Protocol: I8F-MC-GPGV

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study with an Open-Label Extension Assessing the Efficacy, Safety, and Pharmacokinetics/Pharmacodynamics of Tirzepatide in Pediatric and Adolescent Participants with Type 2 Diabetes Mellitus Inadequately Controlled with Metformin, or Basal Insulin, or Both (SURPASS-PEDS)

NCT05260021

Approval Date: 14-Dec-2021

Title Page

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Protocol Number: I8F-MC-GPGV

Amendment Number: Initial protocol

Compound: LY3298176

Brief Title: A Study to Evaluate Tirzepatide Compared to Placebo in Pediatric and Adolescent Participants with Type 2 Diabetes Mellitus Inadequately Controlled with Metformin, or Basal Insulin, or Both

Study Phase: 3

Acronym: SURPASS-PEDS

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number

IND: 128801

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

Approval Date: 14-Dec-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study with an Open-Label Extension Assessing the Efficacy, Safety, and Pharmacokinetics/Pharmacodynamics of Tirzepatide in Pediatric and Adolescent Participants with Type 2 Diabetes Mellitus Inadequately Controlled with Metformin, or Basal Insulin, or Both (SURPASS-PEDS)

Brief Title: A Study to Evaluate Tirzepatide Compared to Placebo in Pediatric and Adolescent Participants with Type 2 Diabetes Mellitus Inadequately Controlled with Metformin, or Basal Insulin, or Both

Rationale:
Type 2 diabetes mellitus (T2DM) is a disease that is primarily diagnosed in adults, and the risk of the disease increases with age (CDC 2020 [WWW]). There has been a significant increase of T2DM in the pediatric and adolescent population in recent years, although the absolute number of youth with T2DM remains low and T1DM accounts for approximately 90% of all diabetes in the pediatric population (Dabelea et al. 2014).

There is an important need for additional safe and effective agents approved to treat the pediatric and adolescent population with T2DM. Unlike adults, the pediatric and adolescent population with the disease have fewer glucose-lowering treatment options that are regulatory approved. Metformin, most insulins, liraglutide, and recently exenatide 2 mg once weekly (QW) are the only agents approved in the United States (US) and/or European Union (EU) for treatment (Tamborlane and Klingensmith 2013; Tamborlane et al. 2019; Victoza® summary of product characteristics [SmPC] and prescribing information [PI]; BYDUREON BCISE® PI 2021).

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and a glucagon-like peptide-1 (GLP-1) receptor agonist. Tirzepatide is administered QW subcutaneously (SC) and is being investigated for its potential use in the treatment of T2DM.

Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
Efficacy • To demonstrate that pooled 5 mg and 10 mg tirzepatide QW is superior to placebo at 30 weeks	• Change in hemoglobin A1c (HbA1c) from baseline
Key Secondary (controlled for type 1 error)	
Efficacy • To demonstrate that 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, is superior to placebo at 30 weeks	• Incidence of HbA1c ≤6.5% • Change in body mass index (BMI) standard deviation score (age- and sex-matched) from baseline • Change in fasting serum glucose (FSG) from baseline
• To demonstrate that 5 mg and 10 mg tirzepatide QW, analyzed as separate treatment arms, is superior to placebo at 30 weeks	• Change in HbA1c from baseline
Additional Secondary (not controlled for type 1 error)	
• To demonstrate that 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, is superior to placebo at 30 weeks	• Incidence of HbA1c <7.0% • Incidence of HbA1c <5.7% • Change in daily average 6-point self-monitored blood glucose profiles from baseline
• To assess the effect of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, at 52 weeks	• Change in HbA1c from baseline • Incidence of HbA1c <7.0% • Incidence of HbA1c ≤6.5% • Incidence of HbA1c <5.7% • Change in BMI standard deviation score (age- and sex-matched) from baseline • Change in FSG from baseline
• To compare 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, to placebo at 30 weeks; and to assess the effect of 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms at 52 weeks	• Change from baseline for serum lipid levels • Incidence of new or worsening of dyslipidemia

