Protocol: I8F-MC-GPIH

A Phase 4, Randomized, Open-Label, Active-Controlled Study to Investigate the Efficacy and Safety of Switching from Weekly Dulaglutide to Weekly Tirzepatide in Adults with Type 2 Diabetes

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Approval Date: 09-Mar-2023

Title Page

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Protocol Number: I8F-MC-GPIH

Amendment Number: b

Compound: tirzepatide (LY3298176)

Brief Title:

A study to investigate the efficacy and safety of switching from weekly dulaglutide to weekly tirzepatide in adults with Type 2 diabetes

Study Phase: 4

Acronym: SURPASS-SWITCH

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 128801

EU Trial Number: 2022-500101-41-00

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

Document ID: VV-CLIN-082267

Lilly Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment (a)	20-Jan-2023
Original Protocol	01-Jul-2022

Amendment (b)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to incorporate feedback from the EU Member States.

Changes and rationale are summarized in the table below. Minor editorial changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Weight and diabetes counseling, training, and education have been added to every visit starting from Visit 3 onwards.	As per feedback from the EU Member States
5.3. Lifestyle Considerations	Participant exercise and diet section revised	As per feedback from the EU Member States

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

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Regulatory Agency Identifier Number(s):

IND: 128801

EU Trial Number: 2022-500101-41-00

Rationale:

No data are currently available on the experience and potential benefits of switching treatment from nonmaximal doses of dulaglutide to tirzepatide as an alternative to maximizing the current dulaglutide dose in adults with Type 2 diabetes (T2D).

This study is designed to investigate the efficacy and safety of switching once weekly dulaglutide 0.75 mg or 1.5 mg to once weekly tirzepatide 15 mg or maximum tolerated dose (MTD), or continuing and escalating to dulaglutide 4.5 mg or MTD in adults with T2D who are currently on a nonmaximal, stable dose of dulaglutide weekly. Data from this study will show whether switching treatment from weekly dulaglutide to tirzepatide rather than intensifying the dulaglutide dose provides additional efficacy in adults with T2D.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To demonstrate that switching from once weekly dulaglutide to once weekly tirzepatide is superior to continuing and escalating dulaglutide for HbA1c change from baseline to Week 40 in participants with T2D	Change from baseline in HbA1c
Key Secondary	
To demonstrate that switching from once weekly dulaglutide to once weekly tirzepatide is superior to continuing and escalating dulaglutide for weight change from baseline to Week 40 in participants with T2D	Change from baseline in weight

Abbreviations: HbA1c = hemoglobin A1c; T2D = Type 2 diabetes.

There will be 2 primary estimands evaluated in this study:

- The treatment-regimen estimand is consistent with the US Prescribing Information. This estimand reflects efficacy when participants with T2D are treated in clinical practice and takes into account both tolerability and efficacy.
- The efficacy estimand focuses on the treatment effect if participants who underwent randomization continued to receive the study treatment without rescue for severe, persistent hyperglycemia, and/or prohibited medication. This estimand will be used in publications to inform prescribers and physicians.

Overall Design:

SURPASS-SWITCH is a Phase 4, randomized, open-label, active-controlled, parallel-group, multicenter, multinational trial to assess the efficacy and safety of tirzepatide 15 mg or MTD compared to dulaglutide 4.5 mg or MTD in participants with T2D.

This study will enroll participants with inadequately controlled T2D who are taking dulaglutide once weekly (0.75 mg or 1.5 mg) for at least 6 months prior to Visit 1, with or without (up to 3) background OAMs.

Participants will be randomly assigned 1:1 to either

- continue with and escalate dulaglutide to 4.5 mg or MTD, or
- tirzepatide 15 mg or MTD.

Participants who are randomly assigned to tirzepatide will discontinue dulaglutide and initiate tirzepatide within 3 days of their next scheduled dose. The starting dose for tirzepatide is 2.5 mg

once weekly for 4 weeks, escalated in 2.5-mg increments every 4 weeks until 15 mg or MTD is achieved.

Brief Summary:

The purpose of this study is to measure HbA1c with switching to tirzepatide compared with continuing and escalating dulaglutide in participants with Type 2 diabetes.

The maximum duration of study participation is approximately 47 weeks. This study includes

- an approximate 3-week screening period
- a 40-week treatment period, and
- a 4-week safety follow-up period.

The visit frequency will be every 4 to 8 weeks.

Study Population:

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

- are ≥18 years of age at screening, or older per local regulations
- have HbA1c of ≥7.0% to ≤9.5%, inclusive, at screening
- are currently on a stable dose of dulaglutide
- are not treated with oral antihyperglycemic medication, or are on a stable dose of up to 3 oral antihyperglycemic medication
- have a stable body weight
- have a body mass index ≥25 kg/m^2 at screening
- 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, and
- give consent to participate.

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

- have a diagnosis of Type 1 diabetes
- have been treated with insulin prior to screening (exception: use for gestational diabetes or short-term use [<14 days])
- have a history of reduction of the dose of dulaglutide due to intolerability, without successful reescalation, and
- have a history or presence of an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with the interpretation of data.

Number of Participants:

Approximately 250 participants will be randomly assigned to study intervention.

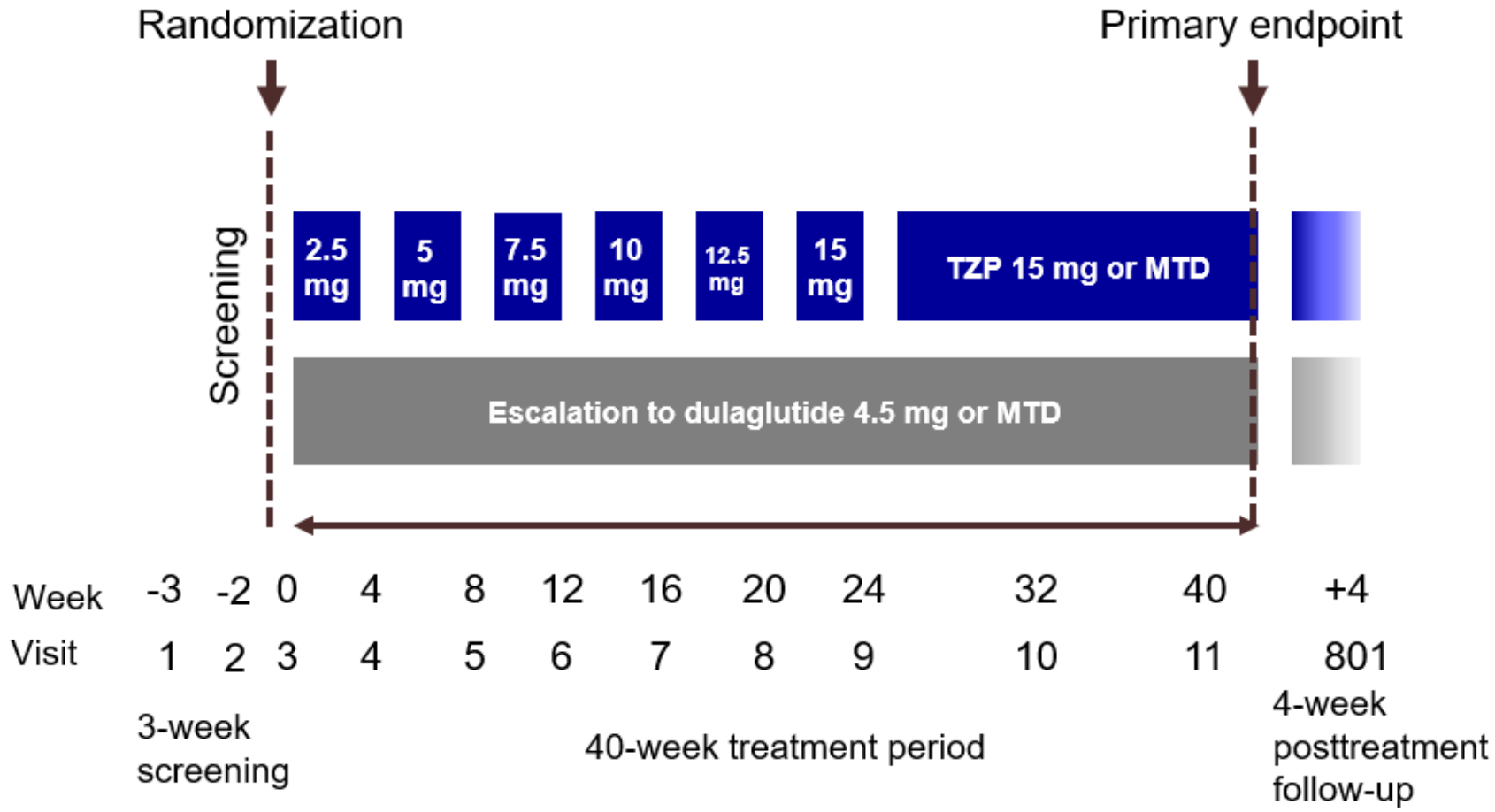
Ethical Considerations of Benefit/Risk:

Overall, known benefits associated with tirzepatide in people with T2D outweigh known risks associated with the therapy. Detailed information about the known and expected benefits and risks and reasonably expected adverse events of tirzepatide may be found in the Investigator's

Brochure and package insert. In addition, detailed information about the known and expected benefits and risks of dulaglutide may be found in the dulaglutide package insert.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: FU = follow-up; MTD = maximum tolerated dose; TZP = tirzepatide.

1.3. Schedule of Activities (SoA)

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 these visits in a nonfasting state, the sample should still be collected.

The visit date is determined in relation to the date of the randomization visit (± the allowed visit window).

