinuation due to AE
- development of comorbidities, and
- development of clinical outcomes.

Discontinuation is expected to be uncommon.

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

A participant may withdraw from the study

- at any time at the participant's own request
- at the request of the participant's designee, for example, legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or
- 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.

A participant will withdraw from the study:

- if a female participant becomes pregnant, or
- if participant undergoes bariatric surgery or a weight-loss procedure, for example, gastric balloon placement, during the study.

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

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

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

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

Primary

The primary efficacy measure is percent body weight change. Body weight measurements will be collected at specific clinic visits as summarized in the SoA. Methods for measuring body weight are described in Section 10.8.

Secondary

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

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

Patient-reported outcomes:

- **36-item Short Form Health Survey, Version 2, acute** (1-week recall version)

The SF-36 v2 acute 1-week recall version is a 36-item, generic, participant-administered measure designed to assess the following 8 domains:

  - Physical Functioning
  - Role-Physical
  - Bodily Pain
  - General Health
  - Vitality
  - Social Functioning
  - Role-Emotional, and
  - Mental Health.

The Physical Functioning domain assesses limitations due to health “now” while the remaining domains assess functioning “in the past week.” Each domain is scored individually and information from these 8 domains are further aggregated into 2 health

component summary scores: Physical Component Summary and Mental Component Summary. Items are answered on Likert scales of varying lengths (3-point, 5-point, or 6-point scales). Scoring of each domain and both summary scores are norm based and presented in the form of T-scores, with a mean of 50 and standard deviation of 10; higher scores indicate better levels of function and/or better health (Maruish 2011).

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

This is a patient-rated assessment of current health limitation and is rated on a 5-point scale ranging from "1 not at all limited" to "5 extremely limited." The recall is during the past week. Impaired physical function at baseline will be defined as a PGIS response at baseline of

  - moderately limited
  - very much limited, or
  - extremely limited.

See Section 3 for specific efficacy endpoints.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

For each participant, measurements including height, weight, and waist circumference should be conducted according to SoA, and following the study-specific recommendations included in Section 10.8.

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

1. cardiovascular
2. respiratory
3. GI
4. neurological systems
5. thyroid examination

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

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA and following the study-specific recommendations included in Section 10.8.

Any clinically significant findings from vital sign measurement that result in a diagnosis and that occur after the participant receives the first dose of study intervention should be reported to Lilly or its designee as an AE via CRF.

8.2.3. Electrocardiograms

For each participant, a single 12-lead digital ECG will be collected according to the SoA. Electrocardiograms must be recorded before collecting any blood samples. Participant must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake

during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will 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, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.
If a clinically significant finding is identified (including, but not limited to, changes in QT/QTc interval from baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed and must document his or her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an adverse event.

8.2.4. Clinical Safety Laboratory Tests

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

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. If repeated testing supports technical issue with a safety laboratory, the investigator is

recommended to contact the sponsor. An alignment to medical interpretation between the investigator and sponsor can occur to allow for potential additional testing as needed to satisfy prioritizing safety and limiting interruption of study intervention if appropriate.

8.2.5. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected as outlined in Sections 8.3.1 and 8.3.2.

WOCBP should be offered home urine pregnancy tests and instructed to test if any concern for pregnancy, for example, late menstrual cycle and new symptoms. WOCBP are recommended to notify site staff of positive home testing and to hold next dose of study intervention until additional testing. Positive test should be confirmed with on-site clinical serum testing.

Study intervention should not be administered after positive home urine test unless that test is confirmed (at least 2 serum tests separated by 14 days) false positive.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Patients with obesity or overweight may occasionally develop suicidal ideation or behavior.

The C-SSRS and PHQ-9 will be performed for baseline assessment of suicidal ideation and behavior and monitoring for intervention emergent 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.

8.2.6.1. C-SSRS

Columbia Suicide Severity Rating Scale is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. (The Columbia Lighthouse Project, Version 2.0)

For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

8.2.6.2. PHQ-9

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

8.2.7. Hepatic Safety Monitoring

Close hepatic monitoring

Laboratory tests (Appendix 2), including ALT, AST, ALP, TBL, D. Bil, GGT, CK, and CBC should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal, and dietary supplements, history of alcohol drinking, and other substance abuse.

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

Comprehensive hepatic evaluation

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

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

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, E; tests for autoimmune hepatitis; and an abdominal imaging study, for example, ultrasound or CT scan (see Section 10.6.1).

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

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

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

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

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

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

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

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

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	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 hours of awareness	SAE CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

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

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

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

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

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

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

8.3.2. 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

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

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

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

- hypoglycemia (Levels 2 and 3)
- thyroid malignancies and C-cell hyperplasia
- arrhythmias and cardiac conductive disorders
- hypersensitivity events
- injection site reactions
- hepatobiliary disorders
- severe GI AEs
- antidrug antibodies
- acute renal events, and
- Major depressive disorder, suicidal ideation, or suicidal behaviors.

Sites should collect additional details and data regarding these safety topics, as instructed on the applicable CRFs, and detailed below.

8.3.3.1. Hypoglycemia

All participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia. Glucose meters will be required to be provided to participants with incident T2D during the course of the trial; investigators should use the following classification of hypoglycemia:

Level 2 hypoglycemia

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

Level 3 hypoglycemia

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

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

Nocturnal hypoglycemia

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

8.3.3.2. Pancreatitis

Diagnosis of acute pancreatitis

Acute pancreatitis is an AE of interest in all studies with tirzepatide or semaglutide, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks 2006; Koizumi 2006):

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

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase
- perform imaging studies, such as abdominal CT 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.

Discontinuation for acute pancreatitis

If acute pancreatitis is diagnosed, the participant must discontinue use of the investigational products, but will continue in the study.