• To assess safety of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, at 30 weeks and at the end of the safety follow-up period	• Treatment-emergent adverse events (TEAEs) • Discontinuation of study intervention due to adverse events (AEs) • Adjudicated pancreatic AEs • Serum calcitonin • Incidence of allergic, hypersensitivity reactions, and injection site reactions • Incidence of treatment-emergent anti-drug antibodies to tirzepatide • Change in systolic and diastolic blood pressure and heart rate from baseline • Incidence of new or worsening of hypertension • Incidence of new or worsening of albuminuria • Occurrence of hypoglycemic events • Incidence of initiation of rescue therapy for severe-persistent hyperglycemia • Incidence of new or worsening of diabetic neuropathy
• To compare 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, to placebo at 30 weeks; and to assess the effect of 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms at 52 weeks	• Change from baseline for physical and developmental measures o Height and weight o Height SDS and weight SDS o Waist circumference, and o Tanner Staging
• To assess the safety of 5 mg and 10 mg tirzepatide QW, analyzed as separate and pooled arms, at 52 weeks for diabetic retinopathy	• Incidence of new or worsening of diabetic retinopathy or diabetic maculopathy in either eye
• Characterize the pharmacokinetics and pharmacodynamic relationships of tirzepatide	• Relationship between tirzepatide exposure and key safety and efficacy measures
• To assess the effect of 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, on patient reported outcomes at 30 and 52 weeks	• Change from baseline for o PedsQL Generic Core Scales o PedsQL (3.2) Diabetic Module from baseline

Abbreviations: AEs = adverse events; BMI = body mass index; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; PedsQL = Pediatric Quality of Life Inventory; QW = once weekly; TEAEs = Treatment-emergent adverse events.

The clinical question of interest for the "treatment-regimen estimand" is the treatment difference between tirzepatide and placebo after 30 weeks of intervention in pediatric and adolescent participants with T2DM, regardless of intervention discontinuation for any reason (excluding inadvertently enrolled participants who have discontinued study intervention for that reason) and regardless of initiation of rescue antihyperglycemic intervention.

The clinical question of interest for the "efficacy estimand" is the treatment difference between tirzepatide and placebo after 30 weeks of intervention in pediatric and adolescent participants with T2DM, ***prior to*** intervention discontinuation for any reason and ***prior to*** the initiation of rescue antihyperglycemic intervention.

Overall Design:

This is a randomized, double-blind, parallel arm, placebo-controlled study with an open-label extension, to assess the efficacy, safety, and pharmacokinetics/pharmacodynamics (PK/PD) of tirzepatide in male and female participants 10 to <18 years of age with T2DM and inadequate glycemic control on diet and exercise with metformin, or basal insulin, or both.

Study GPGV will evaluate 5-mg and 10-mg doses of tirzepatide starting at 2.5 mg and using a dose escalation of 2.5 mg increments every 4 weeks to achieve the assigned maintenance dose.

Brief Summary:

The purpose of this study is to evaluate the safety and efficacy of tirzepatide 5 mg and tirzepatide 10 mg QW, with metformin, or basal insulin, or both, compared to placebo for glycemic control in the pediatric and adolescent population with T2DM over a 30-week period, followed by a 22-week open-label extension.

Number of Participants:

At least 90 participants will be randomized in a 1:1:1 ratio to each study arm until an expected accrual of 90 evaluable participants is achieved. Evaluable participants are those who have been randomized and exposed to at least one dose of study treatment with HbA1c measurements at baseline and at the Week 30 visit.

Intervention Groups and Duration:

The overall study duration is approximately 60 weeks over 4 required study periods. This table describes the study periods.

