Protocol I8F-MC-GPIL

An Open-Label, Single-Arm, Phase 4 Study to Assess Glycemic Control When Adults with Type 2 Diabetes Switch from a GLP-1 RA to Tirzepatide (SURPASS-SWITCH-2)

NCT05706506

Approval Date: 26-Aug-2022

Title Page

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Protocol Number: I8F-MC-GPIL

Amendment Number: This is the initial protocol.

Compound: LY3298176

Brief Title: A study to investigate glycemic control in adults with type 2 diabetes switching to tirzepatide from a GLP-1 RA

Study Phase: 4

Acronym: SURPASS-SWITCH-2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 128801

EudraCT: 2022-002708-18

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

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Medical Monitor Name and Contact Information will be provided separately.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: An Open-Label, Single-Arm, Phase 4 Study to Assess Glycemic Control When Adults with Type 2 Diabetes Switch from a GLP-1 RA to Tirzepatide (SURPASS-SWITCH-2)

Brief Title: A study to investigate glycemic control in adults with type 2 diabetes switching to tirzepatide from a GLP-1 RA

Regulatory Agency Identifier Number(s):

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Rationale:

No study has investigated the effects of switching from glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapy to tirzepatide in people with type 2 diabetes (T2D). This study will inform providers on what to expect when switching from a GLP-1 RA to tirzepatide 5 mg but does not evaluate long-term efficacy, optimal dosing, or comparative improvement to other regimens.

Prior exposure to a GLP-1 RA is associated with less frequent gastrointestinal (GI) intolerance when switching between GLP-1 RAs. Therefore, this study will describe an alternative way to switch from a GLP-1 RA to tirzepatide by using a starting dose of 5 mg and will evaluate changes in glycemic control, body weight, and GI tolerability occurring in the first 12 weeks for the targeted study population.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To demonstrate that participants with T2D switching from a stable dose of GLP-1 RA to tirzepatide 5 mg QW have an improvement in HbA1c at Week 12 compared to baseline	• Change from baseline in HbA1c

Secondary	
To evaluate the changes in CGM-assessed TAR from baseline at Week 4 and at Week 12	Change from baseline in • Percentage of time per day that CGM-derived values are >180 mg/dl (10 mmol/L) • Duration of time in minutes per day that CGM-derived values are >180 mg/dl (10 mmol/L)
To evaluate the change in FSG from baseline at Week 12	• Change from baseline in FSG
To evaluate the changes from baseline in weight at Week 12	• Change from baseline in weight

Abbreviations: CGM = continuous glucose monitoring; FSG = fasting serum glucose; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c; QW = once-weekly; T2D = type-2 diabetes; TAR = time above range (>180 mg/dl or >10 mmol/L).

The primary estimand in this study is the efficacy estimand.

The efficacy estimand focuses on the treatment effect if participants continued to receive the study treatment without prohibited medication. This estimand will be used in publications to inform prescribers or physicians.

Overall Design

SURPASS-SWITCH-2 is an open-label, single-arm, multicenter, multinational, Phase 4 study to assess the changes in glycemic control when switching from a stable dose of a GLP-1 RA directly to tirzepatide 5 mg in participants with T2D.

This study includes a screening period and a 12-week treatment period.

Brief Summary:

Period I: Screening

Preparation for the switch from GLP-1 RA medication to tirzepatide

The investigator will determine the participant's current GLP-1 RA medication administration schedule to ensure the correct timing for initiating tirzepatide 5 mg at Visit 2.

Investigators should ensure that at least 12 days occur between Visit 1 and Visit 2 to allow for an adequate CGM data collection.

Participants taking daily liraglutide at screening should continue taking liraglutide up to the day prior to Visit 2.

Participants taking either weekly dulaglutide or semaglutide should take their last dose of GLP-1 RA medication at least 3 days prior to Visit 2 but no more than 10 days prior to Visit 2.

Training for the study-supplied SMBG monitor and testing frequency recommendations will occur. Training for the CGM sensor and insertion device, including suggestions for successful device maintenance, will also occur in conjunction with the insertion of the CGM sensor for the baseline measurement session.

Period II: Treatment period

Visit 2 Treatment Initiation

Participants arrive to the clinic in the fasting state.

This is the general flow for Visit 2

- Participant returns screening CGM sensor for compliance review and data upload
- Study personnel confirm enrollment criteria
- Study personnel complete all required visit procedures, including the collection of vital signs, all baseline procedures, and sample collection, and
- Treatment initiation for eligible participants.

Study intervention training

Study personnel will provide appropriate training for use of the tirzepatide SDP. The training can be provided using a demonstration device, if available. This training will be repeated at subsequent visits, as needed.

In addition, study personnel will provide product-specific "instructions for use" information to the participants upon request, if available.

First tirzepatide dose

Study personnel will observe as the participant injects the first dose of tirzepatide. The remaining injections will occur at participant's home. The date and time of the first dose of tirzepatide should be recorded on the CRF. Additionally, all medication doses administered at home should be captured, including date and time, in the participant's diary and subsequently recorded in the CRF.

Visit 5 (Week 12) Treatment Period or ED Visit

The investigator will determine a participant's transition from study treatment to another diabetes treatment, including re-initiation of baseline GLP-1 RA.

Study Population:

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

- Are 18 years old or of an acceptable age to provide informed consent according to local regulations, whichever is older.
- Have been diagnosed with T2D based on the World Health Organization classification or other locally applicable diagnostic standards.
- Have an HbA1c ≥6.5% (≥48 mmol/mol) to ≤9.0% (≤75 mmol/mol) as determined by the central laboratory at Visit 1 and in the opinion of investigator may benefit from tirzepatide based on individual patient needs.

- Have been on a stable treatment dose of 1 of the listed GLP-1 RAs for ≥3 months prior to Visit 1:
    - liraglutide 1.2 or 1.8 mg QD
    - dulaglutide 0.75, 1.5, 3, or 4.5 mg QW, or
    - injectable semaglutide 0.5, 1, or 2 mg QW
- No treatment with oral antihyperglycemic medication (OAM) or on stable doses (for at least 3 months before Visit 1) of up to 3 OAM. The OAM may include metformin (at least 1000 mg/day), SGLT-2i, thiazolidinediones, or α-glucosidase inhibitors.
- Have BMI ≥25 kg/m^2 at Visit 1.
- Are reliable and willing to make themselves available for the duration of the study and are willing and able to follow study procedures as required, including compliance with CGM sensor and insertion device.

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

- Have type 1 diabetes.
- Have a history of chronic or acute pancreatitis any time prior to Visit 1.
- Have a clinical history of
    - proliferative diabetic retinopathy
    - diabetic maculopathy, or
    - nonproliferative diabetic retinopathy that requires acute treatment.
- Are at high risk for cardiovascular disease in the investigator's opinion or have a history of any of these cardiovascular conditions within 60 days prior to Visit 1:
    - myocardial infarction
    - percutaneous coronary revascularization procedure
    - carotid stenting or surgical revascularization
    - nontraumatic amputation
    - peripheral vascular procedure (e.g., stenting or surgical revascularization)
    - cerebrovascular accident (stroke), or
    - hospitalization for congestive heart failure
- Have New York Heart Association Functional Classification Class IV congestive heart failure.
- Have a history of ketoacidosis or hyperosmolar state or coma.
- Have a history of severe hypoglycemia or hypoglycemia unawareness within the 6 months prior to Visit 1.

Number of Participants:

The study will enroll approximately 150 participants.

Intervention Groups and Duration:

Participants will be administered with tirzepatide 5 mg once-weekly by subcutaneous injection using a single-dose pen.

Ethical Considerations of Benefit/Risk:

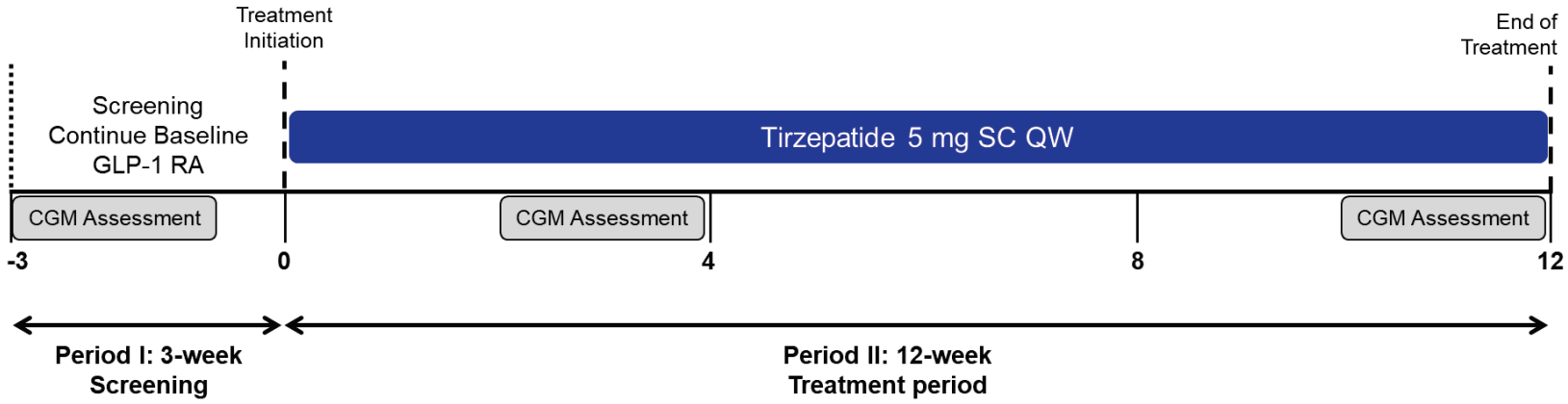
The safety information from the tirzepatide Phase 3 clinical studies is similar to the known safety information as the GLP-1 RA therapies.