Study I8F-MC-GPIH	**Period I - Screening**		**Period II- Treatment Period**										**Period III- Post-treatment Follow-up**	**Comments**
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	ED = early discontinuation
Weeks from randomization	**-3**	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**—**	**4 weeks after the last dose**	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±7	±7	—	±7	
Fasting visit			X	X	X	X	X	X	X	X	X	X		
Informed consent	X													The ICF must be signed before any protocol-specific tests or procedures are performed. See Section 10.1.3 for additional details.
Inclusion and exclusion criteria, review and confirm	X	X	X											Confirm the inclusion and exclusion criteria prior to randomization.
Demographics	X													Includes ethnicity (where permissible), year of birth, sex, and race.
Preexisting conditions and medical history, including relevant surgical history	X													Collect all ongoing conditions and relevant past surgical and medical history.
Prespecified medical history	X													Collect additional data for the indication and comorbidities of interest.
Substance use (alcohol, caffeine, tobacco use)	X													
Prior treatments for indication	X													Add details of T2D medication. Includes medications used for T2D since diagnosis.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study I8F-MC-GPIH	Period I - Screening		Period II- Treatment Period										Period III- Post-treatment Follow-up	Comments
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Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±7	±7	—	±7	
Fasting visit			X	X	X	X	X	X	X	X	X	X		
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent. Collect additional data for safety topics of special interest (Section 8.3.3).
Physical Evaluation														
Height	X													
Weight	X		X	X	X	X	X	X	X	X	X	X	X	
Waist circumference	X		X			X			X		X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes pulse rate and blood pressure. Measure after participant has been sitting at least 5 min and before obtaining an ECG tracing and collection of blood samples for laboratory testing. See Section 8.2.2.
Physical examination	X										X	X	X	See Section 8.2.1.
Symptom-directed physical assessment		X (see Comments)												Symptom-directed physical assessment will be conducted at the discretion of the investigator or qualified healthcare professional per local regulations, as indicated based on participant status and standard of care.

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Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±7	±7	—	±7	
Fasting visit			X	X	X	X	X	X	X	X	X	X		
12-lead ECG (local)			X								X	X	X	Perform prior to collection of blood samples for laboratory testing. Participants should be supine for approximately 5 to 10 min before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit. See Section 8.2.3.
Dilated fundoscopic examination		X												An ophthalmologist or optometrist (if allowed by country) will perform the examination. See Section 8.2.4.
Participant Education and Supplies														
Diabetes counseling, training, and education		X	X	X	X	X	X	X	X	X	X	X	X	Includes counseling on diet and exercise, symptoms, weight, and management of hypoglycemia and hyperglycemia. Repeat training as needed to ensure participant compliance.
BG meter, SMBG training		X												Participant will be trained per the provided instructions. Additional training may occur as needed.
Dispense BG meter/supplies, as needed		X	X	X	X	X	X	X	X	X	X			
Study intervention injection training with demo device			X											Train participant prior to starting any new injectable type. Additional training may occur as needed.

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Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±7	±7	—	±7	
Fasting visit			X	X	X	X	X	X	X	X	X	X		
Remind participants about 7-point SMBG		X								X				Remind participant to monitor 7-point SMBG profiles (prior to and 2 hrs after the 3 main meals and at bedtime) on 2 nonconsecutive days during the 2 weeks preceding the specified visits.
Review 7-point SMBG values collected in the diary			X								X			
Review hypoglycemic events collected in the diary			X	X	X	X	X	X	X	X	X	X	X	
Participant Diary (Electronic)														
Participant diary dispensed		X												eDiary includes SMBG values, collection of intervention administration information on dosing days, and hypoglycemia.
Diary compliance check			X	X	X	X	X	X	X	X	X	X	X	
Diary return												X	X	

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Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±7	±7	—	±7	
Fasting visit			X	X	X	X	X	X	X	X	X	X		
Patient-Reported Outcomes (Electronic) *Complete prior to any clinical assessments*														
Impact of Weight on Self-Perception (IW-SP)			X								X	X		Complete PROs before any other study procedures if the participant is not adversely affected by the fasting condition or after the participant has sufficiently recovered from the preceding visit procedures. Must be completed on eCOA device.
Ability to Perform Physical Activities of Daily Living (APPADL)			X								X	X		
Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT)			X								X	X		
Emotional Impact of Diabetes Treatment Questionnaire – Comparison (EIDTQc)											X	X		
Global Impression of Emotional Health (1 week recall)			X								X	X		
Global Impression of Emotional Health (since study start recall)											X	X		
Laboratory Tests and Sample Collections														
Hematology	X										X	X		
Hemoglobin A1c (HbA1c)	X		X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X		X						X		X	X	X	
Glucose	X		X	X	X	X	X	X	X	X	X	X		
Lipid panel			X						X		X	X		
Serum pregnancy	X													Only for WOCBP and females with a history of tubal ligation. See Section 10.4.

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Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±7	±7	—	±7	
Fasting visit			X	X	X	X	X	X	X	X	X	X		
Urine pregnancy (local)			X								X	X		Collect for WOCBP. Perform additional pregnancy tests, beyond those required per the SoA, 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.
Follicle-stimulating hormone (FSH)	X													Optional. Perform as needed to confirm postmenopausal status. See Section 10.4.
Calcitonin	X										X	X	X	
Pancreatic amylase	X								X		X	X	X	
Lipase	X								X		X	X	X	
Cystatin C	X										X	X	X	
Estimated glomerular filtration rate (eGFR)	X										X	X	X	Calculate using CKD-EPI method.
Urinary albumin/creatinine ratio (UACR)	X										X	X	X	
Anti-GAD antibodies	X													
Randomization and Dosing using IWRS														
Register visit	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization			X											
Dispense study intervention			X	X	X	X	X	X	X	X				Self-administration of study intervention will be done at home and should occur on the day (±3 days) of when the next dulaglutide administration is planned.

Study I8F-MC-GPIH	Period I - Screening		Period II- Treatment Period										Period III- Post-treatment Follow-up	Comments
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	ED = early discontinuation
Weeks from randomization	**-3**	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**—**	**4 weeks after the last dose**	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±7	±7	—	±7	
Fasting visit			X	X	X	X	X	X	X	X	X	X		
Dispense ancillary supplies			X	X	X	X	X	X	X	X				
Participant returns unused study intervention and ancillary supplies				X	X	X	X	X	X	X	X	X		
Assess study intervention compliance				X	X	X	X	X	X	X	X	X		

Abbreviations: BG = blood glucose; CDK-EPI = Chronic Kidney Disease- Epidemiology Collaboration; ECG = electrocardiogram; eCOA = electronic clinical outcome assessment; GAD = glutamic acid decarboxylase; ICF = informed consent form; IWRS = interactive web-response system; PRO = patient-reported outcomes; SoA = Schedule of Activities; SMBG = Self-monitoring of blood glucose; T2D = Type 2 Diabetes; WOCBP = women of childbearing potential.

2. Introduction

2.1. Study Rationale

No data are currently available on the experience and potential benefits of switching treatment from nonmaximal doses of dulaglutide to tirzepatide as an alternative to maximizing the current dulaglutide dose in adults with T2D.

This study is designed to investigate the efficacy and safety of switching once weekly dulaglutide 0.75 mg or 1.5 mg to once weekly tirzepatide 15 mg or MTD, or continuing and escalating to dulaglutide 4.5 mg or MTD in adults with T2D who are currently on a nonmaximal, stable dose of dulaglutide weekly. Data from this study will show whether switching treatment from weekly dulaglutide to tirzepatide rather than intensifying the dulaglutide dose provides additional efficacy in adults with T2D.

2.2. Background

Existing treatment options

Injectable incretin-based treatments, for example, GLP-1RAs, are commonly used alone or in combination with OAMs and/or basal insulin to achieve and maintain glucose control (ADA 2022b).

While associated with lower risk for hypoglycemia and either weight neutral or weight loss effects, current preparations are directed at a single incretin molecular target (for example, GLP-1 receptors). These treatment options offer improved glycemic control, low risk of hypoglycemia, and the potential for clinically relevant weight loss.

Unmet medical need

Despite the availability of GLP-1 RAs and other antihyperglycemic agents, studies continue to show that substantial numbers of patients with T2D do not reach their goals for glycemic and weight control (ADA 2022b).

Therefore, more efficacious treatment options are needed to help more patients with T2D achieve individualized treatment goals, such as reduced HbA1c and body weight, than what can be achieved with currently available therapies, while providing safe options for treatment intensification during disease progression.

Tirzepatide

Tirzepatide is a single-molecule GIP and GLP-1 RA recently approved for the treatment of T2D in the US. The structure of tirzepatide is engineered from the amino acid sequence for GIP and includes a C20 fatty diacid moiety. Tirzepatide has a mean half-life of approximately 5 days, which enables once weekly dosing (Coskun et al. 2018).

Phase 3 clinical studies

Clinical reductions in HbA1c and body weight

In a series of 5 global Phase 3 SURPASS studies evaluating treatment with tirzepatide 5 mg, 10 mg, and 15 mg at different stages of T2D and its treatment continuum, tirzepatide

demonstrated clinically meaningful reductions in HbA1c and body weight, which were greater than placebo, semaglutide 1 mg, titrated insulin degludec, and titrated insulin glargine (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 waist circumference, liver fat content, 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; Dahl et al. 2022; Gastaldelli et al. 2022).

Common adverse events

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

Hypoglycemic 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 the GLP-1 RA class (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022).

Tirzepatide once weekly versus dulaglutide once weekly

A 26-week Phase 2 study provided initial safety, tolerability, and efficacy data for tirzepatide 1 mg, 5 mg, 10 mg, and 15 mg in participants with T2D. Doses of 5 mg, 10 mg, and 15 mg of tirzepatide QW provided significantly greater reductions in HbA1c and body weight compared with dulaglutide 1.5 mg QW. The most common AEs, which were also dose dependent, were mild-to-moderate nausea, vomiting, and diarrhea (Frías et al. 2018).

2.3. Benefit/Risk Assessment

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

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™ package insert [WWW]).

In addition, detailed information about the known and expected benefits and risks of dulaglutide may be found in the dulaglutide package insert (Trulicity® package insert [WWW]; Trulicity® summary of product characteristics).