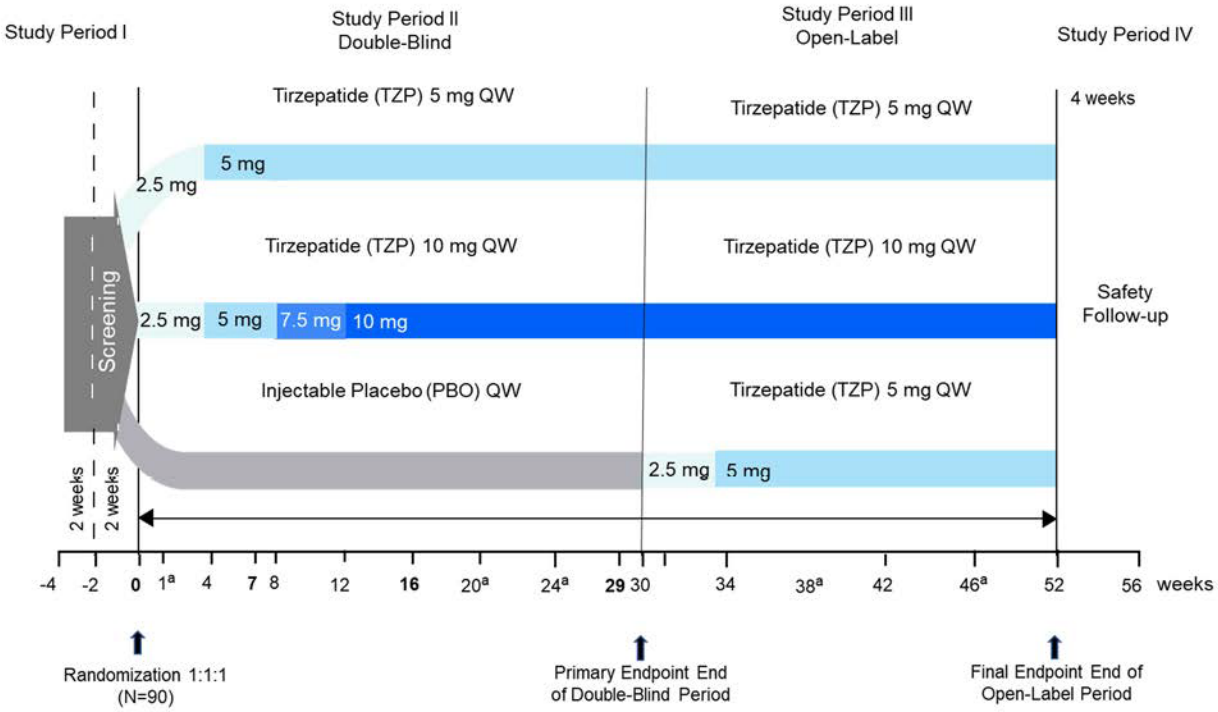
Study Period	Duration	Intervention
Screening/lead-in	Approximately 4 weeks	-----
Double-blind, placebo-controlled	30 weeks	5 mg tirzepatide 10 mg tirzepatide, or placebo
Open-label extension on active treatment period	22 weeks	5 mg tirzepatide, or 10 mg tirzepatide
Post-treatment safety follow-up	30 days	-----

In the 22-week open-label period, participants in 5 mg and 10 mg arms will continue with current treatment while participants randomized to placebo will initiate treatment at 2.5 mg QW and after 4 weeks, will receive 5 mg tirzepatide for the remainder of the period.

Data Monitoring Committee:

An external data monitoring committee (DMC) will have the responsibility to review unblinded interim analyses results to monitor the safety of the participants in the study until the last participant completes the Week 52 visit. More details will be included in the DMC charter.

1.2. Schema



Abbreviations: PK = pharmacokinetics; QW = once weekly; V = visit.

[a] Phone visit.

CCI [redacted]

1.3. Schedule of Activities (SoA)

1.3.1. Screening and Double-Blind Period SoA

Perform procedures as indicated.

Study I8F-MC-GPGV	Screening		Double-Blind Period											Notes
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic CCI	Clinic	Clinic	Clinic	Phone	Phone	Clinic CCI	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	
Week	**-4**	**-2**	**0**	**1**	**4**	**7[a]**	**8**	**12**	**16**	**20**	**24**	**29[a]**	**30**	CCI [redacted]
Allowed Visit Intervals (D)		**±7**	___	**±3**	**±7**		**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit			**X**				**X**		**X**				**X**	Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be temporarily adjusted upon clinical judgment of the investigator.
Procedures														
Informed consent and assent	**X**													Parent/legal guardian signs informed consent form and participant signs assent form before any tests or procedures are performed.
Evaluation of inclusion and exclusion criteria	**X**	**X**	**X**											
Medical history/ preexisting conditions	**X**													Investigators should review the vaccination status of their participants.
Demographics	**X**													Includes ethnicity (United States only), full date of birth, gender, race.
Adverse events (AE)	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	
Concomitant medications	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	
Physical Evaluations														
Physical Exam			**X**						**X**				**X**	
Tanner Staging			**X**						**X**				**X**	Participants who have reached Tanner stage 5 will not be evaluated again. Tanner staging details in Appendix 9, Section 10.9.