Case adjudication and data entry

An independent clinical endpoint committee will adjudicate all suspected cases of acute pancreatitis.

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

8.3.3.3. Thyroid Malignancies and C-Cell Hyperplasia

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

The assessment of thyroid safety during the trial will include reporting of any case of thyroid malignancy (including MTC, papillary carcinoma, and others) and measurements of calcitonin. These data will be captured in specific 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.

8.3.3.4. Calcitonin Measurements

If an increased calcitonin value (see definitions below) is observed in a participant who has been administered a medication that is known to increase serum calcitonin, then this medication should be stopped, and calcitonin levels should be measured after an appropriate washout period.

For participants who require additional endocrine assessment because of increased calcitonin concentration as defined in this section, data from the follow-up assessment will be collected in the specific section of the CRF.

Calcitonin measurements in participants with eGFR ≥60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR ≥60 mL/min/1.73 m^2 is defined below. If a participant's laboratory results meet these criteria, these clinically significant laboratory results should be recorded as an AE.

- *Serum calcitonin value ≥20 ng/L and <35 ng/L AND ≥50% increase from the screening value.* These participants will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the study intervention should be stopped, and the participant encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude any serious adverse event on the thyroid.
- *Serum calcitonin value ≥35 ng/L AND ≥50% over the screening value*. In these participants, study intervention should be stopped, and the participant recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist.

Calcitonin measurement in participants with eGFR <60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR <60 mL/min/1.73 m^2 is defined as a *serum calcitonin value ≥35 ng/L AND ≥50% over the screening value.* If a participant's labs meet these criteria, these clinically significant labs should be recorded as an AE.

In these participants, study intervention should be discontinued (after first confirming the value) and the participant recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist to exclude any serious adverse effect on the thyroid.

8.3.3.5. Major Adverse Cardiovascular Events

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

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

8.3.3.6. Deaths

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

8.3.3.7. Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG. 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.

8.3.3.8. Hypersensitivity Reactions

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

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

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2. Laboratory results are provided to the sponsor via the central laboratory.

8.3.3.9. Injection Site Reactions

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

If an ISR is reported by a participant or site staff for tirzepatide or semaglutide, the ISR CRF will be used to capture additional information about this reaction, for example

- injection site pain
- degree and area of erythema
- induration
- pruritis, and
- edema.

At the time of AE occurrence in the tirzepatide group only, samples will be collected for measurement of tirzepatide antidrug antibodies and tirzepatide concentration.

8.3.3.10. Hepatobiliary Disorders

All events of treatment-emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.2.7.

8.3.3.11. Severe Gastrointestinal Adverse Events

Tirzepatide may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the CRF/AE form. For detailed information concerning the management of GI AEs, please refer to Section 4.1.3.1

8.3.3.12. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute or worsening of chronic renal failure. Gastrointestinal

AEs have been reported with study intervention, including nausea, diarrhea, and vomiting. This is consistent with other GLP-1R agonists (Aroda and Ratner 2011). The events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Participants should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

8.3.3.13. Major Depressive Disorder, Suicidal Ideation, or Suicidal Behavior Monitoring

Participants will be monitored for Major Depressive Disorder and suicidal ideation or suicidal behaviors 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
  - have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS or
  - have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS, and
  - the ideation or behavior occurred within the past month.

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6. Genetics

A whole blood sample will be collected for genetic analysis as specified in the SoA (Section 1.3) where local regulations allow. The genetic sample collection will be discussed during informed consent and participants will designate if they agree to this optional sample collection in the informed consent document. The sample should only be collected if the participant has provided a signed ICF.

The sample collection is scheduled for Visit 11 but if this sample is missed it can be collected at another visit, and does not require fasting.

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

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 7 years after the last participant visit for the study, or for a shorter period if local regulations and/or Ethical Review Boards/Institutional Review Boards impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of tirzepatide or after tirzepatide becomes commercially available.

Molecular technologies are expected to improve during the 7-year storage period and, therefore, cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

Sample retention is described in Section 10.1.12.

8.7. Biomarkers

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

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

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

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum 7 years after the last participant visit for the study, or for a shorter period if local regulations and Ethical Review Boards impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of tirzepatide or after tirzepatide becomes commercially available for chronic weight management.

Sample retention is described in Section 10.1.12.

8.8. Immunogenicity Assessments

Exploratory biomarker samples collected during the study may be used to perform any immunogenicity-related assessments as deemed appropriate.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan will be developed and approved prior to first participant first visit, 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 primary, and key secondary endpoints.

9.1. Statistical Hypotheses

The null hypothesis corresponding to the primary objective of this study is as follows:

- **$H_{1,0}$**: tirzepatide at 15 mg or MTD (10 mg or 15 mg) is not superior to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) with respect to mean percent change in body weight from baseline at Week 72

The null hypotheses corresponding to the key secondary objectives is as follows:

- **$H_{2,0}$**: tirzepatide at 15 mg or MTD (10 mg or 15 mg) is not superior to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) for the percentage of participants who achieve ≥10% body weight reduction from baseline at Week 72
- **$H_{3,0}$**: tirzepatide at 15 mg or MTD (10 mg or 15 mg) is not superior to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) for the percentage of participants who achieve ≥15% body weight reduction from baseline at Week 72
- **$H_{4,0}$**: tirzepatide at 15 mg or MTD (10 mg or 15 mg) is not superior to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) for the percentage of participants who achieve ≥20% body weight reduction from baseline at Week 72
- **$H_{5,0}$**: tirzepatide at 15 mg or MTD (10 mg or 15 mg) is not superior to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) for the percentage of participants who achieve ≥25% body weight reduction from baseline at Week 72
- **$H_{6,0}$**: tirzepatide at 15 mg or MTD (10 mg or 15 mg) is not superior to semaglutide at 2.4 mg or MTD (1.7 mg or 2.4 mg) with respect to change in waist circumference (cm) from baseline at Week 72

Operationally, the hypotheses will be evaluated by 2-sided tests.