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

Considering the information available from previous completed clinical studies in people, and the measures taken to make sure the participants in this study are safe, the potential risks from taking tirzepatide are justified by the potential benefits for adults with T2D.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: CGM = continuous glucose monitoring; GLP-1 RA = glucagon-like peptide-1 receptor agonist; QW = once weekly; SC = subcutaneous.

1.3. Schedule of Activities (SoA)

Screening

Visit 1 may be conducted over more than 1 day to ensure necessary conditions are met.

Fasting visits

Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity before the visit.

If a participant attends a fasting visit in the non-fasting state, the sample should still be collected, and reschedule the fasting laboratory sample collection. This will not be considered a protocol deviation.

Study I8F-MC-GPIL	**Period I - Screening**	**Period II - Treatment Period**					**Comments**
Visit Number	1	2	3	4	5	ED	ED = early discontinuation
Week Relative to Study Intervention Start	-3	0	4	8	12	—	
Visit Interval Tolerance (Days)	+3/-7	0	±3	±3	±3		Flexibility is built into the screening visit to ensure adequate CGM session and appropriate timing for stopping the baseline GLP-1 RA and initiating tirzepatide at Visit 2; see Section 4.1.1.
Fasting Visit		X			X	X	
Informed consent	X						The informed consent form must be signed before any protocol-specific tests or procedures are performed. See Section 10.1.3 for additional details.

Study I8F-MC-GPIL	**Period I - Screening**	**Period II - Treatment Period**					**Comments**
Visit Number	1	2	3	4	5	ED	ED = early discontinuation
Week Relative to Study Intervention Start	-3	0	4	8	12	—	
Visit Interval Tolerance (Days)	+3/-7	0	±3	±3	±3		Flexibility is built into the screening visit to ensure adequate CGM session and appropriate timing for stopping the baseline GLP-1 RA and initiating tirzepatide at Visit 2; see Section 4.1.1.
Fasting Visit		X			X	X	
Inclusion and exclusion criteria, review and confirm	X	X					Confirm inclusion and exclusion criteria prior to administration of first dose of study intervention.
Demographics	X						Includes ethnicity (where allowed), year of birth, sex, and race.
Preexisting conditions and medical history, including relevant surgical history	X						Collect all conditions ongoing and relevant past surgical and medical history.
Prior treatments for indication	X						Add details of T2D medication, which includes medications used for T2D since diagnosis.
Substance use (alcohol, caffeine, tobacco use)	X						
Concomitant medications	X	X	X	X	X	X	See Section 6.8.

Study I8F-MC-GPIL	**Period I - Screening**	**Period II - Treatment Period**					**Comments**
Visit Number	1	2	3	4	5	ED	ED = early discontinuation
Week Relative to Study Intervention Start	-3	0	4	8	12	—	
Visit Interval Tolerance (Days)	+3/-7	0	±3	±3	±3		Flexibility is built into the screening visit to ensure adequate CGM session and appropriate timing for stopping the baseline GLP-1 RA and initiating tirzepatide at Visit 2; see Section 4.1.1.
Fasting Visit		X			X	X	
Adverse events (AEs)	X	X	X	X	X	X	AEs are any events that occur after signing the informed consent. Collect additional data for safety topics of special interest. See Section 8.3.3.
Physical Evaluation							
Height	X						See Section 10.7, Appendix 7
Weight	X	X	X	X	X	X	See Section 10.7, Appendix 7
Waist circumference	X	X	X	X	X	X	See Section 10.7, Appendix 7
Vital signs	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 collection of blood samples for laboratory testing. See Section 8.2.2.

Study I8F-MC-GPIL	**Period I - Screening**	**Period II - Treatment Period**					**Comments**
Visit Number	1	2	3	4	5	ED	ED = early discontinuation
Week Relative to Study Intervention Start	-3	0	4	8	12	—	
Visit Interval Tolerance (Days)	+3/-7	0	±3	±3	±3		Flexibility is built into the screening visit to ensure adequate CGM session and appropriate timing for stopping the baseline GLP-1 RA and initiating tirzepatide at Visit 2; see Section 4.1.1.
Fasting Visit		X			X	X	
Physical examination	X						Excludes pelvic, rectal, and breast examinations unless clinically indicated. See Section 8.2.1.
Symptom-directed physical assessment		X					Symptom-directed physical assessment 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.
12-lead ECG (local)	X						Collect ECG before blood sample collection for laboratory testing if these procedures occur at the same visit. Participants should be supine for approximately 5 to 10 min before ECG collections and remain supine but awake during the ECG collection. ECG may be repeated at the investigator's discretion at any visit. See Section 8.2.3.

Study I8F-MC-GPIL	Period I - Screening	Period II - Treatment Period					Comments
Visit Number	1	2	3	4	5	ED	ED = early discontinuation
Week Relative to Study Intervention Start	-3	0	4	8	12	—	
Visit Interval Tolerance (Days)	+3/-7	0	±3	±3	±3		Flexibility is built into the screening visit to ensure adequate CGM session and appropriate timing for stopping the baseline GLP-1 RA and initiating tirzepatide at Visit 2; see Section 4.1.1.
Fasting Visit		X			X	X	
Dilated fundoscopic examination (local)	X						An ophthalmologist or optometrist (if allowed by country) will perform the examination. Documentation of a previous examination ≤90 days prior to screening is acceptable to confirm eligibility. Document the previous examination results in CRF. See Section 8.2.4.
Participant Education and Supplies							
Diabetes counseling, training, and education		X					Include counseling on diet and exercise, symptoms and management of hypoglycemia and hyperglycemia, etc. See Sections 5.3 and 8.3.3. After Visit 2, conduct as needed.
BG meter, SMBG training	X						Train participant per provided instructions. Provide additional training as needed.
Dispense BG meter/supplies	X	X	X	X			Dispense additional supplies, as needed.

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Visit Number	1	2	3	4	5	ED	ED = early discontinuation
Week Relative to Study Intervention Start	-3	0	4	8	12	—	
Visit Interval Tolerance (Days)	+3/-7	0	±3	±3	±3		Flexibility is built into the screening visit to ensure adequate CGM session and appropriate timing for stopping the baseline GLP-1 RA and initiating tirzepatide at Visit 2; see Section 4.1.1.
Fasting Visit		X			X	X	
Return BG meter/supplies					X	X	
CGM sensor and insertion kit (14-day) application, training, and education	X						Apply and provide instructions to participants for at-home insertion for future visits. Additional training may occur as needed.
Dispense CGM sensor and insertion kit (14-day)	X	X		X			Dispense CGM sensor and insertion kit and instruct participant on dates to collect 14-day data prior to next scheduled visit. Dispense additional supplies if needed.
CGM insertion reminder to participant			X		X		Contact the participants as a reminder to place the CGM device 14 days prior to their scheduled visit.
CGM sensor (14-day) return and data download		X	X		X		Site staff to collect at scheduled visit and perform compliance assessment. If noncompliance is noted at Visit 3, a repeat CGM session starting at Visit 3 can be performed without a protocol deviation. See Section 8.1.2.