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate that switching from once weekly dulaglutide to once weekly tirzepatide is superior to continuing and escalating dulaglutide for HbA1c change from baseline to Week 40 in participants with T2D	Change from baseline in HbA1c
Key Secondary	
To demonstrate that switching from once weekly dulaglutide to once weekly tirzepatide is superior to continuing and escalating dulaglutide for weight change from baseline to Week 40 in participants with T2D	Change from baseline in weight
Additional Secondary	

To assess the treatment effect of switching from once weekly dulaglutide to once weekly tirzepatide compared to continuing and escalating dulaglutide at Week 40 in participants with T2D	• HbA1c <7%, ≤6.5%, and <5.7%
	• Weight loss from baseline of ≥5%, ≥10%, and ≥15%
	• A composite of:
	  ○ HbA1c ≤6.5%
	  ○ weight loss ≥10% from baseline
	  ○ no hypoglycemia, defined as BG <54 mg/dL (<3.0 mmol/L) and/or severe hypoglycemia

To assess the treatment effect of switching from once weekly dulaglutide to once weekly tirzepatide compared to continuing and escalating dulaglutide from baseline to Week 40 in participants with T2D	Change from baseline in • FSG • waist circumference • BMI • Impact of Weight on Quality of Life-Clinical Trials Version (IWQOL-Lite-CT) – Physical Functioning Score

Exploratory	
To assess the treatment effect of switching from once weekly dulaglutide to once weekly tirzepatide compared to continuing and escalating dulaglutide from baseline to Week 40 in participants with T2D	Change from baseline in • lipids (total cholesterol, HDL, LDL, VLDL, and TG) • daily average 7-point SMBG profile • patient-reported outcomes: o IWQOL-Lite-CT: Total, Physical, and Psychosocial Scores o IW-SP o APPADL o EIDTQc o GIEH – 1 week recall o GIEH – since study start recall

Abbreviations: APPADL = Ability to Perform Physical Activities of Daily Living; BG = blood glucose; BMI = body mass index; EIDTQc = Emotional Impact of Diabetes Treatment Questionnaire – Comparison; FSG = fasting serum glucose; GIEH = Global Impression of Emotional Health; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IW-SP = Impact of Weight on Self Perception; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Clinical Trials Version; LDL = low-density lipoprotein; SMBG = self-monitoring of blood glucose; T2D = Type 2 diabetes; TG = triglyceride; VLDL = very-low-density lipoprotein.

Primary and key secondary endpoints are controlled for multiplicity.

Primary estimands

There will be 2 primary estimands evaluated in this study. Both of these estimands are described below:

- The treatment-regimen estimand is consistent with the US Prescribing Information. This estimand reflects efficacy when participants with T2D are treated in clinical practice and takes into account both tolerability and efficacy.
- The efficacy estimand focuses on the treatment effect if participants who underwent randomization continued to receive the study treatment without rescue for severe, persistent hyperglycemia, and/or prohibited medication. This estimand will be used in publications to inform prescribers and physicians.

The treatment-regimen estimand answers the following question of interest for the primary objective: What is the treatment difference in change from baseline in HbA1c after 40 weeks of treatment in participants with T2D regardless of treatment discontinuation for any reason and regardless of initiation of antihyperglycemic rescue or prohibited treatment (except for tirzepatide or dulaglutide) or change in the background OAM?

This estimand is described by the following attributes:

- **Population** - Participants with T2D inadequately controlled with dulaglutide with or without a background of OAM. Further details can be found in Section 5.
- **Endpoint** - Change in HbA1c from baseline to Week 40 after randomization.

- **Treatment condition** - The randomly assigned treatment regardless of treatment discontinuation with or without antihyperglycemic rescue or prohibited medication, except for tirzepatide or dulaglutide, or change in background OAM. Further details on study treatment and concomitant, including rescue, treatments can be found in Section 6.
- **Intercurrent events** - Intercurrent events of interest: "treatment discontinuation for any reason" and "initiation of antihyperglycemic rescue or prohibited treatment (except for tirzepatide or dulaglutide) or change in background OAM" are addressed by the treatment condition.
- **Population-level summary** - Difference in mean changes between treatment conditions.

The efficacy estimand answers the following question of interest for the primary objective: What is the treatment difference in HbA1c change from baseline to Week 40 after randomization in participants with T2D regardless of changes in background OAM assuming that participants had stayed on treatment and not taken antihyperglycemic rescue medication?

This estimand is referred to as the efficacy estimand and is described by the following attributes:

- **Population** - Participants with T2D inadequately controlled with dulaglutide with or without background OAM. Further details can be found in Section 5.
- **Endpoint** - HbA1c change from baseline to Week 40 after randomization.
- **Treatment condition** - The randomly assigned treatment regardless of changes to the background OAM. Further details on study treatment can be found in Section 6.
- **Intercurrent event** - Intercurrent events of interest: "Treatment discontinuation for any reason" and "Initiation of antihyperglycemic rescue treatment" will be addressed using the following strategies:
    - had participants stayed on treatment (hypothetical strategy), and
    - had participants not taken antihyperglycemic rescue or prohibited medication, except for tirzepatide or dulaglutide (hypothetical strategy).
- **Population-level summary** - Difference in mean changes between treatment conditions.

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

4. Study Design

4.1. Overall Design

SURPASS-SWITCH is a Phase 4, randomized, open-label, active-controlled, parallel-group, multicenter, multinational trial to assess the efficacy and safety of tirzepatide 15 mg or MTD compared to dulaglutide 4.5 mg or MTD in participants with T2D.

This study will enroll participants with inadequately controlled T2D who are taking dulaglutide once weekly (0.75 mg or 1.5 mg) for at least 6 months prior to Visit 1, with or without (up to 3) background OAMs.

The maximum duration of study participation is approximately 47 weeks. This study includes

- an approximate 3-week screening period
- a 40-week treatment period, and
- a 4-week safety follow-up period.

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

Participants will be randomly assigned 1:1 to either

- continue with and escalate dulaglutide to 4.5 mg or MTD, or
- tirzepatide 15 mg or MTD.

Participants who are randomly assigned to tirzepatide will discontinue dulaglutide and initiate tirzepatide within 3 days of their next scheduled dose. The starting dose for tirzepatide is 2.5 mg once weekly for 4 weeks, escalated in 2.5-mg increments every 4 weeks until 15 mg or MTD is achieved, as described in Section 6.1.1.

4.1.1. Design Outline

Period I: Screening

Visit 1

Interested individuals will sign the ICF prior to initiating any procedure.

The investigator will review medical history and other inclusion and exclusion criteria prior to any diagnostic procedures. If the participant is eligible after this review, then the site will perform the diagnostic procedures detailed in the SoA to confirm eligibility.

Visit 2

The investigator will review the results of the screening laboratory measures to further assess participant eligibility.

For participants meeting all other eligibility requirements, a dilated fundoscopic examination will be scheduled and completed between Visit 2 and Visit 3.

Participants or caregivers, if applicable, will receive a BG meter and COA device.

Participants and their caregiver(s), if applicable, will receive training on

- COA device, including the eDiary data collection and the electronic PRO data collection
- diabetes self-monitoring and management, including instructions on diet and exercise, education about the signs, symptoms, and treatment of hypoglycemia and hyperglycemia
- recording blood glucose measurements, and
- study requirements.

Participants will be asked to monitor 7-point SMBG profiles (prior to and 2 hours after the 3 main meals and at bedtime) on 2 nonconsecutive days during the 2 weeks preceding prespecified visits, as shown in the SoA (Section 1.3).

At investigator's and participant's discretion, participants should monitor BG any time a hypoglycemic event is suspected or unusual symptoms are present. Additional measurements may be used to monitor trends in BG.

Participants should continue their diet and exercise routine and must not use any glucose-lowering treatment other than the OAM taken prior to the screening visit and should not change their dose or formulation.

Period II: Treatment Period

Visit 3 (Randomization)

See Section 6.1 for intervention details, and Section 6.3 for randomization and stratification factors.

All screening laboratory test results and screening dilated fundoscopic examination results must be reviewed for exclusion criteria prior to randomization and dosing at V3.

This is the general flow for Visit 3:

- Participants arrive to the clinic in the fasting state
- Study personnel confirm enrollment criteria
- Participants are randomly assigned to an intervention group
- Participants complete PRO questionnaires before any other study procedures if the participant is not adversely affected by the fasting condition or complete after the participant has sufficiently recovered
- Study personnel complete all required visit procedures, including the collection of vital signs, all baseline procedures, sample collection, and dispense study intervention
- Participants self-administer study intervention at home. Administration should occur on the day (±3 days) of when the next dulaglutide administration is planned

Study intervention training

Participants who are randomly assigned to tirzepatide will receive appropriate training on using the device.

Participants who are randomly assigned to continue on dulaglutide may be trained at the participant's request.

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

Visit 4 through Visit 10

Participants complete all visit procedures described in the SoA.

Visit 11 or ED visit

Participants complete all visit procedures as described in the SoA.

Participants unable or unwilling to continue the study for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit.

The investigator will determine a participant's transition from study treatment to another antihyperglycemic treatment plan.

Period III: Safety follow-up visit

Visit 801

All participants who complete the treatment period or discontinue the study early (ED) are required to complete Visit 801, a safety follow-up visit, approximately 4 weeks after their last treatment or ED visit.

Participants complete all visit procedures as described in the SoA. Participants will return study eDiaries to the study site.

4.2. Scientific Rationale for Study Design

This study is designed to investigate the efficacy and safety of switching once weekly dulaglutide 0.75 mg or 1.5 mg to once weekly tirzepatide 15 mg or MTD, or continuing and escalating dulaglutide 4.5 mg or MTD in adults with T2D who are currently on a nonmaximal, stable dose of dulaglutide QW. Data from this study will show whether switching treatment from weekly dulaglutide to tirzepatide rather than intensifying the dulaglutide dose provides additional efficacy in adults with T2D.

Primary endpoint

HbA1c was chosen as the primary endpoint because it is an accepted and well-understood endpoint reflecting glycemic control over extended periods of time.

Duration of treatment period and posttreatment follow-up

The planned treatment duration of 40 weeks is appropriate to assess the effects and benefit/risk of tirzepatide 15 mg or MTD and dulaglutide 4.5 mg or MTD on glycemic control, weight, and potentially other clinically relevant outcomes.

Open-label design

An open-label design is used for this study to enable dose escalation and modification.

Choice of comparator

Once weekly dulaglutide was chosen as the active comparator because it is one of the most widely used weekly GLP-1 RAs.

Parallel-group design

The parallel-group design for treatment comparison was chosen to avoid any interaction between treatments that may interfere with the interpretation of the study outcome.

Demographics collection

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

4.3. Justification for Dose

Tirzepatide doses

Tirzepatide 15 mg or MTD administered subcutaneously QW will be evaluated in this study.

The doses and associated escalation scheme were selected based on the results of global registrational Phase 3 studies in people with T2D. The requirement to escalate dose to 15 mg or MTD is based on the finding that tirzepatide lowers blood glucose and provides other metabolic benefits, including weight loss and lipid improvements in a dose-dependent manner.

Dose escalation

Tirzepatide

To mitigate the potential occurrence of GI AEs associated with tirzepatide and permit time for the development of tolerance to GI effects, a dose escalation scheme will be used in the tirzepatide arm. The treatment starts at a dose of 2.5 mg QW for 4 weeks and then escalates by 2.5-mg increments every 4 weeks until the 15-mg dose or maximum tolerated dose is reached (Section 6.1.1).