9.1.1. Multiplicity Adjustment

The primary and the key secondary objectives will be evaluated using both the treatment regimen and the efficacy estimands. Since the purpose for each estimand is different, multiplicity adjustment will be conducted for each estimand separately.

A prespecified graphical scheme (Bretz et al. 2009, 2011) will be implemented to control the family-wise error rate at a 1-sided alpha level of 0.025 for testing the null hypotheses stated in Section 9.1. More specifically, multiple testing adjusted p-values described by Bretz et al. (2009) will be calculated, and any hypothesis tests with a multiple testing adjusted 1-sided p-value of less than 0.025 will be considered statistically significant. This graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all endpoints (Bretz et al. 2009, 2011; Alosh et al. 2014).

The testing scheme will be fully detailed in the statistical analysis plan. Unless otherwise specified, there will be no adjustment for multiple comparisons for any other analyses outside the primary and key secondary endpoints. The testing scheme will be finalized before the first participant visit.

9.2. Analyses Sets

This table defines the analysis populations and datasets for the purposes of analysis based on the estimands defined in Section 3.

Population/Analysis Set	Description
Screened population	All participants who signed informed consent.
Randomized population	All participants who are randomly assigned to a treatment arm.
Modified intent-to-treat population (mITT)	All randomly assigned participants who are exposed to at least 1 dose of study intervention. Participants will be analyzed according to the treatment they were randomly assigned to regardless of the treatment actually received.
Efficacy Analysis Set (EAS): This analysis set will be used to estimate the efficacy estimand	Data obtained during the Treatment Period from the mITT population excluding participants who were inadvertently enrolled, excluding data after permanent discontinuation of treatment or initiation of other anti-obesity medication, bariatric surgery, or other weight management procedures.
Full Analysis Set (FAS): This analysis set will be used to estimate the modified treatment-regimen estimand	Data obtained during the Treatment Period from the mITT population excluding participants who were inadvertently enrolled, regardless of adherence to treatment and regardless of initiation of other anti-obesity medication except for non-study tirzepatide/semaglutide, bariatric surgery, or other weight management procedures.
Safety Analysis Set (SS): This analysis will be used to assess the safety of study treatment	Data obtained during the study from the mITT population, regardless of adherence to treatment and regardless of initiation of other anti-obesity medication or bariatric surgery.

9.3. Statistical Analyses

9.3.1. General Considerations

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

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05/1-sided alpha level of 0.025, unless otherwise stated, and all CIs will be given at a 2-sided (95%) level. In statistical summaries and analyses, all data will be analyzed by randomized treatment

assignment. Participants will be analyzed according to the treatment they were randomly assigned to, regardless of the treatment actually received.

Baseline is defined as the last non-missing measurement recorded on or before the randomization visit, prior to first dose of treatment, unless otherwise specified.

Efficacy analyses will use the efficacy analysis set to evaluate the efficacy estimand and the full analysis set to evaluate the modified treatment-regimen estimand. Safety will be assessed using Safety Analysis Set. Selected safety analyses may be conducted after excluding data after starting another anti-obesity medication, bariatric surgery, or other weight management procedures.

Summary statistics for continuous measures may include sample size, mean, standard deviation, median, minimum, and maximum. The analysis model to make comparisons between treatment groups relative to continuous measurements assessed over time will be an MMRM with terms for

- treatment
- visit
- treatment-by-visit interaction
- prediabetes status at randomization (yes/no)
- sex (female/male),
- baseline BMI category (<35 kg/m^2, ≥35 kg/m^2), and
- baseline measurement as a covariate.

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

Summary statistics for categorical measures, including categorized continuous measures, will include sample size, frequency, and percentages. Fisher's exact test will be used to examine the treatment difference in categorical outcomes. Logistic regression may be used to examine the treatment difference in binary efficacy outcomes. The negative binomial regression model will be used for the treatment comparison of discrete count measures if deemed appropriate.

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

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

9.3.2. Primary Endpoint Analysis

The primary endpoint for this study is percentage change from baseline in body weight to the 72-week visit (Visit 20). This endpoint will be used to evaluate the primary objective of the study for both the modified treatment-regimen and the efficacy estimands (Section 3). The null hypothesis corresponding to the primary objective is specified in Section 9.1.

The primary efficacy analysis will be guided by the modified treatment-regimen estimand and conducted using the Full Analysis Set. This assessment will analyze mean percent change in body weight obtained at the 72-week visit using an ANCOVA. Model will include terms of

treatment, prediabetes status at randomization, sex, and baseline BMI category, and baseline body weight as a covariate. For the purpose of the treatment-regimen estimand, missing body weight for participants who had bariatric surgery during the study will be imputed using the worst value (for example, highest body weight value) from baseline until the last observed value before bariatric surgery or another weight loss procedure. Missing body weight values at the 72-week visit in patients who discontinued study intervention early and did not have bariatric surgery or another weight loss procedure will be imputed based on observed data in the same treatment group from participants who had their efficacy assessed after early discontinuation of study intervention. This analysis will be conducted with multiple imputations, and statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

The primary objective based on the efficacy estimand defined in Section 3 will be evaluated using the Efficacy Analysis Set dataset (Section 9.2). The primary analysis model for body weight percent change over time will be an MMRM. The response variable of MMRM will be the mean percent change in body weight from baseline values obtained at each scheduled post baseline visit. The independent variables of the analysis model are treatment group (tirzepatide 15 mg or MTD, and semaglutide 2.4 mg or MTD), visit, and treatment-by-visit interaction, prediabetes status at randomization, sex, and baseline BMI category, and baseline body weight as a covariate. An unstructured covariance structure will model relationship of within-patient errors. If the analysis fails to converge, the following variance-covariance matrices will be used (in order) until convergence is achieved: heterogeneous compound symmetry, compound symmetry, and first-order autoregressive. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

9.3.3. Secondary Endpoints Analysis

The endpoints corresponding to the secondary study objective subject to Type 1 error rate control are specified in Section 3 under “Key Secondary” (Controlled for Type 1 error) endpoints.