Study I8F-MC-GPIL	Period I - Screening	Period II - Treatment Period					Comments
Visit Number	1	2	3	4	5	ED	ED = early discontinuation
Week Relative to Study Intervention Start	-3	0	4	8	12	—	
Visit Interval Tolerance (Days)	+3/-7	0	±3	±3	±3		Flexibility is built into the screening visit to ensure adequate CGM session and appropriate timing for stopping the baseline GLP-1 RA and initiating tirzepatide at Visit 2; see Section 4.1.1.
Fasting Visit		X			X	X	
Study intervention injection training with demo device		X					Train participant with demo device prior to initial injection.
Review hypoglycemic events collected in the diary		X	X	X	X	X	
Participant Diary							
Participant diary dispensed	X	X	X	X			Diary includes blood glucose values, collection of intervention administration, information on dosing date/time, and hypoglycemia. See Section 8.1.
Diary compliance check		X	X	X	X	X	
Diary return		X	X	X	X	X	
Laboratory Tests and Sample Collections							
Hematology	X						
Hemoglobin A1C (HbA1c)	X	X	X	X	X	X	

Study I8F-MC-GPIL	**Period I - Screening**	**Period II - Treatment Period**					**Comments**
Visit Number	1	2	3	4	5	ED	ED = early discontinuation
Week Relative to Study Intervention Start	-3	0	4	8	12	—	
Visit Interval Tolerance (Days)	+3/-7	0	±3	±3	±3		Flexibility is built into the screening visit to ensure adequate CGM session and appropriate timing for stopping the baseline GLP-1 RA and initiating tirzepatide at Visit 2; see Section 4.1.1.
Fasting Visit		X			X	X	
Clinical chemistry	X	X			X	X	Includes glucose testing.
Lipid panel		X			X	X	
Urinalysis	X						
Serum pregnancy	X						Only for WOCBP and females with a history of tubal ligation. See Section 10.4.2.
Urine pregnancy (local)		X			X	X	Collect for WOCBP only. The result must be available prior to first dose of intervention. Perform additional pregnancy tests if there is clinical suspicion of pregnancy, or as required by local law or regulation.
Follicle stimulating hormone (FSH)	X						Optional; perform as needed to confirm postmenopausal status. See Section 10.4.
Calcitonin	X						

Study I8F-MC-GPIL	**Period I - Screening**	**Period II - Treatment Period**					**Comments**
Visit Number	1	2	3	4	5	ED	ED = early discontinuation
Week Relative to Study Intervention Start	-3	0	4	8	12	—	
Visit Interval Tolerance (Days)	+3/-7	0	±3	±3	±3		Flexibility is built into the screening visit to ensure adequate CGM session and appropriate timing for stopping the baseline GLP-1 RA and initiating tirzepatide at Visit 2; see Section 4.1.1.
Fasting Visit		X			X	X	
Estimated glomerular filtration rate (eGFR)	X						Calculate using CKD-EPI method.
Urinary albumin/creatinine ration (UACR)	X						
Dosing							
Register visit with IWRS	X	X	X	X	X	X	
Dispense study intervention using IWRS		X	X	X			
Observe participant administer study intervention		X					
Dispense ancillary supplies to participant		X	X	X			
Participant returns unused study intervention and ancillary supplies			X	X	X	X	Where applicable as per local regulations.
Assess study intervention compliance			X	X	X	X	

Abbreviations: BG = blood glucose; CKD-EPI = chronic kidney disease - epidemiology collaboration; CGM = continuous glucose monitoring; CRF = case report form; ECG = electrocardiogram; GLP-1 RA = glucagon-like peptide-1 receptor agonist; IWRS = interactive web-response system; PI = Principal Investigator; SoA = Schedule of Activities; SMBG = self-monitoring of blood glucose; T2D = Type 2 diabetes; WOCBP = women of childbearing potential.

2. Introduction

Incretin receptor agonists are an established and important treatment for T2D

Incretin receptor agonists effectively manage glycemic control in patients with T2D and can provide additional weight reduction for those patients who can benefit from an adjunct to comprehensive lifestyle interventions (Buse et al. 2020; Garber et al. 2020; ADA 2022). They vary in terms of pharmacokinetics, dosing regimen, and clinical effects (Neumiller 2011). Switching between GLP-1 RAs occurs to improve HbA1c control, promote additional weight reduction, or mitigate side effects (Almandoz et al. 2020; Jain et al. 2021a). Additionally, patient preference for different medication attributes or pharmacy coverage may also drive switching between agents.

Tirzepatide

Tirzepatide is a recently approved single molecule that acts as glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, which has demonstrated an ability to reduce HbA1c and body weight in adults with T2D across all 3 therapeutic doses: 5, 10, and 15 mg (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022). It is more efficacious in reducing HbA1c and promoting weight reduction than dulaglutide and semaglutide in people not on previous GLP-1 RA therapy (Frías et al. 2018; Frías et al. 2021).

2.1. Study Rationale

No study has investigated the effects of switching from GLP-1 RA therapy to tirzepatide in people with T2D. This study will inform providers on what to expect when switching from a GLP-1 RA to tirzepatide 5 mg but does not evaluate long-term efficacy, optimal dosing, or comparative improvement to other regimens.

Prior exposure to a GLP-1 RA is associated with less frequent GI intolerance when switching between GLP-1 RAs (Hepprich et al. 2021; Jain et al. 2021b). Therefore, this study will describe an alternative way to switch from a GLP-1 RA to tirzepatide by using a starting dose of 5 mg and will evaluate changes in glycemic control, body weight, and GI tolerability occurring in the first 12 weeks for the targeted study population.

2.2. Background

Phase 3 clinical studies

Clinical reductions in HbA1c and body weight

In a series of 5 global Phase 3 SURPASS studies, tirzepatide demonstrated clinically meaningful reductions in HbA1c and body weight, which were greater than placebo and active comparators (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022). These treatment effects were sustained up to 104 weeks (Del Prato et al. 2021).

Improvements in metabolic endpoints

Tirzepatide also demonstrated greater improvements than comparators in other metabolic endpoints, such as fasting serum glucose, 2-hour post meal glucose, CGM-assessed time in euglycemic range, waist circumference, volume of abdominal visceral and SC adipose tissue, and fasting lipid profile (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Battelino et al. 2022; Dahl et al. 2022; Gastaldelli et al. 2022).

Common adverse events

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

Hypoglycemia events

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

2.3. Benefit/Risk Assessment

Overall, the known benefits associated with tirzepatide in people with T2D outweigh known risks associated with the therapy.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of tirzepatide may be found in the IB and package insert (Mounjaro™ USPI [WWW]).

2.3.1. Risk Assessment

Management of risks

Sections 5.1, 5.2, 8.2, and 8.3 address known potential risks associated with tirzepatide.

2.3.2. Benefit Assessment

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

Participants may benefit by receiving personal health information, routine safety assessments, lifestyle management counseling, and frequent engagement with health care providers during the study, which provide opportunities for coaching and support. Following study completion, the participant's data from CGM, describing how their glucose responds to day-to-day activities, will be available for future medical decision-making.

2.3.3. Overall Benefit Risk Conclusion

The safety and efficacy profile seen to date for tirzepatide supports the overall benefit risk for participants in this study. Considering the measures taken to minimize risk to participants in this

study, the potential risks identified in association with tirzepatide are justified by the anticipated benefits that may be afforded to participants living with T2D.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate that participants with T2D switching from a stable dose of GLP-1 RA to tirzepatide 5 mg QW have an improvement in HbA1c at Week 12 compared to baseline	• Change from baseline in HbA1c
Secondary	
To evaluate the changes in CGM-assessed TAR from baseline at Week 4 and at Week 12	Change from baseline in • Percentage of time per day that CGM-derived values are >180 mg/dl (10 mmol/L) • Duration of time in minutes per day that CGM-derived values are >180 mg/dl (10 mmol/L)
To evaluate the change in FSG from baseline at Week 12	• Change from baseline in FSG
To evaluate the changes from baseline in weight at Week 12	• Change from baseline in weight
Exploratory	
To evaluate changes in CGM-derived measures from baseline over the course of 12 weeks	• Change from baseline in o standard CGM metrics (TIR, TBR, GV) o time in TITR o composite of all in-ranges o mean 24-hr daily blood glucose o estimated post-prandial glucose excursion o estimated fasting glucose

Abbreviations: CGM = continuous glucose monitoring; FSG = fasting serum glucose; GLP-1 RA = glucagon-like peptide-1 receptor agonist; GV = glycemic variability; HbA1c = hemoglobin A1c; QW = once-weekly; T2D = type-2 diabetes; TAR = time above range (>180 mg/dl or >10 mmol/L); TBR = time below range (≤70 mg/dl or ≤3.9 mmol/L); TIR = time-in-range (71 to 180 mg/dL or 3.9 to 10 mmol/L); TITR = time in tight target range (71 to 140 mg/dL or 3.9 to 7.8 mmol/L);

Primary estimands

The primary estimand in this study is the efficacy estimand.

The efficacy estimand focuses on the treatment effect if participants continued to receive the study treatment without prohibited medication. This estimand will be used in publications to inform prescribers or physicians.

The primary clinical question of interest is

> What is the change in HbA1c from baseline to Week 12 in participants with T2D, regardless of changes in background OAM, and assuming that participants continue to take treatment without use of prohibited medication?