Study I8F-MC-GPGV	Screening		Double-Blind Period											Notes
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic CCI	Clinic	Clinic	Clinic	Phone	Phone	Clinic CCI	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	
Week	**-4**	**-2**	**0**	**1**	**4**	**7[a]**	**8**	**12**	**16**	**20**	**24**	**29[a]**	**30**	CCI
Allowed Visit Intervals (D)		**±7**	___	**±3**	**±7**		**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit			**X**				**X**		**X**				**X**	Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be temporarily adjusted upon clinical judgment of the investigator.
Symptom-directed physical exam by physician					**X**		**X**	**X**						See Section 8.2.1.
Vital signs	**X**		**X**		**X**		**X**	**X**	**X**				**X**	Vital sign measurements should be taken before collection of blood samples for laboratory testing, at visits where required. For instructions see Appendix 11, Section 10.11.
Height (cm)	**X**		**X**		**X**		**X**	**X**	**X**				**X**	Triplicate measurements must be in centimeters. For instructions see Appendix 11, Section 10.11.
Weight (kg)	**X**		**X**		**X**		**X**	**X**	**X**				**X**	Measurements must be in kilograms. For instructions see Appendix 11, Section 10.11.
Calculation of BMI	**X**													
Waist circumference (cm)			**X**		**X**		**X**	**X**	**X**				**X**	Measurements must be in centimeters. For instructions see Appendix 11, Section 10.11.
Visual acuity checks and dilated fundoscopic examination		**X**												Visual acuity checks and dilated fundoscopic examination will be scheduled between Visit 2 and Visit 3 only after review of laboratory results from Visit 1 (except for GAD65, Islet cell Ab results if sent and pending at Visit 2) and participant qualifying in all other criteria. The exam will be performed by an eye care professional (ophthalmologist or optometrist) for all participants. A previous exam ≤90 days of screening meeting study requirements is acceptable to confirm eligibility. Additional visual acuity checks and dilated fundoscopic examinations should be performed when clinically indicated by any suspicion of worsening retinopathy. See Section 8.3.3.6.

Study I8F-MC-GPGV	Screening		Double-Blind Period											Notes
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic CCI	Clinic	Clinic	Clinic	Phone	Phone	Clinic CCI	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	
Week	**-4**	**-2**	**0**	**1**	**4**	**7[a]**	**8**	**12**	**16**	**20**	**24**	**29[a]**	**30**	CCI [redacted]
Allowed Visit Intervals (D)		**±7**	___	**±3**	**±7**		**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit			**X**				**X**		**X**				**X**	Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be temporarily adjusted upon clinical judgment of the investigator.
ECG			**X**										**X**	Vital Signs should be taken before ECG, see Section 8.2.6.
Establish baseline basal insulin dose (if applicable)			**X**											Visit 1 HbA1c will be used to establish the baseline dose for basal insulin. Once this dose is established, it should remain stable (± 15%) during the study, although it may be decreased at any time if the participant experiences hypoglycemia. Visit 3: All participants with a HbA1c <8% at Visit 1 will reduce their daily dose of basal insulin by 20% to reduce the potential risk of hypoglycemia. (see Management of Increased Risk of Hypoglycemia, Section 6.5.2. for further details.).
Review menstrual cycle history	**X**		**X**		**X**		**X**	**X**	**X**	**X**	**X**		**X**	All applicable female participants.
Participant Education														
Discussion of effective contraception	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	For males who have reached puberty and are sexually active, and for females of childbearing potential. For contraceptive guidance see Appendix 4, Section 10.4
Review hypoglycemic events		**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	Includes SMBG results, hypoglycemic events, date, and exact time of every study intervention injection.
BG meter/SMBG training		**X**												Participant or parent or guardian will be trained at randomization. Additional training may occur as needed.
Dispense BG meter/supplies as needed		**X**			**X**		**X**	**X**	**X**				**X**	