Dulaglutide

Dulaglutide will be escalated until the 4.5-mg dose or MTD is reached. For participants starting at 0.75 mg, dulaglutide will be escalated to 1.5 mg for 4 weeks, followed by 3.0 mg for another 4 weeks and then to 4.5 mg or MTD. For those starting at 1.5 mg, dulaglutide will be escalated to 3.0 mg for 4 weeks and then to 4.5 mg or MTD.

4.4. End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the study 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 HbA1c ≥7.0% (≥53 mmol/mol) to ≤9.5% (≤80 mmol/mol), as determined by the central laboratory at Visit 1.
4. Are currently on a stable dose of dulaglutide weekly (0.75 mg or 1.5 mg) for at least 6 months prior to Visit 1.
5. No treatment with OAM, or on a stable dose of up to 3 OAMs, which may include metformin, SGLT-2i, and/or sulfonylurea, for at least 3 months before Visit 1.

Weight

6. Have had stable body weight (±5%) during the 90 days preceding screening and agree to not initiate a diet and/or exercise program during the study with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment.
7. Have BMI ≥25 kg/m^2 at Visit 1.

Contraceptive/barrier requirements

8. Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   - Males may participate in this trial.
     Please refer to Section 10.4 for additional guidance related to contraception.
   - WOCBP and women not of childbearing potential may participate in the study.
     See Section 10.4 for definitions and additional requirements related to contraception.

Informed consent

9. 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 inclusions

10. 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, but not limited to
    - self-injecting intervention or injection by a caregiver when applicable
    - willing to be assigned to a different injectable at randomization
    - taking provided study interventions as directed
    - maintaining an eDiary, and
    - completing electronic patient-reported questionnaires.

5.2. Exclusion Criteria

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

Medical conditions

11. Have T1D.
12. Have a history of chronic or acute pancreatitis any time prior to screening.
13. Have a history of or diagnosis during screening-dilated fundoscopic examination of
    - proliferative diabetic retinopathy, or
    - diabetic maculopathy, or
    - nonproliferative diabetic retinopathy that requires acute treatment.
14. Have any of these CV conditions within 60 days prior to screening:
    - acute myocardial infarction,
    - cerebrovascular accident (stroke), or
    - hospitalization due to CHF.
15. Have NYHA Functional Classification Class IV CHF.
16. Have a history of ketoacidosis or hyperosmolar state/coma.
17. Have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1.
18. Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction), 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 in this study if their ALT level is ≤3.0 times the ULN for the reference range.
20. Have an eGFR ≤30 mL/min/1.73 m^2, calculated by CKD-EPI as determined by central laboratory at screening.
21. Have evidence of a significant, uncontrolled endocrine abnormality (for example, thyrotoxic or adrenal crises), in the opinion of the investigator.
22. Have family or personal history of MTC or MEN 2.
23. Have a serum calcitonin level ≥35 ng/L, as determined by central laboratory at V1.

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 during the study.
26. Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant.
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:
    a. basal or squamous cell skin cancer
    b. *in situ* carcinomas of the cervix, and
    c. *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 or 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. Female participants who are pregnant or breast feeding or intending to become pregnant during the course of the study.
31. Have a history of an underlying disease, presence of an underlying disease such as active SARS-CoV-2 infection, 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

32. Have been treated with insulin prior to screening.
    Exception: use of insulin for gestational diabetes or short-term use (<14 days) for acute conditions, such as acute illness, hospitalization, or elective surgery.
33. Have a history of reduction of dose of dulaglutide weekly, due to intolerability, without successful reescalation, any time prior to Visit 1.
34. Have within 90 days prior to screening received treatment with medications intended to promote weight loss. This includes prescribed or over-the-counter or alternative remedies. See Section 6.8.3 for list of prohibited medications.
35. Are receiving chronic (>14 days) systemic glucocorticoid therapy or have received such therapy within 1 month of Visit 1 or between Visits 1 and 3.
    Exceptions: topical, intraocular, intranasal, or inhaled preparations.

Prior/concurrent clinical study experience

36. 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.

37. 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 screening.
38. Have previously completed or withdrawn from this study or any other study investigating tirzepatide.

Other exclusions

39. Are Lilly employees or are employees of any third party involved in the study who require exclusion of their employees.
40. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

5.3. Lifestyle Considerations

Diabetes management counseling

Per 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, 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 and/or exercise (weight reduction) program during the study other than the lifestyle and dietary measures for diabetes treatment.

Dietary counseling will be reviewed throughout the study at every visit, including counseling and management with regard to the weight loss known to be associated with tirzepatide and dulaglutide.

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 is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials 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 be rescreened at investigator discretion on 1 occasion. Rescreened participants should be assigned a new participant number.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable for this study.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational interventions, marketed products, placebo, or medical devices intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Intervention Name	Tirzepatide	Dulaglutide
Dosage Levels	2.5 mg QW 5 mg QW 7.5 mg QW 10 mg QW 12.5 mg QW 15 mg QW	0.75 mg QW 1.5 mg QW 3 mg QW 4.5 mg QW
Route of Administration	SC	
Authorized as defined by EU CTR No 536/2014[a]	Not authorized as defined by EU CTR	Authorized as defined by EU CTR and used according to EU Marketing Authorization

Abbreviations: CTR = Clinical Trial Regulation; EU = European Union; QW = weekly.

[a] "Authorized investigational medicinal product" means a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product; "Authorized auxiliary medicinal product" means a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an auxiliary medicinal product.

Packaging and labeling

Study interventions will be supplied in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.1.1. Dose Escalation

Tirzepatide dose escalation

Tirzepatide treatment will follow a fixed dose escalation as follows:

- start at 2.5 mg QW. After 4 weeks, increase the dose to 5 mg QW, and
- increase by 2.5 mg every 4 weeks until 15 mg or MTD is achieved.

Dulaglutide dose escalation

Dulaglutide treatment will follow a fixed dose escalation as follows:

- increase to 1.5 mg QW for 4 weeks at randomization, only needed for those starting on 0.75 mg
- increase to 3 mg QW for 4 weeks, and
- increase to and maintain at 4.5 mg QW or MTD for the duration of the study.

Intolerance to dose escalation

If a participant does not tolerate the dose escalation, refer to Section 6.5 for additional instructions.

6.1.2. Administration Instructions

Tirzepatide

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.

If a dose is missed, it should be administered as soon as possible within 4 days (96 hours) after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

All participants will inject tirzepatide subcutaneously in the stomach area (abdomen) or upper leg (thigh) using the SDPs provided. If the injection is given by someone else, they may inject in the upper arm. A new SDP will be used for each injection. If tirzepatide is to always be injected in the same body region, participants should be advised to use a different injection site each week.

Dulaglutide

Participants in the dulaglutide group will self-administer dulaglutide according to the respective local product labeling.

6.1.3. Medical Devices

Medical devices for tirzepatide and dulaglutide 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.

Instructions for medical device use of dulaglutide are provided in the respective local product labeling.

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

6.1.4. Rescue Therapy

If a participant develops severe, persistent hyperglycemia after randomization, an additional antihyperglycemic medication may be medically indicated after investigator assessment.

Investigators will be trained on the application of criteria for deciding when and how to intervene with participants who do not reach glycemic targets.

First, investigators should confirm participant compliance with the assigned intervention and that they do not have an acute condition causing severe, persistent hyperglycemia.

Conditions for rescue therapy

The criteria for rescue therapy will be based on either FBG or HbA1c as described below.

FBG conditions

This table describes FBG conditions for rescue therapy.

If any of the FBG values exceed the limits outlined below for 2 consecutive weeks and no intercurrent cause of the hyperglycemia can be identified, participants should be treated with rescue medication as an add-on to randomly assigned treatment.

If a participant has persistently elevated FBG defined as…	**during this time…**	**then...**
FBG >270 mg/dL (>15.0 mmol/L)	from baseline (V3) to Week 8	participants should be treated with rescue medication as an add-on to randomly assigned treatment.
FBG >240 mg/dL (>13.3 mmol/L)	from Week 9 to Week 16	
FBG >200 mg/dL (>11.1 mmol/L)	Any time after Week 16	

Abbreviation: FBG = fasting blood glucose.

HbA1c conditions

This table describes HbA1c conditions for rescue therapy.

If a participant has an…	**during this time…**	**then...**
HbA1c ≥8.5% (≥64 mmol/mol)	any time after Week 24	participants should be treated with rescue medication as an add-on to randomly assigned treatment.

Abbreviation: HbA1c = glycated hemoglobin.

Allowed rescue treatments

The choice of rescue treatment for persistent hyperglycemia will be at the discretion of the investigator. Investigators should follow current published standards of care from the American Diabetes Association and/or the consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (Buse et al. 2020; ADA 2022).

GLP-1 RAs, DPP-4 inhibitors, and pramlintide are not allowed as rescue therapy.

Additionally, tirzepatide is not allowed as rescue therapy for the dulaglutide group.

Rescue therapy will be continued and adjusted per the investigator's discretion.

Rescue therapy may not include modifying the tirzepatide or dulaglutide dose.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization

All participants will be centrally assigned through block randomization with a block size of 2 using an IWRS. Before the study is initiated, the login information and directions for the IWRS will be provided to each site.

Participants will be randomly assigned in a 1:1 ratio to tirzepatide or dose escalation of dulaglutide.

Participants will be stratified based on

- starting dulaglutide dose at Screening (0.75 mg, 1.5 mg)
- region (NA, EU)
- number of OAM (0-1 or 2-3), and
- HbA1c (≤8.5% or >8.5%).

Blinding

This is an open-label study.

6.4. Study Intervention Compliance

Participants will enter the intervention dose information in their eDiary.

The investigator or trained designee will assess treatment compliance at each visit based on review of the participant's glycemic control, eDiary completion, and adherence to prescribed dose and study procedures.

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

For general dose escalation, see Section 6.1.1.

Missed doses of study intervention are described in Section 7.1.3.

6.5.1. Management of Participants with Gastrointestinal Symptoms

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

This table describes steps the investigator should follow to mitigate GI symptoms and manage participants with intolerable GI AEs for both the tirzepatide and dulaglutide treatment groups.

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 + Treat with 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 + Manage GI symptoms, including considering dose interruption. Temporarily interrupt study intervention; 1 dose can be omitted per 4 weeks. After the interruption, the investigator should restart the dose or escalate the dose as required, 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. Refer to Section 6.5.1. for additional details.
STEP 4	If intolerable GI symptoms persist despite the above measures, the investigator may decide to reduce the dose to the previous MTD.