This estimand is described by the following attributes:

- Population: participants with T2D on a GLP-1 RA who may benefit from additional therapy regardless of background OAM. Further details can be found in Section 5.
- Endpoint: changes from baseline to Week 12 in HbA1c.
- Treatment condition: treatment with tirzepatide regardless of changes to the background OAM. Further details on study treatment can be found in Section 6.
- Intercurrent events of interest: "Treatment discontinuation for any reason" and "Initiation of prohibited medication" will be addressed using the following strategies:
    - As if participants stay on the treatment (hypothetical strategy)
    - As if participants did not receive prohibited medication (hypothetical strategy).
- Population-level summary: difference in mean changes within treatment condition.

4. Study Design

4.1. Overall Design

SURPASS-SWITCH-2 is an open-label, single-arm, multicenter, multinational, Phase 4 study to assess the changes in glycemic control when switching from a stable dose of a GLP-1 RA directly to tirzepatide 5 mg in participants with T2D.

This study includes a screening period and a 12-week treatment period.

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

4.1.1. Design Outline

Period I: Screening

Preparation for the switch from GLP-1 RA medication to tirzepatide

The investigator will determine the participant's current GLP-1 RA medication administration schedule to ensure the correct timing for initiating tirzepatide 5 mg at Visit 2.

Investigators should ensure that at least 12 days occur between Visit 1 and Visit 2 to allow for an adequate CGM data collection.

Participants taking daily liraglutide at screening should continue taking liraglutide up to the day prior to Visit 2.

Participants taking either weekly dulaglutide or semaglutide should take their last dose of GLP-1 RA medication at least 3 days prior to Visit 2 but no more than 10 days prior to Visit 2.

Training for the study-supplied SMBG monitor and testing frequency recommendations will occur. Training for the CGM sensor and insertion device, including suggestions for successful device maintenance, will also occur in conjunction with the insertion of the CGM sensor for the baseline measurement session.

Period II: Treatment Period

Visit 2 Treatment Initiation

Participants arrive to the clinic in the fasting state. See Section 6.1 for intervention details.

This is the general flow for Visit 2:

- Participant returns screening CGM sensor for compliance review and data upload
- Study personnel confirm enrollment criteria
- Study personnel complete all required visit procedures, including the collection of vital signs, all baseline procedures, and sample collection, and
- Treatment initiation for eligible participants

Study intervention training

Study personnel will provide appropriate training for the use of the tirzepatide SDP. The training can be provided using a demonstration device, if available. This training will be repeated at subsequent visits, as needed.

In addition, study personnel will provide product-specific "instructions for use" information to the participants upon request, if available.

First tirzepatide dose

Study personnel will observe as the participant injects the first dose of tirzepatide. The remaining injections will occur at participant's home. The date and time of the first dose of tirzepatide should be recorded on the CRF. Additionally, all medication doses administered at home should be captured, including date and time, in the participant's diary and subsequently recorded in the CRF.

Visit 5 (Week 12) Treatment Period or ED Visit

The investigator will determine a participant's transition from study treatment to another diabetes treatment, including re-initiation of baseline GLP-1 RA.

4.2. Scientific Rationale for Study Design

This study is designed to describe the changes in glycemic control and GI tolerability of people with T2D who are on stable doses of GLP-1 RAs as they transition to tirzepatide 5 mg.

Primary endpoint

The primary endpoint of the study is to assess the change in HbA1c from baseline to Week 12 in participants transitioning from a stable GLP-1 RA to tirzepatide 5 mg. HbA1c is the well-established measure of glycemic status. CGM-derived measures will secondarily provide the daily patterns of glycemic control during the first 12 weeks of therapy.

Duration of treatment period

The duration of the treatment period is 12 weeks. This is based on the time required for the HbA1c value to reflect the change to tirzepatide 5 mg as well as the time during which most GI intolerance occurs after initiating tirzepatide therapy.

The 12-week study period provides several timepoints to assess changes in intermediate glycemic control via CGM sensor and then overall assessment of glycemic control with change in HbA1c at 12 weeks.

Open-label design

A single-arm study supports an open-label design.

Demographics collection

In this study, collection of demographic information includes race and ethnicity as allowed per local regulations. 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

The current US product label specifies that tirzepatide should be started at 2.5 mg (initiation dose) and escalated to 5 mg after 4 weeks. This dosing was based on GLP-1 RA naive participants to optimize tolerability and clinical efficacy. For participants with T2D who are

already on GLP-1 RA therapy, providers may consider starting at tirzepatide 5 mg dose instead of the 2.5 mg initiation dose for additional benefit.

Tirzepatide at 5 mg, administered subcutaneously QW, was efficacious in reducing A1c and body weight in the Phase 3 program and will be evaluated in this study. Continued dose escalation is not required to assess the initial changes in glycemic control.

4.4. End of Study Definition

The end of the study is defined as the date of the 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. Are 18 years old or of an acceptable age to provide informed consent according to local regulations, whichever is older.

Type of participant and disease characteristics

2. Have been diagnosed with T2D based on the World Health Organization classification or other locally applicable diagnostic standards.
3. Have an HbA1c ≥6.5% (≥48 mmol/mol) to ≤9.0% (≤75 mmol/mol) as determined by the central laboratory at Visit 1 and in the opinion of investigator may benefit from tirzepatide based on individual patient needs.
4. Have been on a stable treatment dose of 1 of the listed GLP-1 RAs for ≥3 months prior to Visit 1:
    - liraglutide 1.2 or 1.8 mg QD
    - dulaglutide 0.75, 1.5, 3, or 4.5 mg QW, or
    - injectable semaglutide 0.5, 1, or 2 mg QW.
5. No treatment with OAM or on stable doses (for at least 3 months before Visit 1) of up to 3 OAM. The OAM may include metformin (at least 1000 mg/day), SGLT-2i, thiazolidinediones, or α-glucosidase inhibitors.

Weight

6. Have BMI ≥25 kg/m2 at Visit 1.

Sex and contraceptive/barrier requirements

7. 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, Appendix 4.

Informed consent

8. Are capable of giving signed informed consent as described in Section 10.1.3, Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusion criteria

9. Are reliable and willing to make themselves available for the duration of the study and are willing and able to follow study procedures as required, including compliance with CGM sensor and insertion device (defined in Section 4.1.1).

5.2. Exclusion Criteria

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

Medical conditions

10. Have T1D.
11. Have a history of chronic or acute pancreatitis any time prior to Visit 1.
12. Have a clinical history of
    - proliferative diabetic retinopathy
    - diabetic maculopathy, or
    - nonproliferative diabetic retinopathy that requires acute treatment.
13. Are at high risk for CVD in the investigator's opinion or have a history of any of these CV conditions within 60 days prior to Visit 1:
    - myocardial infarction
    - percutaneous coronary revascularization procedure
    - carotid stenting or surgical revascularization
    - nontraumatic amputation
    - peripheral vascular procedure (e.g., stenting or surgical revascularization)
    - cerebrovascular accident (stroke), or
    - hospitalization for congestive heart failure.
14. Have NYHA Functional Classification Class IV congestive heart failure.
15. Have a history of ketoacidosis or hyperosmolar state or coma.
16. Have a history of severe hypoglycemia or hypoglycemia unawareness within the 6 months prior to Visit 1.
17. Have a known clinically significant gastric emptying abnormality, for example, severe diabetic gastroparesis or gastric outlet obstruction.
18. Have undergone or plan to have during the course of the study gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or chronically take drugs that directly affect GI motility.
19. Have acute or chronic hepatitis, signs and symptoms of any liver disease other than NAFLD, or ALT level >3.0 times the ULN for the reference range, as determined by the central laboratory at study entry. Participants with NAFLD are eligible to participate if their ALT level is ≤3.0 times the ULN for the reference range.
20. Have an estimated glomerular filtration rate <30 mL/min/1.73 m^2, or lower than the country-specific threshold for discontinuing metformin therapy (if used) or SGLT-2i (if used) per local label, calculated by Chronic Kidney Disease-Epidemiology equation by the central laboratory at Visit 1.
21. Have evidence of a significant, uncontrolled endocrine abnormality, for example, thyrotoxicosis or adrenal crises, in the opinion of the investigator.
22. Have family or personal history of MTC or MEN2.
23. Have a serum calcitonin level of ≥35 ng/L, as determined by central laboratory at Visit 1.
24. Have known or suspected hypersensitivity to study product(s) or related products.
25. Have evidence of a significant, active autoimmune abnormality, for example, lupus or rheumatoid arthritis, that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 4 months.

26. Have had a transplanted organ or awaiting an organ transplant. Exception: corneal transplants (keratoplasty).
27. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy for less than 5 years.

Exceptions:

- basal or squamous cell skin cancer
- in situ carcinomas of the cervix, and
- in situ or Grade 1 (for example, Gleason 6 or lower) prostate cancer.

28. Have a history of any other condition, such as known drug, alcohol abuse, or psychiatric disorder that, in the opinion of the investigator, may preclude the participant from following and completing the protocol.
29. Have any chronic hematological condition that may interfere with HbA1c measurement, such as hemolytic anemias and sickle cell disease.
30. 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.