The null hypotheses corresponding to the key secondary objectives can be found in Section 9.1.

Key secondary objectives will be evaluated based on the modified treatment-regimen and the efficacy estimands, similar to the primary objective.

Change from baseline in waist circumference at the 72-week visit will be conducted in a manner similar to the primary efficacy analyses (Section 9.3.2).

Body weight reductions from baseline of ≥10%, ≥15%, ≥20%, and ≥25% at Week 72 will be analyzed.

Missing body weight measurement at Week 72 will be imputed as follows:

- For the modified treatment-regimen estimand, the same imputation methods described in Section 9.3.2 will be applied.
- For the efficacy estimand, missing body weight in participants who discontinue study intervention drug early, or initiate other anti-obesity medications (AOMs) will be imputed by multiple imputation based on missing at random (MAR) assumption using the EAS.

Dichotomized data (Yes or No) will then be derived based on the continuous imputed values for each weight loss category.

A logistic regression model with terms of treatment group, baseline BMI category, sex, and prediabetes status at randomization as fixed effects, and baseline body weight as a covariate will be used. The marginal mean for each treatment group will be calculated based on g-computation (FDA guidance, May 2023), and then the benefit difference (the difference in the proportions) and relative benefit (the ratio of the proportions) will the calculated. The standard errors for these quantities will be estimated using the delta-method (Ge et al. 2011). Two-sided 95% CI and p-values will be derived.

Endpoints for additional secondary objectives are described in Section 3 and will be evaluated based on the efficacy estimand.

Additional details will be provided in the SAP.

9.3.4. Safety Analyses

Safety assessments will be conducted using the Safety Analysis Set (see Section 9.2) irrespective of adherence to study intervention and initiation of anti-obesity medication or bariatric surgery, unless indicated otherwise.

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities and reported with preferred terms and system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized Medical Dictionary for Regulatory Activities Queries. Summary statistics will be provided for incidence of TEAEs, SAEs, and study discontinuation due to AEs, study intervention discontinuation due to AEs, or deaths from the time of first dose through the end of study participation.
Counts and proportions of participants experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

9.3.4.1. Adverse Event of Special Interest

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 (see Section 8.3.3). Summaries and analyses for incidence of AESIs will be provided by treatment. The details of analysis of AESI will be provided in the SAP.

9.3.4.2. Major Depressive Disorder, Suicidal Ideation and Suicidal Behavior

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

9.3.4.3. Gastrointestinal Events

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

9.3.4.4. Events Related to Potential Abuse Liability

To identify AE terms suggestive of potential abuse liability, narrow terms from Standardized MedDRA Queries of Drug abuse and dependence (20000101) will be used. Summaries and

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

9.3.4.5. Central Laboratory Measures, Vital Signs, and Electrocardiograms

Values and change from baseline to postbaseline values of central laboratory measures and vital signs will be summarized at each scheduled visit. The analysis model to make comparisons between treatment arms relative to continuous change from baseline values assessed over time will be an MMRM, with terms: treatment, visit, and treatment-by-visit interaction, stratifying factors, and baseline measurement as covariates. An unstructured covariance structure will model relationship of within-participant errors.

9.3.5. Subgroup Analysis

Details of the subgroup analyses will be shown in the SAP. The following subgroup variables will be considered, but not limited to:

- age group: < 65 years, ≥ 65 years
- sex: female, male
- baseline BMI: <35, ≥35 kg/m^2
- race: white vs black vs other
- ethnicity: Hispanic vs not Hispanic, and
- glycemic status at randomization (normoglycemia vs prediabetes).

9.4. Interim Analysis

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

9.5. Sample Size Determination

Approximately 700 participants (350/group) will be randomly assigned in a 1:1 ratio to each study arm.

For the treatment-regimen estimand, this sample size provides approximately 90% power to show that tirzepatide 15 mg or MTD is superior to semaglutide 2.4 mg or MTD in the mean percent change from baseline at Week 72 using the following assumptions:

- a 2-sample t-test with a 2-sided significance level of 0.05
- a study intervention discontinuation rate of 20% resulting in a common SD of 12%, and
- a 3% treatment difference.

For the efficacy estimand, this sample size also provides at least 90% power to show that tirzepatide 15 mg or MTD is superior to semaglutide 2.4 mg or MTD in the mean percent change from baseline at Week 72 using the following assumptions:

- a 2-sample t-test with a 2-sided significance level of 0.05
- a common SD of 10%
- a 3% treatment difference, and
- study intervention discontinuation rate of 20%.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - applicable ICH GCP Guidelines, and
  - applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents, for example, advertisements, must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
  - reporting 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 participant, or the participant's legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.4. Data Protection

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

10.1.5. Committees Structure

Prospective adjudication of major adverse cardiovascular events, pancreatic AEs, and deaths will be performed for this study.

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 trial, after anonymization, with the exception of pharmacokinetic 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, statistical analysis plan, clinical study report, and blank, or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal.

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

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically, for example, laboratory data. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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

Data Capture System

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

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

Additionally, COA data (clinician-focused outcome instrument) for suicidality assessments and weight history questionnaire will be collected by the authorized study personnel, via a paper source document and will be transcribed by the authorized study personnel into the EDC system.

Additionally, COA data (participant-focused outcome instrument) will be directly recorded by the participant, into an instrument, for example, hand-held smart phone, or tablet. The COA data

will serve as the source documentation, and the investigator does not maintain a separate written or electronic record of these data.