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

6.5.2. Study Intervention Dose Modification

If a participant experiences GI tolerability issues despite the measures listed in Section 6.5.1, then follow the guidance in this table.

If a participant is currently taking…	then…
Tirzepatide 2.5 mg or 5 mg, or dulaglutide 0.75 mg	permanently stop study intervention, remain in the study, and initiate another antihyperglycemic medication.
Any other tirzepatide or dulaglutide dose	reduce the dose to the previous tolerated dose. Note: If a participant's dose is reduced, the investigator may re-escalate the dose twice when considered appropriate.

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

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

GLP-1 RAs and tirzepatide are not allowed as antihyperglycemic medication.

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

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

Study intervention will not be provided to participants after completion of the study. At the end of study participation, participants will be treated according to local practice for type 2 diabetes and according to what is available in local markets. Treatment decisions can be made by the participant's primary physician but may also be made by the study investigator.

6.7. Treatment of Overdose

Tirzepatide overdose is defined as administration of tirzepatide with more than the intended dose (more than 1 injection) in less than 72 hours.

Dulaglutide overdose is defined and will be treated, according to the locally approved labeling and packaging.

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

- contact the Lilly medical monitor immediately
- evaluate the participant to determine, in consultation with the Lilly medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention no longer has a clinical effect, and report the overdose event as an AE and document, and
- appropriate supportive treatment should be initiated according to the participant’s clinical signs and symptoms.

6.8. Concomitant Therapy

6.8.1. Concomitant Therapy Regimens

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

Prohibited medications are listed in Section 6.8.3.

Permitted use of antihyperglycemic treatments other than study intervention is described in Section 6.8.4.

Reduction and/or discontinuation of concomitant antihyperglycemic treatments other than study intervention are described in Section 6.8.5.

Participants should consult with authorized study personnel before taking any new medications or supplements during the study. Authorized study personnel should consult the Lilly medical monitor if there are any questions about concomitant therapies during the study.

6.8.2. Concomitant Therapy Data Collection

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

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

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

6.8.3. Prohibited Concomitant Medications

The medications prohibited in the study include medications intended to promote weight loss and non-study GLP-1 RA, DPP-4 inhibitors, and amylin mimetics. This includes prescribed or over-the-counter or alternative remedies. Examples include, but are not limited to

- pramlintide
- semaglutide
- sibutramine
- saxagliptin
- sitagliptin
- Contrave®
- orlistat
- Plenity®
- lorcaserin
- lixisenatide
- liraglutide
- alogliptin
- linagliptin
- zonisamide
- topiramate
- phentermine
- mazindol

6.8.4. Allowed Antihyperglycemic Treatments other than Study Interventions

Antihyperglycemic medications other than study interventions are ONLY allowed during these circumstances:

- for participants who require permanent discontinuation of study intervention but remain in the study
- for rescue therapy after randomization due to severe, persistent hyperglycemia, as described in Section 6.1.4
- during the safety follow-up period or ED visit, and
- short-term insulin use for up to 14 days is allowed for certain clinical situations, for example, elective surgery, during hospitalization, and hyperosmolar states, and must be differentiated from insulin use as rescue therapy when reported in the CRF.

6.8.5. Reduction and/or Discontinuation of Concomitant Antihyperglycemic Medications

Temporary discontinuation of concomitant antihyperglycemic medications <14 consecutive days is allowed for certain clinical situations, for example, severe dehydration, elective surgery, or need for radiologic examination involving IV iodinated contrast dye.

After randomization, discontinuation, dose modification, or formulation change of metformin, sulfonylurea, or SGLT-2i are not permitted except in the following situations:

- If a participant in on a sulfonylurea and develops hypoglycemia, defined as glucose <70 mg/dL, or is at risk of developing hypoglycemia, then the sulfonylurea dose can be reduced or discontinued.
- If a participant meets the criteria for severe, persistent hyperglycemia (Section 8.3.3.7) or discontinues study intervention, then the sulfonylurea dose may be increased according to country-specific label.
- In certain situations that require short-term discontinuation in line with the product(s) local labeling.
- In the event of multiple (>1) hypoglycemic episodes (glucose concentration <54 mg/dL or severe hypoglycemia), in participants on any oral treatment combination not including sulfonylurea, but on dual or single oral treatment of metformin and/or SGLT-2i, the dose of metformin or SGLT-2i can be reduced or discontinued.

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.

7.1. Discontinuation of Study Intervention

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

A participant must be permanently discontinued from study intervention if

- the participant becomes pregnant during the study
- 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 MEN 2 after randomization or has calcitonin value ≥35 ng/L that has increased at least 50% over baseline after randomization
- the participant is diagnosed with an active malignancy or if a previously treated malignancy becomes known after randomization
- the participant experiences a significant study intervention-related hypersensitivity reaction after administration of study intervention
- any other AE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons
- 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 intervention occurs prior to introduction of the new agent.

Additionally, a participant should be permanently discontinued from dulaglutide according to the locally approved labeling and packaging.

7.1.1. Liver Chemistry Stopping Criteria

7.1.1.1. Interrupting Study Drug based on Elevated Liver Tests

The study drug should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.7.1) if one or more of these conditions occur:

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	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.

7.1.1.2. Resuming Study Drug after Elevated Liver Tests

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

7.1.2. QTc Stopping Criteria

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

7.1.3. Temporary Discontinuation of Study Intervention

The investigator may temporarily interrupt study intervention, for reasons other than tolerability, 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 study intervention.

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

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

Tirzepatide

This table shows how to manage treatment if there are missed tirzepatide doses.

If the number of missed consecutive tirzepatide doses is...	Then...
2 or less	the study treatment can be restarted at the last administered dose, if it was well-tolerated prior to interruption.
3 or more	the IWRS will dispense 5 mg tirzepatide irrespective of the dose the participant was receiving before the interruption and subsequently escalate as required by the protocol until the 15-mg dose, or maximum tolerated dose is reached.

Abbreviation: IWRS = interactive web-response system.

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.

Dulaglutide

Missed dulaglutide doses should be managed according to the locally approved labeling and packaging.

Recording temporary discontinuation of study intervention

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 will be discontinued from the study:

- at any time at the participant's own request
- at the request of the participant's designee, for example, legal guardian
- if the participant is diagnosed with T1D or LADA
- if the participant is diagnosed with a malignancy after randomization
    - **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, and
- 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.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an ED visit and posttreatment follow-up, if applicable, as shown in the SoA (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.

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

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

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

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

The primary efficacy measurement in this study is change in HbA1c values from baseline to Week 40, as determined from the central laboratory values. Blood samples for HbA1c measurements will be collected at specific clinic visits as summarized in the SoA, Section 1.3.

8.1.2. Other Efficacy Assessments

Other efficacy assessments include change in weight, FSG, waist circumference, IWQOL-Lite-CT, fasting lipids, BMI, 7-point SMBG, and PROs will be assessed based on data collected at the times shown in the SoA (see Section 1.3).

8.1.2.1. Self-Monitoring of Blood Glucose (SMBG)

Participants must use only the study-provided BG 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.

The 7-point SMBG values should be measured before each meal; 2 hours after breakfast, lunch, and dinner; and at bedtime according to SoA (Section 1.3).

Glucometer data transfer

The study-provided glucometer will wirelessly transmit blood glucose measurements to the participant's eDiary. Site personnel will be able to view SMBG data that have been transmitted to the eDiary 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), when there is perceived, increased risk related to changes in dietary intake, physical activity, or inadvertent or atypical insulin dosing.

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.

8.1.2.2. Patient-Reported Outcomes Assessments

8.1.2.2.1. Impact of Weight on Quality of Life-Clinical Trials Version (IWQOL-Lite-CT)

The IWQOL Lite-CT (Kolotkin et al. 2017, 2019) is a 20-item, obesity-specific PRO instrument developed for use in weight management clinical studies.

The IWQOL-Lite-CT assesses 2 primary domains of obesity-related, health-related quality of life:

- Physical (7 items) and
- Psychosocial (13 items).

A 5-item subset of the Physical domain – the Physical Function composite – is also reported. Items in the Physical Function composite describe physical impacts related to general and specific physical activities.

All items are rated on either

- a 5-point frequency ("never" to "always") scale, or
- a 5-point truth ("not at all true" to "completely true") scale.

The IWQOL-Lite-CT has a total score, which includes all 20 items. The IWQOL-Lite-CT scores range from 0-100, where raw and transformed scores are calculated, with higher composite scores indicating higher levels of functioning.

8.1.2.2.2. Impact of Weight on Self-Perceptions Questionnaire

The Impact of Weight on Self-Perceptions Questionnaire (IW-SP) (Hayes and Delozier 2015) is a patient-reported outcomes instrument that assesses the "current" impact of weight on the self-perception of people with Type 2 diabetes mellitus and obesity.

The IW-SP contains 3 items that assess how often a participants' body weight affects how happy they are with their appearance and how often they feel self-conscious when out in public. Each item is rated on a 5-point scale ranging from 1 = "always" to 5 = "never." Total scores for the IW-SP are derived by summing the item scores and dividing by the number of items. The score is typically transformed to a range from 0 to 100. Higher IW-SP scores correspond to better self-perception.

8.1.2.2.3. Ability to Perform Physical Activities of Daily Living

The Ability to Perform Physical Activities of Daily Living (Hayes et al. 2012) is a patient-reported outcomes instrument that assesses the current ability of people living with T2D and obesity to perform physical activities of daily living.

The Ability to Perform Physical Activities of Daily Living contains 7 items that assess how difficult it is for participants to engage in certain activities considered to be integral to normal daily life, such as walking, standing, and climbing stairs (Hayes et al. 2012). Items are scored on a 5-point numeric rating scale, where 5 = "not at all difficult" and 1 = "unable to do." A raw overall score is calculated by simply summing the scores of the 7 items, and a transformed overall score is obtained by linearly transforming the raw overall score to a 0 to 100 scale. A higher raw overall score and a higher transformed overall score are indicative of better ability to perform activities of daily living.

8.1.2.2.4. Emotional Impact of Diabetes Treatment Questionnaire-Comparison

The EIDTQc is a brief 14-item measure developed to determine how a participant's current diabetes study medication has affected them emotionally in the past week compared to their previous diabetes study medication. The questionnaire consists of 14 items which are evaluated on a 5-point scale ranging from "Much more" to "Much less." Higher item scores indicate better reported emotional health associated with the impact of diabetes.