Prior/concomitant therapy

31. Have been treated with other glucose-lowering agents, not listed in Inclusion Criterion 5, in the 3 months prior to Visit 1.
    Exception: use of insulin for gestational diabetes or short-term use (≤14 days) for acute conditions, such as acute illness, hospitalization, or elective surgery within the 3 months prior to Visit 1.
32. Have within 90 days prior to Visit 1 received treatment with medications intended to promote weight loss. This includes prescribed, over-the-counter, or alternative remedies. See Section 6.8.4 for list of prohibited medications.
33. Are receiving chronic (>2 weeks or 14 days) systemic glucocorticoid therapy or have received such therapy within 1 month of Visit 1 or between Visits 1 and 2.
    Exceptions: topical, intraocular, intranasal, or inhaled preparations.

Prior/concurrent clinical study experience

34. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
35. Have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives, or 30 days, whichever is longer, should have passed prior to Visit 1.
36. Have previously completed or withdrawn from this study or any other study investigating tirzepatide.

Other exclusion criteria

37. Are Lilly employees or are employees of any third-party involved in study who require exclusion of their employees.

38. 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.
39. Female participants who are pregnant or breastfeeding or intending to become pregnant.

5.3. Lifestyle Considerations

Diabetes management counseling

Per the SoA (Section 1.3), qualified medical staff will provide diabetes management counseling, which will include instructions on diet and exercise and education about the signs, symptoms, and management of hypoglycemia or hyperglycemia, should it occur.

Participant exercise and diet

Participants should continue their usual exercise habits and generally follow a healthy meal plan (with consistent meal size and time of day) throughout the course of the study.

Participants should not initiate an organized diet or exercise (weight reduction) program during the study other than the lifestyle and dietary measures for diabetes treatment.

Dietary counseling may be reviewed throughout the study, as needed.

Blood product donation

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

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study but is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the 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 visit intervals in the SoA (Section 1.3).

See Section 10.8 for changes in study conduct during exceptional circumstance.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

The planned treatment is tirzepatide 5 mg (Section 6.5).

This table lists the interventions used in this clinical study.

Intervention Name	Tirzepatide (LY3298176)
Dosage Level(s)	5 mg
Route of Administration	Subcutaneous using an SDP
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU

Abbreviation: SDP = single-dose pen.

Administration and timing of dose administration

Tirzepatide is administered QW by SC injection. There are no restrictions on the time of day each weekly dose of study intervention is given, but it is advisable to administer the SC injections on the same day and same time each week, with or without meals.

Anatomical location of injections

Acceptable locations for injection include the abdomen, thigh, or upper arm if another person gives the injection.

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

Packaging and labeling

Tirzepatide will be supplied by the sponsor in SDPs in accordance with current Good Manufacturing Practice. SDPs will be packaged in cartons to be dispensed and will be labeled as appropriate for country requirements.

Tirzepatide will be dispensed at the study visits summarized in SoA (Section 1.3).

Returned tirzepatide should not be re-dispensed to the participants.

Missed doses

If a dose is missed, the participant should take their dose as soon as possible, within 4 days (96 hours) after the missed dose. If more than 4 days have passed, that dose should be skipped, and the next dose should be taken at the appropriate time.

6.1.1. Medical Devices

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

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

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

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

6.1.2. Rescue Therapy

The incidence of severe hyperglycemia in the Phase 3 SURPASS clinical program was low for participants randomly assigned to tirzepatide 5 mg. This study will include participants with a baseline A1c ≤9.0%, which further decreases the possibility of severe hyperglycemia occurring in the study population within a 12-week treatment period.

No rescue therapy will be initiated, but at the investigators' discretion, insulin can be used on a short-term basis (≤14 days) for acute conditions, such as acute illness, hospitalization, or elective surgery. This treatment will not be considered rescue therapy, and participant will continue in the study as long as the tirzepatide treatment continues. Insulin use must be reported in the CRF as concomitant medication, not as rescue therapy.

6.1.3. Background Therapy

Participant eligibility requires them to be on a stable dose of a GLP-1 RA as listed in the inclusion requirements (See section 5.1). The GLP-1 RA will be stopped, and tirzepatide 5 mg will be started at Visit 2.

If participants are using background OAM therapy, they will continue that therapy without dose modification. If the participant develops hypoglycemia or is at risk, the background OAM therapy can be reduced. Any dosing changes should be reported in the CRF.

6.2. Preparation, Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention.

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

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

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization

This is a descriptive study with baseline-to-endpoint comparisons; no randomization will occur.

Blinding

This is an open-label study.

6.4. Study Intervention Compliance

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

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

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

6.5. Dose Modification

This study is designed to assess the transition from a GLP-1 RA to tirzepatide 5 mg, and hence no dose escalation will be employed during the trial. The goal is to initiate tirzepatide at 5 mg on Visit 2 (Week 0) and maintain until Visit 5 (Week 12).

6.5.1. Management of Participants with Gastrointestinal Symptoms

The dose scheme is designed to assess the glycemic transition from a GLP-1 RA directly to 5 mg and assess the development of intolerable GI symptoms. Every effort should be made by the investigator to maintain the 5 mg dose throughout the trial.

This table describes steps the investigator should follow to mitigate GI symptoms and manage participants with intolerable GI AEs.

STEP 1	Advise participants to eat smaller meals, for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full.
STEP 2	Continue STEP 1 + Prescribe symptomatic medication, for example, anti-emetic or anti-diarrheal medication, per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the CRF.

STEP 3	Continue STEP 1 + STEP 2 + Temporarily interrupt tirzepatide; omit 1 dose. After the interruption, the investigator should restart tirzepatide 5 mg, with the participant taking medication to alleviate their GI symptoms. The data related to temporary interruption of study treatment should be documented in source documents. STEP 3 may be repeated once, i.e., 2 non-consecutives doses of tirzepatide 5 mg can be omitted during the 12-week study, each with an attempt to restart the subsequent dose.
STEP 4	If intolerable GI symptoms or events persist despite the above measures, the investigator may discontinue study drug intervention.

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

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

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

6.7. Treatment of Overdose

6.7.1. Tirzepatide Overdose

Tirzepatide overdose was defined as administration of more than a total of 15 mg in less than a 72-hour period. An overdose will be reported as an AE per Section 10.3.

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

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted
- closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate until, for example, study intervention no longer has a clinical effect, and
- initiate appropriate supportive treatment according to the participant's clinical signs and symptoms.

6.8. Prior and Concomitant Therapy

6.8.1. Allowed Concomitant Therapy

Participants are allowed 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 intervention.

6.8.2. Changing Concomitant Therapy

Reduction and/or discontinuation of concomitant antihyperglycemic treatments other than study intervention are described in Section 6.1.3.

Changes in other concomitant medications will be allowed at the discretion of the investigator as clinically indicated in accordance with local standard of care and professional society guidelines.

Authorized study personnel should consult the medical monitor if there are any questions about concomitant therapies during the study.

6.8.3. Concomitant Therapy Data Collection

Any concomitant medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study; authorized study personnel should collect

- name of medication, vaccine, or therapy
- reason for use
- dates of administration, including start and end dates, and
- dosage information, including dose and frequency for concomitant therapy of special interest.

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

6.8.4. Prohibited Concomitant Medications

See Section 5 for prohibited antihyperglycemic medications.

Medications intended to promote weight loss are prohibited in this study. This includes prescribed, over-the-counter, or alternative remedies. Examples include, but are not limited to

- Liraglutide 3.0 mg
- Semaglutide 2.4 mg
- Sibutramine
- Mazindol
- Lorcaserin
- Naltrexone or bupropion
- Zonisamide
- Topiramate
- Orlistat
- Phenylpropanolamine
- Phentermine
- Phentermine or topiramate combination, or
- Pramlintide

6.8.5. Allowed Antihyperglycemic Treatments other than Tirzepatide

No new additional antihyperglycemic treatment is permitted in this study other than tirzepatide.

As noted in Section 6.1.2, initiation of insulin is ONLY allowed for ≤14 days for certain clinical situations, for example, elective surgery, during hospitalization, or hyperosmolar states. Insulin use must be reported in the CRF as concomitant medication, not as rescue 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 Section 10.1.9, Appendix 1.

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from tirzepatide. If so, the participant will remain in the study and follow procedures for remaining study visits, as shown in the SoA (Section 1.3).

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study (see Section 8.3.2)
- the participant is diagnosed with T1D or LADA
- the participant requests to discontinue intervention
- the participant develops confirmed pancreatitis; if not confirmed, study intervention may be restarted
- the participant is diagnosed with MTC, C-cell hyperplasia, or multiple endocrine neoplasia syndrome
- the participant is diagnosed with an active malignancy or if a previously treated malignancy becomes known after enrollment
- the participant experiences a significant study intervention-related hypersensitivity reaction after administration of study intervention
- any other AE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken, or
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons.