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

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

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

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on 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 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 site open and is considered the first act of recruitment and will be the study start date.

Study or site termination

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

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

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

For study termination

- discontinuation of further study intervention development

For site termination

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

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

10.1.10. Publication Policy

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

10.1.11. Investigator Information

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

10.1.12. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3298176 or after LY3298176 become(s) commercially available.

Sample Type	Custodian	Maximum Retention Period after Last Patient Visit[a]
Genetics	Sponsor or designee	7 years
Exploratory biomarkers	Sponsor or designee	7 years
Tirzepatide antidrug antibodies (ADA)[b]	Sponsor or designee	15 years

Abbreviation: ADA = antidrug antibody

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

[b] Sample collection only for hypersensitivity and injection site reactions.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory unless designated as local in the SoA and in the table below.

- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing, in the table below, the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.
- In the event that the site needs to collect laboratories for urgent medical evaluation, local laboratories should be completed as necessary. It is requested that simultaneous samples are collected for laboratories to be analyzed by the central laboratory if possible.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Differential	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	

Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Lipid Panel	
High-density lipoprotein (HDL-C)	Generated by Lilly-designated laboratory.
Low-density lipoprotein (LDL-C)	Generated by Lilly-designated laboratory. If triglycerides are >400; LDL will be measured.
Very low-density lipoprotein (VLDL-C)	
Cholesterol	Assayed by Lilly-designated laboratory.
Triglycerides	Assayed by Lilly-designated laboratory.
Hormones (female)	
Serum pregnancy	Assayed by Lilly-designated laboratory.
Urine pregnancy	Assayed and evaluated locally.
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory.
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI) calculated using creatinine	Results will not be provided to the investigative sites.
eGFR (CKD-EPI) calculated using cystatin-C	Results will not be provided to the investigative sites.
eGFR (CKD-EPI) calculated using creatinine and cystatin-C	
Additional Testing	Assayed by Lilly-designated laboratory.
HbA1c	
Thyroid-stimulating hormone (TSH)	
Insulin	
Cystatin-C	
Calcitonin	
Pancreatic amylase	
Lipase	
Stored Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Genetics sample (whole blood)	
Exploratory biomarker samples	
Serum	

Whole blood (epigenetic sample)	
Plasma (EDTA)	
Plasma (P800)	

Abbreviations: CKD-EPI = Chronic kidney disease epidemiology; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate.

10.2.1. Appendix 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	Preferred Sample Type[a]	Laboratory Test[b]
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.	Serum	Total tryptase
	Serum	Complements (C3)
	Plasma	Complements (C3a and C5a)
	Serum	Cytokine panels (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.	Serum	LY3298176 ADA
	Plasma	LY3298176 concentration

Abbreviations: ADA = antidrug antibodies; C = complement component; IL = interleukin.

[a] Sample type may be different depending on local requirements.

[b] 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 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.

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 or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure, for example, endoscopy and appendectomy: the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:
a. Results in death
b. Is life-threatening The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability or incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly or birth defect

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

f. Other situations:

- Medical or scientific judgment should be exercised 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 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

10.3.3. Definition of Product Complaints

Product Complaint

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  - deficiencies in labeling information, and
  - use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

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

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

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

Assessment of Intensity

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

- Mild: A type of adverse event 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 adverse event 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 adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. 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 and/or Product Information, for marketed products, in their assessment
- For each AE/SAE, the investigator **must** document in the medical notes that he or she has reviewed the AE/SAE and has provided an assessment of causality
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 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 post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on an SAE paper form (see next section) or to the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the study training materials.

SAE Reporting via Paper Form

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

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information, for example, summary or listing of SAEs, from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
WOCBP	Adult females are considered WOCBP unless they are WNOCBP.
WNOCBP	Females are considered WNOCBP if they • have a congenital anomaly such as Mullerian 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 • 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 an FSH >40 mIU/mL • 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, Selective Estrogen Receptor Modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

Guidance for women

WOCBP and WNOCBP may participate in this trial.

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 for at least the duration of the trial and 30 days after the last dose of the study intervention. Note: Females who had bilateral tubal ligation should use a second form of contraception.

Examples of different forms of contraception

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization, for example, bilateral tubal ligation • 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, or
	• barrier method with use of a spermicide
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide
	Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, or female condom with spermicide) to be considered effective.

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

Guidance for men

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for 5 half-lives plus 90 days
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 5 half-lives plus 90 days
Contraception for men in exclusively same-sex relationships, as their preferred, and usual lifestyle	Are not required to use contraception

Examples of highly effective, effective, and unacceptable methods of contraception

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives

	• injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  o condom with spermicide
	  o diaphragm with spermicide, or
	  o female condom with spermicide
	
	Note: The barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, and female condom with spermicide) to be considered effective.

Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • post coital douche • lactational amenorrhea

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity, and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to study intervention or obesity and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to study intervention and/or interventions of this drug class and obesity. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the 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 study intervention or study interventions of this class or indication continues but no longer than the sample retention limits described in Section 10.1.12, or other period as per local requirements.

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

10.6.1. Hepatic Evaluation Testing

See Section 8.2.7 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.