8.1.2.2.5. Global Impression of Emotional Health questions

The Global Impression of Emotional Health question is a participant-rated question that measures emotional health. For this study, the participant is instructed as follows: "Please choose the response below that best describes your emotional health over the past week" at baseline and at ED or study endpoint. The follow-up participant-reported ratings of emotional health at ED or study endpoint is phrased as follows: "Please choose the response below that best describes the overall change in your emotional health since the start of the study." The Global Impression of Emotional Health includes a range of possible responses, from "Excellent" or "Much better" to "Poor" or "Much worse." Higher scores indicate better overall patient-reported emotional health.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

- skin
- CV
- respiratory
- GI
- neurological systems
- thyroid examination, and
- foot examination, including evaluation for diabetic neuropathy.

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

Physical exams 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).

Vital signs including pulse rate and blood pressure 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. Refer to Section 7.1.2 for QTc stopping criteria.

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.

8.2.4. Dilated Fundoscopic Examination

A dilated fundoscopic examination will be performed by an ophthalmologist or optometrist for all participants between Visit 2 and Visit 3 if the participant meets all qualifications for the study at Visit 1.

A previous examination ≤90 days of screening meeting study requirements is acceptable to confirm eligibility. Additional dilated fundoscopic examinations should be performed when clinically indicated by any suspicion of worsening retinopathy and as outlined in the SoA (see Section 1.3).

8.2.5. Clinical Safety Laboratory Tests

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

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

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

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Lilly 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, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

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

8.2.6. Pregnancy Testing

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

Serum pregnancy tests 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 or must be performed with the result 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 (Section 7).

8.2.7. Hepatic Monitoring

8.2.7.1. Close Hepatic Monitoring

Laboratory tests (Section 10.2), 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 one or more of these conditions occur:

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

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

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

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

8.2.7.2. Comprehensive Hepatic Evaluation

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

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x 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 patients 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 patients 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%.

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

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

8.2.7.3. Additional Hepatic Data Collection (hepatic safety CRF) in Study Participants who have Abnormal Liver Tests during the Study

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

- Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests, if baseline ALT <1.5x ULN
    - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
- Elevated TBL to ≥2x ULN (if baseline TBL <1.5x ULN), except for cases of known Gilbert's syndrome
    - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline

- Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests, if baseline ALP <1.5x ULN
    - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
- Hepatic event considered to be an SAE
- Discontinuation of study drug due to a hepatic event

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

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

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

- AEs
- SAEs
- PCs

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

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

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

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

For 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 10.3.4.

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 ICF	Start of intervention	Immediately without exceeding 24 hrs	SAE CRF	SAE paper form
SAE[a] and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Immediately without exceeding 24 hrs	SAE CRF	SAE paper form
SAE[b] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	Until 1 month after the last dose of study intervention	Within 24 hrs (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form

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

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

a Death caused by disease progression should not be reported as an SAE.

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

8.3.3. Safety Topics of Special Interest

The safety topics of special interest are

- gastrointestinal (Section 8.3.3.1)
- dehydration (Section 8.3.3.2)
- renal safety (Section 8.3.3.3)
- exocrine pancreas safety (Section 8.3.3.4)
- thyroid C-cell hyperplasia and C-cell neoplasms (Section 8.3.3.5)
- hypoglycemia (Section 8.3.3.6)
- severe, persistent hyperglycemia (Section 8.3.3.7)
- major adverse cardiovascular event (MACE) (Section 8.3.3.8)
- arrythmias and cardiac conduction disorders (Section 8.3.3.9)
- hypersensitivity reactions (Section 8.3.3.10)
- injection-site reactions (Section 8.3.3.11)

- diabetic retinopathy complications (Section 8.3.3.12), and
- hepatobiliary disorders (Section 8.3.3.13).

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. Many of the reported adverse renal events occurred in participants who had experienced nausea, vomiting, diarrhea, or dehydration. 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

The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks 2006; Kouzumi 2006):

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

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase and lipase, via the central laboratory and, if needed, via a local laboratory as well, and
- 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

1) are present, and
2) are confirmed by
    a) laboratory values (lipase or amylase [total and/or pancreatic]), and
    b) 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.

Pancreatic hyperenzymemia

Each participant will have measurements of pancreatic amylase and lipase, assessed at the central laboratory, as shown in Section 1.3 to assess the effects of the investigational doses of study intervention on pancreatic enzyme levels.

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic participants (Koizumi 2006; Steinberg 2017 a, 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia, lipase and/or pancreatic amylase 3x ULN or more is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

Only cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis will be submitted for adjudication.

Case adjudication and data entry

An independent clinical endpoint committee will adjudicate all suspected cases of acute or chronic pancreatitis. The adjudication committee will also receive data on AEs of severe or serious abdominal pain of unknown etiology to assess for possible pancreatitis or other pancreatic disease.

Study site staff will enter relevant data for participants with acute or chronic pancreatitis or those with AEs of severe or serious abdominal pain into a specifically designed CRF page. The adjudication committee representative will enter the results of adjudication into a corresponding CRF page.

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

Individuals with personal or family history of MTC and/or MEN 2 will be excluded from the study.

The assessment of thyroid safety during the study will include reporting of any case of thyroid malignancy including MTC and papillary carcinoma and measurements of calcitonin. Calcitonin measurements will assess the potential of study intervention to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms. These data will be captured in specific CRFs.

If an increased calcitonin value (≥35 ng/L AND an increase by ≥50% compared with baseline) is observed in a participant who has administered a medication that is known to increase serum calcitonin, this medication must be stopped, and calcitonin levels must be measured after an appropriate washout period. A consultation with a thyroid specialist or an endocrinologist should be obtained. See Section 7.1 for thyroid-related discontinuation criteria.

If the confirmed calcitonin value is <35 ng/L, tirzepatide should be restarted when it is safe to do so.

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 CRF at each visit.

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

Hypoglycemia classification and definitions

Level 1

Glucose ≥54 mg/dL (≥3.0 mmol/L) and <70 mg/dL (<3.9 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 hypoglycemic event, including severe hypoglycemia, that **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.

Investigators will be trained on the application of criteria for deciding when and how to intervene with participants who do not reach glycemic targets. An additional therapeutic intervention should be considered in participants who develop severe, persistent hyperglycemia after randomization. Participants will be treated with rescue medication as an add-on to randomly assigned treatment, and participants will continue to follow the protocol-specified visit schedule as described in Section 6.1.4.

8.3.3.8. Major Adverse Cardiovascular Events

Deaths and nonfatal CV AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. The nonfatal CV AEs to be adjudicated include the following:

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

8.3.3.9. Arrythmias and Cardiac Conduction Disorder

Participants who develop any event from these groups of disorders should undergo an ECG. Additional diagnostic tests to determine exact diagnosis should be performed, as needed.

The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Appendix 3, Section 10.3 must be reported as SAEs.

After enrollment, if a clinically significant finding is identified by ECG including, but not limited to, changes from baseline in QT/QTc interval, the investigator or qualified designee will determine if any change in study participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding must be reported as an AE or SAE (if applicable).

8.3.3.10. Hypersensitivity Reactions

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

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 generalized urticaria or anaphylaxis, 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, after consultation with the Lilly medical monitor, determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant should be permanently discontinued from the intervention, and the Lilly 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.

8.3.3.11. 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, caregiver, or site staff, the ISR CRF will be used to capture additional information about this reaction, for example, injection-site pain, degree and area of erythema, induration, pruritis, and edema.

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

8.3.3.12. Diabetic Retinopathy Complications

Dilated retinal fundoscopic examination for all participants will be performed by a qualified eye care professional (ophthalmologist or optometrist) between Visit 2 and Visit 3 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.

A follow-up dilated fundoscopic examination occurs when clinically indicated by any AE of suspected worsening of retinopathy. The findings will be recorded on the retinopathy CRF.

8.3.3.13. 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.

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

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

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. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan will be developed and approved prior to first participant first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

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

- **$H_{1,0}$**: Switching from dulaglutide to 15 mg or MTD of tirzepatide is not superior to continuing and escalating to dulaglutide 4.5 mg or MTD with respect to HbA1c mean change from baseline at Week 40 in participants who entered the study on a nonmaximal dose of dulaglutide.

The null hypothesis corresponding to the key secondary objective is as follows:

- **$H_{2,0}$**: Switching from dulaglutide to 15 mg or MTD of tirzepatide is not superior to continuing and escalating to dulaglutide 4.5 mg or MTD with respect to weight mean change from baseline at Week 40 in participants who entered the study on a nonmaximal dose of dulaglutide.

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

9.1.1. Multiplicity Adjustment

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

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoint will be carried out in the hierarchical order as described in Section 9.1. This means that statistically significant results for the comparison in the higher rank (primary) is required to initiate the testing of the next comparison in the lower rank (key secondary). Since a step-down procedure is used, each comparison will be tested at a significance level of 1-sided 0.025 and an overall alpha level of 1-sided 0.025 will be preserved.

9.2. Analysis Sets

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

Population/Analysis Set	Description
Screened population	All participants who signed informed consent.
Randomized population	All participants who are randomly assigned to a treatment arm.
Modified intent-to-treat population (mITT)	All randomly assigned participants who are exposed to at least 1 dose of study intervention. Participants will be analyzed according to the treatment they were randomly assigned to regardless of the treatment actually received.
Efficacy Analysis Set (EAS): This analysis set will be used to estimate the efficacy estimand for the primary and key secondary objectives	Data obtained during the Treatment Period from the mITT population excluding patients who were inadvertently enrolled, excluding data after permanent discontinuation of treatment or initiation of antihyperglycemic rescue medication or prohibited medication.
Full Analysis Set (FAS): This analysis set will be used to estimate the treatment-regimen estimand for the primary and key secondary objectives	Data obtained during the Treatment Period from the mITT population excluding patients who were inadvertently enrolled, regardless of adherence to treatment or initiation of antihyperglycemic rescue medication or prohibited medication.
Safety Analysis Set (SS): This analysis will be used to assess the safety of study treatment	Data obtained during the Treatment Period plus Safety Follow-up from the mITT population, regardless of adherence to treatment or initiation of rescue antihyperglycemic medication or 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. In statistical summaries and analyses, all data will be analyzed by randomly assigned treatment assignment. Participants will be analyzed according to the treatment they were randomly assigned to, regardless of the treatment actually received.