Participants who stop tirzepatide permanently will receive another locally approved antihyperglycemic medication, if needed per clinical judgment of investigator, and will continue participating in the study according to the protocol to collect all planned measurements per SoA (Section 1.3), Adverse Events (Section 8.3), and Safety Assessments (Section 8.2) of this protocol.

The choice of antihyperglycemic medication, including restarting the prestudy GLP-1 RA, will be at the discretion of the investigator. The investigators should follow current published standards of care from the American Diabetes Association and/or a consensus report by the American Diabetes Association and the European Association for Study of Diabetes (ADA 2022, Buse et al. 2020).

The new antihyperglycemic medication will be recorded on the CRF for antihyperglycemic medications.

7.1.1. Liver Chemistry Stopping Criteria

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

In study participants with normal or near normal baseline liver tests (ALT, AST, ALP <1.5x ULN), the study drug should be **interrupted** and close hepatic monitoring initiate (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	

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

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

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

Elevation	Exception
ALT or AST >4x baseline	
ALT or AST >3x baseline for more than 2 weeks	
ALT or AST >2x baseline and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2x ULN.
ALT or AST >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

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

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

Resuming study 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. Temporary Discontinuation of Study Intervention

The investigator may temporarily interrupt tirzepatide due to

- an AE
- clinically significant laboratory value
- hospital visits or medical procedures
- travel or shortage of study treatment supply, or
- any other event necessitating temporary discontinuation of tirzepatide.

If tirzepatide is temporarily interrupted for reasons other than tolerability, participants should be encouraged to restart tirzepatide as soon as it is safe to do so.

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

If the tirzepatide interruption is due to intolerable persistent GI AE, such as nausea, vomiting, or diarrhea, the participant should be treated as suggested in Section 6.5.1.

Recording temporary discontinuation of tirzepatide

The dates of study intervention interruption and restart must be documented in source documents and entered on the CRF.

Participant noncompliance should not be recorded as interruption of study intervention on the CRF.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

- at any time at the participant's own request for any reason or without providing any reason
- if the participant is diagnosed with T1D or LADA
- if the participant is diagnosed with a malignancy after enrollment
    - **Exceptions**:
        - basal or squamous cell skin cancer
        - in situ carcinomas of the cervix, and
        - in situ or Grade 1 (for example, Gleason 6 or lower) prostate cancer.
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if a female participant becomes pregnant; see Section 8.3.2
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an ED visit, as shown in the SoA (Section 1.3).

If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

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

8. Study Assessments and Procedures

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

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

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

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

8.1. Efficacy Assessments

Primary efficacy assessment

The primary efficacy measurement in this study is change in HbA1c from baseline to Week 12 (Section 1.3).

Other efficacy assessments

Other efficacy assessments include change in weight, and fasting serum glucose from baseline to Week 12. CGM-derived assessments will be assessed over the course of this 12-week study, including specific endpoints at 4 and 12 weeks.

8.1.1. Self-Monitoring of Blood Glucose (SMBG)

Participants must use only the study-provided monitors, provided per local guidelines, during the study.

Glucometer for participant use during the study

Participants will receive a glucometer and related testing supplies for use during the study.

Glucometer training

Site personnel will train the participant on correct use of the glucometer for self-monitoring blood glucose and reporting of hypoglycemia data.

When to measure FBG during the study

Site personnel will train the participant to measure FBG daily when possible, and a minimum of 2 times per week using the study-provided glucometer.

The FBG should be measured upon waking in the morning, prior to food or caloric beverage intake.

Glucometer data transfer

The study-provided glucometer will wirelessly transmit blood glucose measurements to the participant's diary. Site personnel will be able to view SMBG data that have been transmitted to the diary through a web-based portal as well as any reported events of hypoglycemia.

SMBG for hypoglycemia or hyperglycemia

Participants should perform SMBG with the study-provided BG meter whenever hypoglycemia is experienced or suspected, with or without symptoms. SMBG should also be measured when there is perceived or increased risk related to changes in dietary intake, or physical activity.

Participants may perform SMBG more frequently to check for instances of hyperglycemia, or as directed by the investigator. Investigators may also instruct participants to collect SMBG, at time points other than at fasting, to evaluate glycemic control or based on the investigator clinical judgment.

8.1.2. Continuous Glucose Monitoring

The study-provided CGM sensor will be used in blinded mode during the study. The blinded CGM sensor will not display the sensor glucose readings to the participant or investigator, and high and low glucose alerts will not be available to the participant.

Participants are not allowed to use a personal, non-study CGM device during the study or connect the CGM sensor to a personal smartphone, smartphone application, or other system.

Continuous glucose monitoring procedure

At Visit 1, trained medical site staff will train participants and have them insert the CGM sensor using the supplied insertion device. Site staff must check expiration date on components prior to insertion. Participants will wear the CGM sensor for a 14-day session. At Visit 2, prior to any study drug injection, the system will be collected and data transmitted. Participants will place a new CGM sensor at home 2 weeks prior to study Visits 3 (Week 4) and 5 (Week 12). The CGM sensors will be collected and data downloaded at Visits 3 and 5.

Site personnel will dispense CGM supplies and initiate blinded CGM sessions at the times specified according to the SoA. Participants will be trained on the CGM sensor and insertion device before use and will be required to replace the sensor at designated intervals per the investigator instruction.

The participant will be instructed to monitor fasting blood glucose and blood glucose during hypoglycemia by finger stick SMBG per study protocol.

Continuous blood glucose monitoring system compliance assessment

At the end of each CGM session, participants will return the CGM sensor(s) to the site. Site personnel will upload the CGM data to a vendor-hosted online portal to view data capture compliance using the available reports and visualization tools. The compliance threshold of 70% (at least 10 days of the 14-day session) for each session is defined as the percentage of actual data versus expected data collected during a session. Site personnel will re-educate participants on CGM operation and requirements when session compliance is <80%.

To minimize data loss, the CGM service vendor will review site uploads and notify site users and/or site monitor when sessions do not meet the compliance thresholds.

As noted in the SoA, if a participant does not have a compliant CGM session at Visit 3, the CGM sensor should be inserted during the study visit with re-education of the participant to ensure proper collection of this session and the subsequent CGM session prior to 12 weeks. This replacement session is not a protocol deviation, but the updated start date/time and respective study week should be documented in the CRF. The replacement CGM session data must be collected, uploaded, and assessed for compliance no later than the next study visit. A replacement CGM session is not available at Visit 5 as no additional study drug will be administered.

Continuous blood glucose monitoring device safety evaluations

It is the responsibility of the investigator to report safety concerns as outlined in the Study GPIL protocol. A 24-hour toll-free number will be provided to the site personnel in case the personnel or participants have questions or complaints regarding the CGM sensor or insertion device.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

- skin
- CV
- Respiratory system
- GI tract
- neurological systems
- thyroid, and
- feet, including evaluation for diabetic neuropathy.

The examination excludes pelvic, rectal, and breast examinations, unless clinically indicated.

Physical examinations during in-clinic visits will be performed by a physician or other qualified healthcare professional.

Height, weight, and waist circumference will be measured and recorded, per Appendix 7, Section 10.7. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Symptom-directed physical assessment after screening

These examinations are performed based on participant status and standard of care by a physician or other qualified healthcare professional.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3) and following the study-specific recommendations mentioned in Appendix 7, Section 10.7.

Vital signs including pulse rate (beats per minute) and blood pressure (mm Hg) will be measured after participant has been sitting for at least 5 minutes and before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required.

8.2.3. Electrocardiograms

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

The ECGs must be interpreted by the investigator or qualified designee at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, for immediate participant management, if needed. The investigator or designee must document their review of the ECG. If a clinically relevant abnormality is observed on the participant's ECG, then the investigator should assess the participant for symptoms, such as palpitations, near syncope, syncope, or chest pain.

The original ECG must be retained at the investigative site. The investigator or qualified designee's interpretation will prevail for immediate participant management purposes.

8.2.4. Dilated Fundoscopic Examination

A dilated retinal fundoscopic examination will be performed by a qualified eye care professional (ophthalmologist or optometrist) for all participants between Visit 1 and Visit 2 to exclude participants with proliferative diabetic retinopathy, diabetic macular edema, or non-proliferative diabetic retinopathy that requires acute treatment. The results from this examination will be recorded on a specific retinopathy CRF as a baseline measure of retinopathy. An adequate examination performed ≤90 days prior to screening can replace the study examination; results should be similarly recorded.

A follow-up dilated fundoscopic examination should be performed by a qualified eye care professional (ophthalmologist or optometrist) when clinically indicated by any AE suspected of worsening retinopathy, and the findings should be recorded on the retinopathy eCRF.