Study I8F-MC-GPGV	Screening		Double-Blind Period											Notes
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic CCI	Clinic	Clinic	Clinic	Phone	Phone	Clinic CCI	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	
Week	**-4**	**-2**	**0**	**1**	**4**	**7[a]**	**8**	**12**	**16**	**20**	**24**	**29[a]**	**30**	CCI [redacted]
Allowed Visit Intervals (D)		**±7**	___	**±3**	**±7**		**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit			**X**				**X**		**X**				**X**	Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be temporarily adjusted upon clinical judgment of the investigator.
Remind patients about 6-point SMBG		**X**									**X**			Patient is required to collect two 6-point SMBGs on 2 nonconsecutive days prior to the next visit. A 6-point SMBG consists of measurement before and 2 hours after each of 3 main meals within the same day. These SMBG profiles will be collected by the patient within 2 weeks prior to the assigned visits.
Review 6-point SMBG values collected in the diaries			**X**										**X**	
Lifestyle management instruction (ie, diet and exercise)		**X**			**X**		**X**	**X**	**X**				**X**	See Section 5.3.
Participant diary (electronic)														
Dispense e-diary to participant and train on use		~~**X**~~												
Laboratory Testing														
Islet cell Ab (IA2)	**X**													
GAD65	**X**													
Hematology	**X**		**X**				**X**		**X**				**X**	See Appendix 2. Section 10.2
Clinical chemistry	**X**		**X**				**X**		**X**				**X**	See Appendix 2. Section 10.2
Lipid Panel			**X**				**X**		**X**				**X**	
Serum glucose	**X**		**X**		**X**		**X**	**X**	**X**				**X**	
HbA1c	**X**		**X**		**X**		**X**	**X**	**X**				**X**	
Pancreatic amylase	**X**								**X**				**X**	

Study I8F-MC-GPGV	Screening		Double-Blind Period											Notes
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic CCI	Clinic	Clinic	Clinic	Phone	Phone	Clinic CCI	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	
Week	**-4**	**-2**	**0**	**1**	**4**	**7[a]**	**8**	**12**	**16**	**20**	**24**	**29[a]**	**30**	CCI
Allowed Visit Intervals (D)		**±7**	___	**±3**	**±7**		**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit			**X**				**X**		**X**				**X**	Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be temporarily adjusted upon clinical judgment of the investigator.
Lipase	**X**								**X**				**X**	
Thyroid-stimulating hormone (TSH)	**X**												**X**	
Thyroxine (T4, free)	**X**												**X**	
Calcitonin	**X**								**X**				**X**	
eGFR (CKD-EPI)	**X**		**X**				**X**		**X**				**X**	
Urinary albumin/creatinine ratio			**X**										**X**	
Serum pregnancy test	**X**								**X**					For females of childbearing potential a serum pregnancy test will be performed at Visits 1 and 9 and additional times if needed based on the clinical judgment of the investigator.
Urine pregnancy test			**X**	**X[b]**	**X**		**X**	**X**	**X**	**X[b]**	**X[b]**		**X**	Females of childbearing potential: Must complete a local urine pregnancy test at Visit 3 with the result available prior to randomization and prior to receiving study intervention at all subsequent visits. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period. [b] If pregnancy is suspected, the participant should come to the clinic for a urine and serum test. If a local urine pregnancy test is performed at the clinic, collect serum pregnancy test at the same time and send to central laboratory.
Insulin			**X**				**X**		**X**				**X**	
Proinsulin, intact			**X**				**X**		**X**				**X**	