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

Efficacy analyses will use the EAS to evaluate the efficacy estimand and the FAS to evaluate the treatment-regimen estimand. Safety will be assessed using Safety Analysis Set. Selected safety analyses may be conducted after excluding data on rescue therapy or data after starting another antihyperglycemic medication.

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

- treatment
- visit
- treatment-by-visit interaction
- number of background OAMs (0-1 or 2-3)
- dulaglutide dose at screening (0.75 mg or 1.5 mg)
- region (NA, EU)
- baseline HbA1c category (≤8.5% or >8.5%), and
- baseline measurement as a covariate.

For analyses of HbA1c, the baseline HbA1c category will not be included in the model. An unstructured covariance structure will model the relationship of within-participant errors.

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

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

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

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

9.3.2. Primary Endpoint Analysis

The primary endpoint for this study is change from baseline in HbA1c to the 40-week visit (Visit 11). This endpoint will be used to evaluate the primary objective of the study for both the treatment-regimen and the efficacy estimands (Section 3). The null hypothesis corresponding to the primary objective is specified in Section 9.1.

The primary objective based on the treatment-regimen estimand defined in Section 3 will be evaluated based on the FAS dataset (Section 9.2) using an ANCOVA for change from baseline in HbA1c at Week 40 with terms for

- treatment (tirzepatide, dulaglutide)
- number of background OAMs (0-1 or 2-3)
- dulaglutide dose at screening (0.75 mg or 1.5 mg)
- region (NA, EU), and
- baseline value.

For the purpose of the treatment-regimen estimand, missing HbA1c values at the 40-week visit will be imputed based on observed data in the same treatment group from participants who had their efficacy assessed after ED of study intervention. This analysis will be conducted with multiple imputations, and statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

The primary objective based on the efficacy estimand defined in Section 3 will be evaluated using the 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 treatment, visit, treatment-by-visit interaction, number of background OAMs, dulaglutide dose at screening, region as fixed effects, and baseline HbA1c as covariate. Missing data will be addressed by the MMRM model. No explicit imputation methods for missing data will be employed.

9.3.3. Secondary Endpoint Analysis

The endpoint corresponding to the secondary study objective subject to type 1 error rate control is specified in Section 3 under "Key Secondary" (Controlled for Type 1 error) endpoints.

The null hypothesis corresponding to the key secondary objective can be found in Section 9.1.

The key secondary objective will be evaluated based on the treatment-regimen and the efficacy estimands (Section 3), similar to the primary objective.

The analysis of change from baseline in body weight at the 40-week visit (Visits 11) will be conducted in a manner similar to the primary efficacy analyses (Section 9.3.2). Baseline HbA1c category (≤8.5% or >8.5%) will be added to the model.

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

Additional details will be provided in the SAP.

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

9.3.5.1. Hypoglycemic Events

Incidence of documented symptomatic hypoglycemic events and severe hypoglycemia will be summarized and compared between the tirzepatide and dulaglutide arms. Rate of hypoglycemic episodes will be analyzed using a generalized linear mixed-effects model assuming negative binomial distribution for hypoglycemic episodes if data warrant. Some analyses may be conducted excluding data after introducing another antihyperglycemic therapy.

9.3.5.2. Gastrointestinal Events

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

9.3.5.3. Adjudicated Cardiovascular Events

Listing of deaths, myocardial infarctions, strokes, and hospitalization for unstable angina confirmed by an independent clinical endpoint committee will be provided. The dates of randomization, event, first dose and last dose of study intervention, and time from randomization to event will be listed.

9.3.5.4. Central Laboratory Measures and Vital signs

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

The analysis model to make comparisons between treatment arms relative to continuous change from baseline values assessed over time will be an MMRM, with terms: treatment, visit, and treatment-by-visit interaction, number of background OAMs (0-1, 2-3), dulaglutide dose at screening, region, 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 and compared between treatment groups by using Fisher’s exact test.

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 the SAP.

9.3.6. Subgroup Analyses

Subgroup analyses of the primary endpoint (change from baseline in HbA1c) will be made to assess consistency of the intervention effect across the following subgroups:

- age group: <65 years, ≥65 years
- sex: female, male
- race: white, black, other
- ethnicity: Hispanic, non-Hispanic
- duration of diabetes (≤5 years, >5 to ≤10 years, >10 years)
- baseline HbA1c (≤8.5%, >8.5%), and
- region: NA, EU

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

Approximately 250 participants will be randomly assigned in a 1:1 ratio to each study arm. This sample size provides at least 90% power to detect a difference between treatment arms at Week 40 irrespective of adherence to treatment, changes in background OAMs or introduction of rescue antihyperglycemic medication. This sample size is based on an assumed treatment difference of 0.58% with a common standard deviation of 1.3%, using a two-group t-test and a 0.05 two-sided significance level. The treatment difference is based on the following assumptions for the dose distribution for maximum dose or MTD:

- Tirzepatide MTD will be comprised of the following doses:
  - 15 mg dose: 80% of the participants
  - 10 mg dose: 15% of the participants, and
  - 5 mg dose: 5% of the participants.
- Dulaglutide MTD will be comprised of the following doses:
  - 4.5 mg dose: 80% of the participants
  - 3.0 mg dose: 15% of the participants, and
  - 1.5 mg dose: 5% of the participants.

In addition, the planned sample size provides at least 95% power to detect a difference between treatment arms at Week 40 after randomization regardless of changes in background OAM assuming that participants stay on treatment and do not take rescue antihyperglycemic medication. This sample size is based on a treatment difference of 0.60% with a common standard deviation of 1.1%, using a two-group t-test and a 0.05 two-sided significance level. The treatment differences are based on the same assumptions stated above for the treatment-regimen estimand with a 15% discontinuation rate.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - International Organization for Standardization (ISO) 14155
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
  - Reporting significant issues related to participant safety, participant rights, or data integrity
- Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or the participant's legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center. Persons under legal protection may participate in this study if the investigator or the investigator's representative deems that individual is able to understand the risks and benefits of participating in the study and is able to complete all aspects of the study, including but not limited to the questionnaires and diary. The legally authorized representative may then sign the ICF on behalf of the individual.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

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

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

- The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure information security, data integrity, and data protection, including transfer, unauthorized access, disclosure, dissemination, alteration or loss of information and personal data processed. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.
- The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.1.5. Committees Structure

External Clinical Endpoint Committee

An independent clinical endpoint committee, external to Lilly, will be formed to adjudicate major adverse cardiovascular events and acute pancreatitis. This committee will be blinded to treatment assignment.

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 trial, after anonymization, with the exception of PK or genetic data.

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

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

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

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

10.1.7. Data Quality Assurance

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

Quality tolerance limits

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

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.

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

Records retention and audits

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

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

Data capture system

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

Electronic data capture system

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

Clinical outcome assessments

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

Data storage and access

Data collected via the sponsor-provided data capture systems will be stored at third parties.

The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive 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 PC management system.

10.1.8. Source Documents

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

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

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

10.1.9. Study and Site Start and Closure

First act of recruitment

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

The first act of recruitment is the first 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
- Total number of participants included earlier than expected.

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

10.1.10. Publication Policy

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

10.1.11. Investigator Information

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

10.1.12. Sample Retention

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

Sample Type	Custodian	Retention Period After Last Participant Visit[a]
Tirzepatide anti-drug antibodies (ADA)[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 (RBC and WBC), if indicated	
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	

Clinical Laboratory Tests	Comments
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	
Lipid Panel	Assayed by Lilly-designated laboratory.
Total cholesterol	
Triglycerides	
High-density lipoprotein cholesterol (HDL-C)	
Low-density lipoprotein cholesterol (LDL-C)	Generated by Lilly-designated laboratory. Direct LDL will be measured only when triglycerides >400 mg/dL.
Very-low-density lipoprotein cholesterol (VLDL-C)	
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	Results will not be provided to the investigative sites.
eGFR (CKD-EPI) calculated using cystatin C	Results will not be provided to the investigative sites.
eGFR (CKD-EPI) calculated using creatinine and cystatin C	
Urinary albumin/creatinine ratio (UACR)	
Additional Testing	Assayed by Lilly-designated laboratory.
Glucose	
HbA1c	
Calcitonin	
Pancreatic amylase	
Lipase	
Cystatin C	
Anti-glutamic acid decarboxylase antibody (Anti-GAD)	

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

Abbreviation: IL = interleukin.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability or incapacity

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

e. Is a congenital anomaly or birth defect

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

f. Other situations

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

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

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

AE, SAE, and PC Recording

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

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

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

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

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

Assessment of Causality

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

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

Follow-up of AEs and SAEs

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

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) 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 an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. ● The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. ● An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential	Adult females are considered women of childbearing potential unless they are women not of childbearing potential.
Women not of childbearing potential	Females are considered women not of childbearing potential if they • have a congenital anomaly, such as Mullerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • at least 40 years of age and up to 55 years old 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, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

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
	  o calendar
	  o ovulation
	  o symptothermal, or
	  o post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

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

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

Guidance for males

The table below describes contraception guidance for all men.

Topic	Guidance
All male participants	Should refrain from sperm donation for the duration of the study and for 120 days (4 months) after the last study intervention injection
Contraception for men with female partners of childbearing potential	• Either remain abstinent (if this is their preferred and usual lifestyle), OR • Must use condoms during intercourse for the duration of the study and • for 120 days (4 months) after the last study intervention injection
Contraception for men in exclusively same-sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

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

Hepatic evaluation testing

See protocol Section 8.2.7 for guidance on appropriate test selection.

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

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

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)	**Hepatis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA [a]
Basophils	**Hepatis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA [a]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	**Hepatitis E virus (HEV) testing:**
Direct bilirubin	HEV IgG antibody
Alkaline phosphatase (ALP)	HEV IgM antibody
Alanine aminotransferase (ALT)	HEV RNA [a]
Aspartate aminotransferase (AST)	**Anti-nuclear antibody (ANA)**
Gamma-glutamyl transferase (GGT)	**Anti-smooth muscle antibody (ASMA)** [b]
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 [a]	Urine

Abbreviations: INR = international normalized ratio; RNA = ribonucleic acid.

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

[b] Not required if anti-actin antibody is tested.