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)	**Hepatis 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	Hepatitis B core IgG antibody
Basophils	HBV DNA[a]
Eosinophils	**Hepatis C virus (HCV) testing:**
Platelets	HCV antibody
Cell morphology (RBC and WBC)	HCV RNA[a]
Hepatic Clinical Chemistry Panel	**Hepatitis D virus (HDV) testing:**
Total bilirubin	HDV 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	

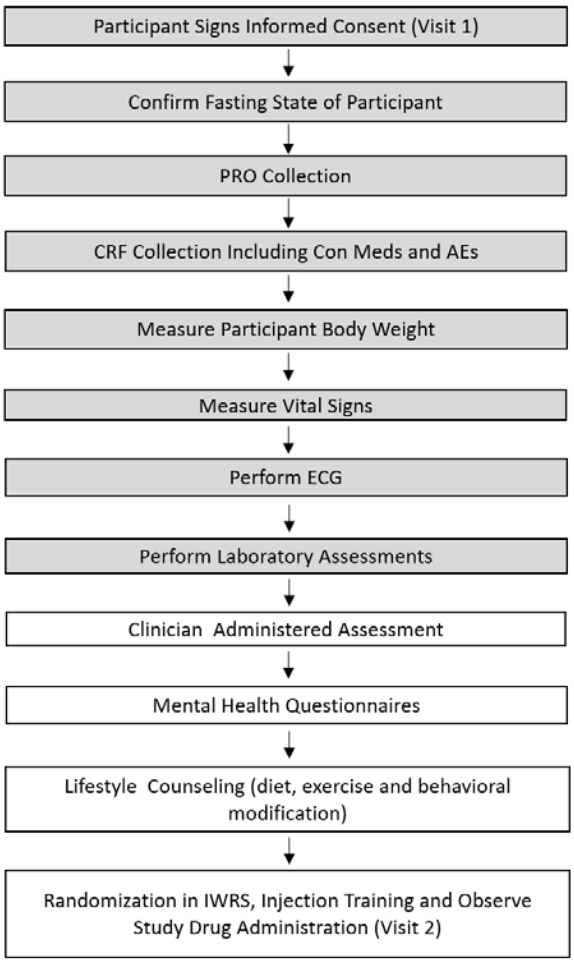
Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Epstein-Barr virus (EBV) testing:**
Acetaminophen protein adducts	EBV antibody
Alkaline phosphatase isoenzymes	EBV DNA[a]
Ceruloplasmin	**Cytomegalovirus (CMV) testing:**
Copper	CMV antibody
Ethyl alcohol (EtOH)	CMV DNA[a]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

[a] Reflex or 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: Suggested Visit Structure



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

Abbreviations: AE = adverse event, con meds = concomitant medicines; CRF = case report form; ECG = electrocardiogram; IWRS = interactive web response system; PRO = patient-reported outcomes.

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

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

Measuring height

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

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

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

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

Measuring weight

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

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

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

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

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

Measuring waist circumference

- Waist circumference should be measured in the horizontal plane and at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.

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

Step 1. Ask the participant to wear light clothing (if available, patient gowns could also be used). Measurement should be completed over light clothing or gown. If this is not possible or is impairing accuracy, then measurement can be completed directly over skin. The same approach should be used for each time waist circumference is measured in the study.

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

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

Vital sign measurements (blood pressure and heart rate)

- Vital sign measurements (BP and heart rate, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing
- The participant should sit quietly for 5 minutes before vital signs measurements are taken
- For each parameter, 3 measurements will be taken using the same arm, preferably the nondominant arm
- The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and BP needs to be recorded in the CRF
- Blood pressure must be taken with an automated BP instrument
- If BP and pulse measurements are taken separately, pulse should be taken prior to BP.

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

Electrocardiogram

- All digital ECGs will be obtained using local ECG machines.
- 12-lead ECGs should be obtained after the participant has rested in a supine position for 5 to 10 minutes.
- Electrocardiograms should be collected prior to collection of blood samples for laboratory testing.

10.9. Appendix 9: World Health Organization Classification of Diabetes and American Diabetes Association Diagnostic Criteria

Type 1 Diabetes: Type 1 diabetes is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary not only to control hyperglycemia but also to prevent spontaneous ketosis and death.

Type 2 Diabetes: Type 2 diabetes, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, and weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in Type 2 diabetes but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness, for example, severe infection or mesenteric artery thrombosis, due to an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with Type 2 diabetes later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998). For this study, the diagnosis of prediabetes and T2D will be consistent with ADA recommendations. The T2D diagnosis requires classic symptoms of hyperglycemia with a random plasma glucose ≥ 200 mg/dL or 2 abnormal tests from the same sample or in 2 separate test samples.

ADA Criteria for the diagnosis of diabetes

- FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours. *OR*
- 2-hour PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. *OR*
- A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. *OR*
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

(ADA, 2022)

Abbreviations: DCCT = Diabetes Control, and Complications Trial; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test; WHO = World Health Organization; 2-h PG = 2-h plasma glucose.

ADA Criteria for the diagnosis of prediabetes

- FPG 100 mg/dL to 125 mg/dL *OR*
- 2-hour PG during 75 gm OGTT 140 mg/dL to 199 mg/dL *OR*
- HbA1c 5.7-6.4%.

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 requirements in which notification is required, for example, upon implementation, and suspension of changes. All approvals and notifications must be retained in the study records.

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

Considerations for making a change

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

Informed consent

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

- participation in remote visits, as defined in Section "Remote Visits"
- 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

- adverse events
- concomitant medications
- review of study participant diary (including study intervention compliance)
- review diet and exercise goal log
- review home weight
- C-SSRS (Since Last Visit Version), and
- PHQ-9.

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 product complaints remain unchanged.