8.2.5. Clinical Safety Laboratory Tests

See Section 10.2, Appendix 2 for the list of Clinical Laboratory Tests to be performed and the SoA (Section 1.3) for the timing and frequency.

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

The laboratory results must be retained with source documents unless 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 Section 10.2, Appendix 2, must be conducted in accordance with the SoA (Section 1.3), standard collection requirements, and laboratory manual.

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

8.2.6. Pregnancy Testing

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

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

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

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

8.2.7. Hepatic Monitoring

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

Laboratory tests, including ALT, AST, ALP, TBL, direct bilirubin, GGT, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur. This table shows if a repeat laboratory test is needed.

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

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

What to do if the abnormal condition persists or worsens

If the abnormal liver test result 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 medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including

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

Frequency of monitoring

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests.

Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize.

Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Special care should be taken to minimize the volume of blood taken during hepatic monitoring.

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of the conditions in this table 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 or symptoms[a], or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs or symptoms[a], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants with Gilbert's syndrome)

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

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

What a comprehensive evaluation should include

At a minimum, this evaluation should include

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

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

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

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

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

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

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

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

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

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

See Section 10.5 for hepatic laboratory tests.

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

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

- AEs
- SAEs, and
- PCs.

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

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

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

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

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

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Adverse Event					
AE	Signing of the ICF	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 h 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 h 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	Participation in study has ended	Within 24 h (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 h of awareness	Product Complaint Form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint Form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; PC = product complaint; SAE = serious adverse event.

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

8.3.2. 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. 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. Safety Topics of Special Interest

8.3.3.1. Gastrointestinal Adverse Event

Tirzepatide may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as anti-emetic/anti-diarrheal use will be collected in the CRF/AE form.

For detailed information concerning the management of GI AEs, refer to Section 6.5.1.

8.3.3.2. Dehydration

Severe gastrointestinal events may lead to dehydration and volume depletion, which can cause a deterioration in renal function, including acute renal failure. Participants should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal adverse reactions or other AEs and take precautions to avoid fluid depletion.

8.3.3.3. Renal Safety

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 disease.

8.3.3.4. Exocrine Pancreas Safety

Diagnosis of acute pancreatitis

Acute pancreatitis is an AE of special interest in all studies with tirzepatide, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks et al. 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, or
- 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 and lipase, via a local laboratory
- perform imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound.

Discontinuation and rescue intervention for acute pancreatitis

If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the participant must discontinue therapy with investigational product(s) but will continue in the study on another glucose-lowering regimen; details on rescue intervention will be provided. The most appropriate diabetes therapeutic regimen will be decided by the investigator, based on the participant's clinical status. A review of the participant's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Reporting adverse events and serious adverse events of acute pancreatitis

Each event of pancreatitis must be reported as an AE or SAE.

The investigator must report the event as an SAE if the typical signs and/or symptoms of pancreatitis are present and are confirmed by

- laboratory values (lipase or amylase [total and/or pancreatic]), and
- imaging studies.

If a potential event does not meet all of these criteria, the investigator will decide the seriousness of the event, either AE or SAE.

The investigator will also review the participant's concomitant medications to assess any potential causal relationship with pancreatitis and will report the relatedness of study intervention(s) to the event.

8.3.3.5. Thyroid C-Cell Hyperplasia and C-Cell Neoplasms

Individuals with personal or family history of MTC and/or MEN2 will be excluded from the study.

8.3.3.6. Hypoglycemia

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

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

CGM data will not be used to evaluate hypoglycemia.

Hypoglycemia classification and definitions

Level 1

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

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

Level 2

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

Level 2 hypoglycemia is also referred to as documented or 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 Severe

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

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

Examples of severe hypoglycemia in adults are

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

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

Nocturnal hypoglycemia

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

Reporting of severe hypoglycemic events

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

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

8.3.3.7. Severe, Persistent Hyperglycemia

Severe, persistent hyperglycemia will be assessed during the study to determine the risk of extreme imbalance in glycemic control.

Severe, persistent hyperglycemia is defined as an FBG (via SMBG) >270 mg/dL (>15 mmol/L) during the first 4 weeks or >240 mg/dL (>13.3 mmol/L) from Weeks 5-12 occurring for at least 2 consecutive weeks. No rescue therapy should be used, see section 6.1.2.

8.3.3.8. Hypersensitivity Reactions

Many drugs, particularly 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 hypersensitivity event, additional blood samples should be collected as described in Appendix 2, Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the 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.

8.3.3.9. Injection-Site Reactions

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

If an ISR is reported by a participant or study personnel, 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, samples will be collected for measurement of tirzepatide anti-drug antibodies and tirzepatide concentration.

8.3.3.10. Diabetic Retinopathy Complications

Dilated retinal fundoscopic examination for all participants will be performed by a qualified eye care professional (ophthalmologist or optometrist) between Visit 1 and Visit 2 or at a previous examination ≤90 days of screening meeting study requirements. The results from this examination will be recorded on a specific retinopathy CRF as a baseline measure of retinopathy.

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

8.3.3.11. 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.

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5. Pharmacodynamics

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

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity will not be proactively assessed in this study.

In the case of hypersensitivity or ISR, samples will be collected if needed as described in Section 10.2.1.

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.

9.1. Statistical Hypotheses

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

- **$H_{1,0}$**: Mean change from baseline in HbA1c is greater than or equal to zero at Week 12 in tirzepatide 5 mg arm.

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

9.2. Analyses Sets

This table defines the analysis population 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
Modified intent-to-treat population (mITT)	All participants who are exposed to at least 1 dose of study intervention.
Efficacy Analysis Set (EAS): This analysis set will be used to estimate the efficacy estimand for the primary objective	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 prohibited medication
Safety Analysis Set (SS): This analysis will be used to assess the safety of study treatment	Data obtained during the Treatment Period from the mITT population, regardless of adherence to treatment or initiation of prohibited medication

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 statistical analysis plan or clinical study report. 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 confidence intervals will be given at a 2-sided 95% level.

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

Analyses will use the EAS population set to evaluate the efficacy estimand.

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

- visit
- country
- baseline HbA1c (≤8.0%, >8.0%), and
- baseline measurement as a covariate.

For analyses of HbA1c, continuous baseline HbA1c will be included in the model instead of baseline HbA1c category. An unstructured covariance structure will model the relationship of within-participant errors.

Summary statistics for categorical measures, including categorized continuous measures, will include sample size, frequency, and percentages. Logistic regression may be used to examine the treatment effect from baseline at 12 weeks in binary efficacy outcomes. The negative binomial regression model will be used to measure the within treatment effect of discrete count measures if deemed appropriate.

Adjustments to the planned analyses are described in the final clinical study report or in the SAP.

9.3.2. Primary Endpoint Analysis

The primary endpoint for this study is change from baseline in HbA1c at Week 12. This endpoint will be used to evaluate the primary objective of the study (Section 3).

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

The primary objective based on the efficacy estimand defined in Section 3 will be evaluated using the EAS dataset (Section 9.2). The primary analysis model for HbA1c measurements over time will be an MMRM. The response variable of MMRM will be change in HbA1c values from baseline obtained at each scheduled postbaseline visit. The independent variables of the MMRM model are visit, and country as fixed effects and baseline HbA1c as covariates. Missing data will be addressed by the MMRM model. No explicit imputation methods for missing data will be employed. The *P* values obtained for the least square means for change from baseline will be used to determine the statistical significance to achieve the primary objective.

9.3.3. Secondary Endpoints Analysis

Endpoints for 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. Exploratory Endpoints Analysis

Endpoints for exploratory objectives are described in Section 3 and will be evaluated based on the efficacy estimand. Additional details will be provided in the SAP.

9.3.5. Safety Analyses

Safety assessments will be done using the Safety Analysis Set (see Section 9.1) irrespective of adherence to study intervention or initiation of prohibited medication, 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 end of study. Counts and proportions of participants experiencing AEs will be reported.

9.3.5.1. Hypoglycemic Events

Incidence of documented symptomatic hypoglycemia events and severe hypoglycemia will be summarized. Rate of hypoglycemic episodes will be analyzed using a generalized linear mixed-effects model assuming negative binomial distribution for hypoglycemic episodes if data warrant.

9.3.5.2. Gastrointestinal Events

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

9.3.5.3. Central Laboratory Measures and Vital Signs

Values and changes from baseline to postbaseline values of appropriate central laboratory measures and vital signs will be summarized at each scheduled visit.

The analysis model to make comparisons within treatment relative to continuous change from baseline values assessed over time will be an MMRM, with terms: visit, country, and baseline measurement as covariates.

An unstructured covariance structure will model relationship of within-participant errors.

The percentages of participants with treatment-emergent abnormal, high, or low laboratory measures at any time will be summarized.

A treatment-emergent abnormal value is defined as a change from normal value at baseline to an abnormal value at any time during the follow-up.

A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time during the Treatment and Follow-Up periods.