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

10.6. Appendix 6: Country-specific Requirements

10.6.1. Germany

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

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

Protocol Section Number and Name	Description of the Change	Brief Rationale
5. Study Population	Clarified that recruitment of participants will be completed by a physician or by a member of the study team who is a physician.	Per Article 28 Paragraph 1 letter b) of EU Regulation Number 536/2014 in conjunction with Section 40b Paragraph 2 of the German Drug Law (Arzneimittelgesetz – AMG)
5.2. Exclusion Criteria	Added an exclusion criterion for individuals who are committed to an institution.	Per Article 34 of EU Regulation No. 536/2014 in conjunction with Section 40(a) S. 1 No. 2 of the AMG
8.3. Adverse Events, Serious Adverse Events, and Product Complaints 10.9. Appendix 9: Abbreviations and Definitions	Deleted references to "legally authorized representative"	The AMG requires per Paragraph 40 (1-3) and Paragraph 41 (3) that adult participants act on their own behalf and provide their own written informed consent. If written consent is not possible, verbal consent with a witness is acceptable. No legal representative consent is accepted.
10.1.9. Study and Site Start and Closure	Updated the criteria for study closure.	Per Annex I Section D Number 17 letter p) of EU Regulation No 536/2014 and Article 77 of the Regulation (EU) Number 536/2014 i.c.w. Section 42 Paragraph 6 AMG. 5.4.19
10.8. Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances	Replaced references to "exceptional circumstances" with the "COVID-19 pandemic"	Temporary measures may only be used in response to the COVID-19 pandemic.

The revised text in the following sections shows the changes applicable to adult participants at study sites in Germany. Deletions are identified by ~~strikethrough format~~ and additions by underlined text.

Section 5. Study Population

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

Recruitment of participants will be completed by a physician or by a member of the study team who is a physician.

Section 5.2. Exclusion Criteria

41. Are committed to an institution.

Section 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~~.

Section 10.1.9. Study and Site Start and Closure

Study or site termination

…

For study termination:

- Discontinuation of further study intervention development
- If the approval of the responsible National Competent Authority has been revoked.

Section 10.8. Appendix 8: Provisions for Changes in Study Conduct ~~During Exceptional Circumstances~~ due to the COVID-19 Pandemic

Implementation of this appendix

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

~~Exceptional circumstances~~ Study disruptions due to the COVID-19 pandemic

Individual, site, or regional restrictions due to the COVID-19 pandemic ~~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~~ during the COVID-19 pandemic

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

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

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

Considerations for making a change

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

Informed consent

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

- participation in remote visits, as defined in Section "Remote Visits"
- 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~~ the COVID-19 pandemic

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

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

To ensure the quality of data and the well-being of participants, it will be ensured that the investigator sites and their staff are following GCP principles and are meeting the sponsor responsibilities of Section 5 of ICH GCP. Throughout these activities the participant remains under the care of the primary investigator.

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 eDiary, 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~~ the COVID-19 pandemic 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, administering PROs, 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.

Other alternative locations:

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

Screening period guidance

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, nonrandomized participants whose participation in the study must be paused due to ~~exceptional circumstances~~ the COVID-19 pandemic:

- 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~~ the COVID-19 pandemic. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at the screening visit to ensure participant eligibility by Visit 2.

Visit 2 to Visit 3

To ensure safety of study participants, laboratory values and other eligibility assessments taken at Visit 2 are valid for a maximum of 30 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to ~~exceptional circumstances~~ the COVID-19 pandemic:

- If screening is paused for less than 30 days from Visit 2 to Visit 3: the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 30 days from randomization.
    - 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 Visit 2: The participant must be discontinued because of screening interruption due to ~~an exceptional circumstance~~ the COVID-19 pandemic. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at Visit 2 to ensure participant eligibility by Visit 3.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.
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, Visit 11 (Week 40), should be completed per original schedule whenever possible and safe to do so. The visit window should be within ±7 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~~ the COVID-19 pandemic. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

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

Section 10.9. Appendix 9: Abbreviations and Definitions

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

10.7. 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 (~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 GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

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

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

Changes in study conduct 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 eDiary, 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, administering PROs, 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.

Other alternative locations:
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 ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

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, nonrandomized 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.
    - 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.

Visit 2 to Visit 3

To ensure safety of study participants, laboratory values and other eligibility assessments taken at Visit 2 are valid for a maximum of 30 days. The following rules will be applied for active,

nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 30 days from Visit 2 to Visit 3: the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 30 days from randomization.
    - 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 Visit 2: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at Visit 2 to ensure participant eligibility by Visit 3.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.
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, Visit 11 (Week 40), should be completed per original schedule whenever possible and safe to do so. The visit window should be within ±7 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
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
authorized IMP	Applicable to the EU only: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product
BG	blood glucose
BMI	body mass index
CFR	Code of Federal Regulations
CHF	congestive heart failure
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CSR	clinical study report
CV	cardiovascular

DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DPP-4	Dipeptidyl-peptidase-4
EAS	efficacy analysis set
ECG	electrocardiogram
eCOA	Electronic clinical outcome assessment
ED	early discontinuation
eGFR	estimated glomerular filtration rate
EIDTQc	Emotional Impact of Diabetes Treatment Questionnaire-Comparison
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FAS	full analysis set
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 RA	glucagon like peptide 1 receptor agonist
HbA1c	Glycated hemoglobin
HDL-C	high-density lipoprotein cholesterol
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.
INR	international normalized ratio
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
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 assigned 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.
IW-SP	Impact of Weight on Self-Perceptions Questionnaire
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite
IWRS	interactive web-response system
LADA	Latent autoimmune diabetes in adults
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events

medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the 5 “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MEN 2	Multiple Endocrine Neoplasia Type 2
MTC	Medullary Thyroid Cancer
MTD	maximum tolerated dose
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
NAFLD	nonalcoholic fatty liver disease
NIMP	Non-investigational Medicinal Product. See AxMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment.
NYHA	New York Heart Association
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
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PT-INR	prothrombin time – international normalized ratio
QTc	corrected QT interval

QW	weekly
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SDP	Single-dose pen
SGLT-2i	sodium-glucose cotransporter 2 inhibitor
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	women of childbearing potential

10.10. Appendix 10: Protocol Amendment History

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

Amendment (a): (20-JAN-2023)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to address regulatory feedback.

Changes and rationale are summarized in the table below. Minor editorial changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Hemoglobin A1c (HbA1c): added an X for the post-treatment follow-up visit.	For consistency with other parameters (secondary endpoints and AEs)
2.2. Background	Changed the "Dulaglutide once weekly" subheading to "Tirzepatide once weekly versus dulaglutide once weekly".	For consistency with the section content
5.2. Exclusion Criteria	Exclusion Criterion [31]: updated to read "Have a history of an underlying disease, ~~or~~ presence of an underlying disease such as active SARS-CoV-2 infection, 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."	For clarity
6.3. Measures to Minimize Bias: Randomization and Blinding	First paragraph, first sentence: updated to read "All participants will be centrally assigned through block randomization with a block size of 2 ~~to randomly assigned study intervention~~ using an IWRS.	For clarity
6.6. Continued Access to Study Intervention after the End of the Study	Added the following: "At the end of study participation, participants will be treated according to local practice for type 2 diabetes and according to what is available in local markets. Treatment decisions can be made by the participant's primary physician but may also be made by the study investigator."	For clarity

Section # and Name	Description of Change	Brief Rationale
7.1. Discontinuation of Study Intervention	Second paragraph, first sentence: updated to read "A participant ~~should~~ must be permanently discontinued from study intervention if".	Discontinuation from the study intervention is mandatory in case of safety concerns
8.3.1. Timing and Mechanism for Collecting Events	"Timing for Reporting to Sponsor or Designee" column for the "SAE and SAE updates" rows: revised from "Within 24 hr of awareness" to "Immediately without exceeding 24 hrs".	For clarity
8.4. Pharmacokinetics	Added the following sentence: "In the case of hypersensitivity or ISR, samples will be collected if needed as described in Section 10.2.1".	For clarity and consistency with Section 8.8. Immunogenicity Assessments
10.1.3 Informed Consent Process	Revised to read: • The first bullet: "The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or the participant's legally authorized representative and answer all questions regarding the study." • The second bullet: "Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center. Persons under legal protection may participate in this study if the investigator or the investigator's representative deems that individual is able to understand the risks and benefits of participating in the study and is able to complete all aspects of the study, including but not limited to the questionnaires and	For clarity

Section # and Name	Description of Change	Brief Rationale
	diary. The legally authorized representative may then sign the ICF on behalf of the individual." • Last bullet: "A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file."	
10.1.4. Data Protection	Updated as follows: • The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process. • The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. • The sponsor has processes in place to ensure ~~data protection,~~ information security, ~~and~~ data integrity, and data protection, including transfer, unauthorized access, disclosure, dissemination, alteration or loss of information and personal data processed. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.	For clarity

Section # and Name	Description of Change	Brief Rationale
	• The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).	
10.1.12. Sample Retention	Added footnote "b": "Sample collection only for hypersensitivity and injection site reactions."	For clarity
Appendix 2, Clinical Laboratory Tests	Hematology table: updated to read • Neutrophils~~, segmented~~ • ~~Bands~~ • Cell morphology (RBC and WBC), if indicated	For accuracy
Appendix 2, Section 10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event	"Sample Type" column: for complements, revised to read "Serum/plasma".	For clarity
Appendix 6, Section 10.6.1. Germany	Updated the table to indicate which sections of the protocol were updated per German regulations.	Per German regulations
	Added the following (the underscore indicates additions to the initial protocol text):	
	Section 5. Study Population Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Recruitment of participants will be completed by a physician or by a member of the study team who is a physician."	
Appendix 6, Section 10.6.1. Germany, continued	Section 5.2. Exclusion Criteria 41. Are committed to an institution.	Per German regulations

Section # and Name	Description of Change	Brief Rationale
	Section 10.1.9. Study and Site Start and Closure For study termination: • Discontinuation of further study intervention development. • <u>If the approval of the responsible National Competent Authority has been revoked.</u>	
Appendix 6, Section 10.6.1. Germany (section for Appendix 8: Provisions for Changes in Study Conduct <u>due to the COVID-19 Pandemic)</u>, and Appendix 8, Provisions for Changes in Study Conduct During Exceptional Circumstances	"Study intervention and ancillary supplies (including participant diaries)" section, second paragraph, first bullet: revised to read "Alternate delivery of study intervention should be performed in a manner that ~~does not compromise treatment blinding and~~ ensures product integrity."	This is an open-label study.
Page with manually added approvers' names	Deleted	This information will be generated automatically in the Lilly document management system.

11. References

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