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for lipid samples. 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 ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site, for example, participant's home, the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality, that is, storage conditions maintained, and intact packaging upon receipt.
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

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

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

Adjustments to visit windows

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

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 1 (screening)	No change

Visit 2	Within 90 days after Visit 1
Visit 3 through 7	Within 7 days before or after the intended date
Visit 8 through 20	Within 14 days before or after the intended date
Visit 20	Within 14 days before the intended date, or up to 28 days after the intended date

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

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing or 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 antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
BMR	basal metabolic rate
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
COA	clinical outcome assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computerized tomography

D. Bil	direct bilirubin
DCCT	Diabetes Control and Complications Trial
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
ED	early discontinuation
EDC	electronic data capture system
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
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIPR	GIP receptor
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
HbA1c	hemoglobin A1c
HRT	hormone replacement therapy
IB	Investigator's Brochure
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.
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."
IP	investigational product
IRB/IEC	Institutional Review Board/Institutional Ethics Committee
ISR	injection site reaction
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
LDL	low-density lipoprotein
MDD	major depressive disorder
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 errors generally involve a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MEN-2	multiple endocrine neoplasia Type 2
MI	myocardial infarction
MMRM	mixed model for repeated measures

MTC	medullary thyroid cancer
MTD	maximum-tolerated dose
NAFLD	nonalcoholic fatty liver disease
NGSP	National Glycohemoglobin Standardization Program
OGTT	oral glucose tolerance test
participant	Equivalent to Clinical Data Interchange Standards Consortium 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
PG	plasma glucose
PGIS Physical Activity	Patient Global Impression of Status for Physical Activity
PK/PD	pharmacokinetics/pharmacodynamics
PHQ-9	Patient Health Questionnaire-9
PPS	per-protocol set: The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PT-INR	prothrombin time-international normalized ratio
QTc	corrected QT interval
QTL	quality tolerance limits
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
SF-36 v2	Short Form Health Survey Version 2
SIB	suicide ideation and behavior
SoA	Schedule of Activities

T1D	Type 1 diabetes
T2D	Type 2 diabetes
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TEE	total energy expenditure
TSH	thyroid-stimulating hormone
UACR	urine albumin creatinine ratio
ULN	upper limit of normal
VLDL	very low-density lipoprotein
WOCBP	women of childbearing potential
WNOCBP	women not of childbearing potential

10.12. Appendix 12: Protocol Amendment History

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

Amendment [b]: 20-Jun-2023

Overall Rationale for the Amendment:

The protocol is being amended from a global study to a US only study and language related to non-US countries is being removed. This amendment includes updates to the study intervention dispensing strategy that were previously included in a US only addendum. The goal of the addendum was reducing site inventory management burden and adding flexibility for participants with direct-to-participant study intervention access. A genetics sample collection has also been added to the protocol. The collection will be offered during informed consent and participants will designate if they agree to this optional sample collection in the informed consent document.

Clarifications and additional changes are outlined in the table below.

Section # and Name	Description of Change	Brief Rationale
Throughout	Updated “study drug” and “study treatment” to “study intervention”	For consistency
Throughout	Updated “participant diary” to “electronic diary”	Clarification
1.3 Schedule of Activities (SoA)	Participant Diary: Updated “Participant Diary” to “Participant Electronic Diary” and updated “Diary review” to “Electronic diary review”	Clarification
	Added new section “Participant Paper 3-day Diet and Exercise Log”, including rows for “Dispense paper log” and “Paper log review” and removed “Diet and exercise paper log review” row	Clarification
	Stored Samples: Added a row for “Genetics”	Genetic sample will be collected at Visit 11

Section # and Name	Description of Change	Brief Rationale
	Randomization and Dosing: "Register visit with IWRS" row: removed X from all visits after Visit 2	Updated to align with new study intervention dispensing strategy
	Removed "via IWRS" from Dispense study intervention and removed X from all visits after Visit 2	Updated to align with new study intervention dispensing strategy
	Updated "Dispense study drug to participant (for at-home dosing)" row to "Site transmits study intervention prescription for central pharmacy study intervention dispensing" starting at Visit 3 and updated frequency to every 4 weeks	Updated to align with new study intervention dispensing strategy
	Removed language about returning ancillary supplies from "participant returns study drugs and ancillary supplies" row and moved information about ancillary supplies being resupplied from central pharmacy to "Dispense ancillary supplies to participant" row	Updated to align with new study intervention dispensing strategy
2.3 Benefit/Risk Assessment	Removed reference to summary of product characteristics	The US package insert contains the information
4.1.2.2 Treatment Period	**End of Visit 2 to Visit 8** Removed language about demonstration device and added a reference to instructions for use	Demonstration device will no longer be used for injection training
	End of Visit 8 to Visit 20 Added information about study intervention prescription transmission to central pharmacy	To align with new study intervention dispensing strategy
6.1 Study Intervention(s) Administered	Removed EU authorization information	This information is no longer needed
6.2.1 Investigator Site Responsibilities	A new section has been added to describe investigator site responsibilities for study intervention	For clarity
6.2.2 Preparation, Handling,	A new section has been added with additional information about direct-to-participant study intervention access.	Updated to align with new study intervention dispensing strategy

Section # and Name	Description of Change	Brief Rationale
Storage, and Accountability		
6.3 Measures to Minimize Bias: Randomization and Blinding	Removed country, added "(yes, no)" to prediabetes status, and added baseline BMI to the list of stratification criteria	The study will only include sites in the US
6.5 Dose Modification	Added instruction that the participant will continue to follow the lifestyle program if study intervention is interrupted	Clarification
7.1 Discontinuation of Study Intervention	Added instruction that the participant will continue to follow the lifestyle program if study intervention is discontinued	Clarification
7.1.3 Temporary Discontinuation	Added instruction that the participant will continue to follow the lifestyle program if study intervention is interrupted	Clarification
	Removed reference to IWRS for distributing study intervention at the correct dose	Updated to align with new study intervention dispensing strategy
	Removed instruction to enter data related to temporary interruption of study treatment on the CRF	The information will be documented in source documents
8.2.4 Clinical Safety Laboratory Tests	Additional information has been added about repeated testing for safety laboratory tests and recommendation to contact the sponsor if technical issues arise	To provide clarification about resolving technical issues with safety laboratory tests
8.2.7 Hepatic Safety Monitoring	CBC has been added to the list of laboratory tests to be repeated to confirm abnormality	Based upon recent guidance on hepatic monitoring
8.3.3 Adverse Events of Special Interest	Updated "depression" to "major depressive disorder" and updated "behavior monitoring" to "suicidal behaviors"	For consistency with the SURMOUNT program
8.3.3.9 Injection Site Reactions	Added a clarification that ISR information is collected for both tirzepatide and semaglutide	Clarification
8.3.3.13 Major Depressive Disorder, Suicidal	Updated title of Section from "Depression, Suicidal Ideation, or Behavior Monitoring" to "Major Depressive Disorder, Suicidal Ideation, or Suicidal Behavior Monitoring"	For consistency with the SURMOUNT program