A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time during the Treatment and Follow-Up periods.

High and low limits will be provided in SAP.

9.3.6. Subgroup Analyses

Subgroup analyses of the primary and secondary endpoint will be made to assess consistency of the improvement from baseline across the following subgroups

- Age group: < 65 years vs ≥ 65 years

- Sex: female vs male
- Race: white vs black vs other
- Ethnicity: Hispanic vs not Hispanic
- Baseline GLP-1 RA: liraglutide vs semaglutide vs dulaglutide
- Baseline GLP-1 RA equivalent doses (adapted from Almandoz et al. 2020):
    - dulaglutide 0.75 mg and liraglutide 1.2 mg vs
    - dulaglutide 1.5 mg, semaglutide 0.5 mg, and liraglutide 1.8 mg vs
    - dulaglutide 3 mg and semaglutide 1 mg vs
    - dulaglutide 4.5 mg and semaglutide 2 mg, and
- Baseline HbA1c (≤8.0%, >8.0%).

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.

9.5. Sample Size Determination

A sample size of 150 participants will provide at least 90% power to show an improvement in HbA1c from baseline at Week 12. This sample size is using the following assumptions:

- a 1-sample t-test with 2-sided significance level of 0.05
- within treatment difference from baseline at Week 12 is 0.3%, and
- intra-subject variability of 1.1%.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH Good Clinical Practice Guidelines
- International Organization for Standardization (ISO) 14155, 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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
- Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

A copy of the ICF(s) must be provided to the participant and is kept on file.

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

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

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

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

The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Committees Structure

10.1.5.1. Internal Assessment Committee

Not applicable.

10.1.5.2. External Clinical Endpoint Committee

Not applicable.

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, study not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

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

Investigator responsibilities

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically, for example, laboratory data.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

Quality tolerance limits

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

Data monitoring and management

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

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

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

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

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

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

Electronic data capture system

An electronic data capture system (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, other data (study drug administration and hypoglycemia information) will be collected by the participant, via a paper source document, and will be transcribed by the authorized study personnel into the EDC system and will serve as the source documentation.

Data storage and access

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 or 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 Section 10.1.7.

10.1.9. Study and Site Start and Closure

First act of recruitment

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

The first act of recruitment is the first site's first participant visit (Visit 1) 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 study.

10.1.12. Sample Retention

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

Sample Type	Custodian	Retention Period after Last Patient Visit[a]
Tirzepatide concentration[b]	Sponsor or designee	1 year
Tirzepatide anti-drug antibodies[b]	Sponsor or designee	15 years

[a] Retention periods may differ locally.

[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 Lilly-designated laboratory or by the local laboratory as specified.

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

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

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

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

Investigators must document their review of the laboratory safety results.

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,	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs) if indicated	
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	Assayed by Lilly-designated laboratory.
Total cholesterol	
Triglycerides	
High-density lipoprotein (HDL-C)	
Low-density lipoprotein (LDL-C)	Generated by Lilly-designated laboratory. If triglycerides are >400, direct LDL will be measured.

Very low-density lipoprotein (VLDL-C)	Generated 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.
Urine Chemistry	Assayed by Lilly-designated laboratory.
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI) calculated using creatinine	
Urinary albumin/creatinine ratio (UACR)	
Additional Testing	Assayed by Lilly-designated laboratory.
HbA1c	
Calcitonin	

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 test results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

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

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

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

Abbreviation: IL = interleukin.

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.
- Section 8.3.1 provides information on the timing and mechanism for collecting events.
- Section 8.3.3 provides more information on the collection and reporting of AEs and SAEs for the clinical endpoints.

10.3.1. Definition of AE

AE definition

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

Events meeting the AE definition

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

- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure, for example, endoscopy 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:

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

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

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

10.3.3. Definition of Product Complaints

Product complaint

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

Follow-up of AEs and SAEs

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

10.3.5. Reporting of SAEs

SAE reporting via an electronic data collection tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

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

SAE reporting via paper form

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

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

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

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

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

Abbreviation: SERMs = selective estrogen receptor modulators.

10.4.2. Contraception Guidance

10.4.2.1. Females

Women of childbearing potential (WOCBP) and women not of childbearing potential (WNOCBP) may participate in this study. See Section 10.4.1 for definitions and additional requirements related to contraception.

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 the study, 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 agree to 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 first dose of study intervention. See the protocol Schedule of Activities 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 30 days after the last dose of the study intervention.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide, or o diaphragm with spermicide, or o female condom with spermicide.
Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

10.4.2.2. Men

The table below describes contraception guidance for all men.

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for 5 half-lives of study intervention, plus 90 days, corresponding to 4 months after the last injection
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 of study intervention, plus 90 days, corresponding to 4 months after the last injection
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 can be found below.

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, 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, and • lactational amenorrhea

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic evaluation testing

See protocol Section 8.2.7 or guidance on appropriate test selection.

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

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

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

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

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing**
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA[b]
Ceruloplasmin	**Herpes simplex virus (HSV) testing**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA[b]

Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology**
Ethyl glucuronide (EtG)	Culture:
Epstein-Barr virus (EBV) testing	Blood
EBV DNA[b]	Urine

a Not required if anti-actin antibody is tested.

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

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

10.6. Appendix 6: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

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

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

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

Measuring height

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

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

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

Step 4. Ask the participant to breathe in and stand tall. If using a stadiometer or fixed measuring device, move the device's measurement arm gently down onto the top of the participant's head. Record the participant's height in centimeter (cm) to 1 decimal place.

Measuring weight

- Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilogram.
- All weights for a given participant should be measured using the same scale, whenever possible.
- Participants should be lightly clothed but not wearing shoes while their weight is measured.

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

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

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

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

Measuring waist circumference

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

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

Step 2. Ask participant to relax.

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

Calculation of BMI

Height and weight measurements will be used to calculate BMI.

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

Calculation of BMI with amputation or limb loss

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

Vital sign measurements (blood pressure and heart rate)

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

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

Step 2. For each parameter, 3 measurements will be taken using the same arm, preferably the nondominant arm.

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

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

10.8. Appendix 8: 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 Good Clinical Practice, 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. The study site should capture the visit location and method with a specific explanation for any data missing because of missed in-person site visits in source document and CRF. Examples of assessments to be completed in this manner include AEs and PCs, concomitant medications, review study participant diary, including study intervention compliance, review diet, and exercise goals.

Mobile healthcare:

Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor and permitted by local regulations. Procedures performed at such visits may include, but are not limited to, weight measurement, blood sampling, vital signs, conducting physical assessments, and collecting health information.

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

Additional consent from the participant will be obtained for participants if needed per local regulations.

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for calcitonin. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, 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.

If study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, this additional requirement must be met:

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

Screening period guidance

Visit 1 to Visit 2

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening are valid for a maximum of 30 days. The following rules will be applied for active participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 30 days from screening to Visit 2: the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 14 days from first screening.
    - 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 30 days from screening: The participant must be discontinued because of screening interruption due to an exceptional

circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at the screening visit to ensure participant eligibility by Visit 2.

Adjustments to visit windows

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

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.

The primary endpoint visit and end of treatment visit, Visit 5 (Week 12), should be completed per original schedule whenever possible and safe to do so. The visit window should be within ±3 days relative to the target visit date.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents 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.

10.9. Appendix 9: Abbreviations and Definitions

Term	Definition
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADA	American Diabetes Association
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Anti-GAD	anti-glutamic acid decarboxylase
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease - epidemiology collaboration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements
CONSORT	Consolidated Standards of Reporting Trials
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
CT	computed tomography
CV	cardiovascular
CVD	cardiovascular disease
Device deficiencies	equivalent to product complaint

EAS	efficacy analysis set
ECG	electrocardiogram
EDC	electronic data capture
ED	early discontinuation
eGFR	estimated glomerular filtration rate
enroll	the act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment
enter	participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives
FBG	fasting blood glucose
FSG	fasting serum glucose
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
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.
interim analysis	an interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created or locked

investigational product	a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP"
IRB/IEC	Institutional Review Board/Independent Ethics Committee
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
IW-SP	Impact of Weight on Self Perception
LADA	latent autoimmune diabetes in adults
medication error	errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves 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, pre-filled pens, or both.
misuse	use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MEN2	multiple endocrine neoplasia syndrome type 2
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma

MTD	maximum tolerated dose
NAFLD	nonalcoholic fatty liver disease
OAM	oral antihyperglycemic medication
participant	equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
QTc	corrected QT interval
QD	once-daily
QW	once-weekly
RA	receptor agonist
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
SDP	single-dose pen
SGLT-2i	sodium-glucose cotransporter-2 inhibitor
SMBG	self-monitoring of blood glucose
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
ULN	upper limit of normal
WOCBP	woman of childbearing potential

WNOCBP	women not of childbearing potential

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