Section # and Name	Description of Change	Brief Rationale
Ideation, or Suicidal Behavior Monitoring		
8.6 Genetics	Added additional information about optional genetics sample collection	To align with the genetics sample collection at Visit 11
	Added “obesity-related diseases”	For consistency with the SURMOUNT program
8.7 Biomarkers	Updated information about biomarker research and collection	To provide additional information
9.3.1 General Considerations	Removed geographic area from the analysis model and added baseline BMI category in the model.	This study will only include sites in the US
9.3.2. Primary Endpoint Analysis	Removed geographic area from the analysis model and added baseline BMI category in the model.	This study will only include sites in the US
9.3.3 Secondary Endpoints Analysis	Removed geographic area from the analysis model and added baseline BMI category in the model.	This study will only include sites in the US
	Updated analysis method for categorical endpoints	Alignment with regulatory guidance and considerations for missing data imputation
9.3.4.2 Major Depressive Disorder, Suicidal Ideation and Suicidal Behavior	Updated title of Section from “Depression, Suicidal Ideation and Behavior” to “Major Depressive Disorder, Suicidal Ideation and Suicidal Behavior”	For consistency with the SURMOUNT program
10.1.5 Committees Structure	Added deaths to the list of events that will be adjudicated by an independent committee	To align with Section 8.3.3
10.2 Appendix 2: Clinical Laboratory Tests	Updated the “Genetics Sample” section to “Stored Samples”, moved “Exploratory biomarker samples” to “Stored Samples” section, and added whole blood for genetics and epigenetic samples.	To align with the genetics sample collection at Visit 11

Section # and Name	Description of Change	Brief Rationale
10.4.2 Contraception Guidance	Added "bilateral tubal ligation" as an example of female sterilization	Clarification
10.10 Appendix 10: Country-Specific Requirements	This section has been removed.	This study will only include sites in the US
11. References	Additional references have been added	To align with content added to Section 9.3.3
	Reference for Wegovy SMPC has been removed	This information is no longer needed in Section 2.3
	Reference for Wegovy package insert has been updated	To reflect the most recent information

Amendment [a]: 29-Jul-2022

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The purposes for this amendment are outlined in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities (SoA)	Corrected format issue regarding ECG schedule	Error correction
	Added language to distinguish paper log from electronic diary	For clarity
	Added separate line for paper log review	
	Added line for weight history questionnaire	To specify when questionnaire should be administered
	Added line for study intervention injection training	To specify when training should occur
Section 4.1. Overall Design	Corrected statement as follows:	Error correction

Section # and Name	Description of Change	Brief Rationale
	"Study GPHJ is a Phase 3b, multicenter, randomized, parallel-arm, open-label, comparator-controlled, 72-week trial that will investigate the efficacy and safety of 15 mg or MTD tirzepatide…"	
Section 5.3.1. Meals and Dietary Restrictions	Modified statement as follows: "Additionally, if a BMI ≤22 kg/m^2 is reached in participants receiving tirzepatide, the site physician should contact Lilly for consideration of a single dose reduction for remainder of trial (for example, 15 mg to 10 mg or 10 mg to 5 mg)."	Modification to improve participant experience and limit IP discontinuation and to reduce potential safety risk of reaching below the normal BMI range
Section 8.2.6. Suicidal Ideation and Behavior Risk Monitoring	Corrected statement to read as follows: "The C-SSRS and PHQ-9 will be performed for baseline assessment of suicidal ideation and behavior and monitoring for intervention emergent suicidal ideation and behavior."	For clarity
Section 8.3.3.10. Antidrug Antibodies	Removed original section	To clarify that antidrug antibodies are only being collected for hypersensitivity or injection site reactions
Section 8.6. Genetics	Corrected sample retention period from 15 years to 7 years	Error correction
Section 8.8. Immunogenicity Assessments	Replaced wording in section with the following: "Exploratory biomarker samples collected during the	To clarify that immunogenicity assessments may occur

Section # and Name	Description of Change	Brief Rationale
	study may be used to perform any immunogenicity-related assessments as deemed appropriate."	
Section 10.1.7. Data Quality Assurance	Added reference to weight history questionnaire in Data Capture System subsection	To note that data from questionnaire will be collected by authorized study personnel
Section 10.1.12. Sample Retention	Revised "Hypersensitivity (ADA) samples" to "Tirzepatide antidrug antibodies (ADA)[b]" and defined footnote b	To clarify that antidrug antibodies are only being collected for hypersensitivity or injection site reactions
Section 10.2. Appendix 2. Clinical Laboratory Tests	Removed first bullet: "Local laboratory results…must be recorded" and added bullet: "In the event…if possible."	To modify laboratory language in response to site feedback
Section 10.2.1. Appendix 10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event	Separated complements C3 and C3a/C5a into their correct sample types	Error correction
Section 10.5. Appendix 5. Genetics	Replaced incorrect sample retention period (15 years) with reference to section 10.1.12	
Section 10.7. Appendix 7. Suggested Visit Structure	Corrected diagram by switching first and second boxes	
Throughout	"Telehealth" corrected to "telephone"	To align with current study language
Throughout	Minor editorial changes	For clarity

11. References

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