Study I8F-MC-GPGV	Screening		Double-Blind Period											Notes
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic CCI	Clinic	Clinic	Clinic	Phone	Phone	Clinic CCI	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	
Week	**-4**	**-2**	**0**	**1**	**4**	**7[a]**	**8**	**12**	**16**	**20**	**24**	**29[a]**	**30**	CCI
Allowed Visit Intervals (D)		**±7**	___	**±3**	**±7**		**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit			**X**				**X**		**X**				**X**	Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be temporarily adjusted upon clinical judgment of the investigator.
C-peptide			**X**				**X**		**X**				**X**	
Glucagon			**X**				**X**		**X**				**X**	
Adiponectin, total			**X**				**X**		**X**				**X**	
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]		CCI [redacted]
Immunogenicity			**X**		**X**			**X**					**X**	In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional blood samples will be collected including ADA, CCI and exploratory immune safety samples. Immunogenicity samples must be taken prior to intervention administration (see Appendix 2, Section 10.2).
CCI [redacted]			[redacted]		[redacted]			[redacted]					[redacted]	[redacted]
Stored Samples														
Genetics			**X**											
Exploratory biomarkers			**X**				**X**		**X**				**X**	

Study I8F-MC-GPGV	Screening		Double-Blind Period											Notes
	Clinic	Clinic	Clinic	Phone	Clinic	Clinic CCI	Clinic	Clinic	Clinic	Phone	Phone	Clinic CCI	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	
Week	**-4**	**-2**	**0**	**1**	**4**	**7[a]**	**8**	**12**	**16**	**20**	**24**	**29[a]**	**30**	CCI
Allowed Visit Intervals (D)		**±7**	___	**±3**	**±7**		**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit			**X**				**X**		**X**				**X**	Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be temporarily adjusted upon clinical judgment of the investigator.
Patient Rated Outcomes (PRO) (electronic) Note: Complete questionnaires before any other study procedures														
EQ-5D-Y			**X**										**X**	
PedsQL Generic Core Scales			**X**										**X**	Age appropriate PedsQL should be used at baseline and the same version used for the entire study.
PedsQL (3.2) Diabetes Module			**X**										**X**	Age appropriate PedsQL should be used at baseline and the same version used for the entire study.
Randomization and Dosing														
Randomization			**X**											
Study intervention injection training			**X**											Use demonstration pen which does not have a needle and is filled with air. Training at Visit 3 is required. Additional training may occur as needed.
Distribute study intervention			**X**		**X**		**X**	**X**	**X**				**X**	
Participant returns study interventions and injection supplies					**X**		**X**	**X**	**X**				**X**	
Assess study intervention compliance					**X**		**X**	**X**	**X**	**X**	**X**		**X**	

Abbreviations: Ab = antibodies; ADA = anti-drug antibodies; AE = adverse event; BG = blood glucose; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; D = days; ECG = electrocardiogram; e-diary = electronic diary; eGFR = estimated glomerular filtration rate; GAD65 = glutamic acid decarboxylase 65 autoantibodies; HbA1c = hemoglobin A1c; IA2 = tyrosine phosphatase-like insulinoma antigen 2 autoantibodies; IWRS = Interactive Web-Response System; PedsQL = Pediatric Quality of Life Inventory; CCI PRO = Patient Reported Outcomes; SMBG = self-monitored blood glucose; V = visit.

1.3.2. Open-Label and Follow-up Period SoA

Perform procedures as indicated.

FhStudy I8F-MC-GPGV	Open-Label Period							Follow-up Period	Notes
	Phone	Clinic	Phone	Clinic	Phone	Clinic	Clinic	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**ET**	**V801**	
Week	**31**	**34**	**38**	**42**	**46**	**52**		**56**	
Allowed Visit Intervals (D)	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit						**X**	**X**		Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be adjusted upon clinical judgment of the investigator.
Procedures									
Adverse events	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Physical Evaluations									
Physical Exam						**X**	**X**	**X**	
Tanner Staging						**X**	**X**		Participants who have reached Tanner stage 5 will not be evaluated again. Tanner staging details in Appendix 9, Section 10.9
Symptom-directed physical exam by physician				**X**					See Section 8.2.1.
Vital signs				**X**		**X**	**X**	**X**	Vital sign measurements should be taken before collection of blood samples for laboratory testing, at visits where required. See Appendix 11, Section 10.11
Height (cm)				**X**		**X**	**X**	**X**	Measurements must be in centimeter. For instructions see Appendix 11 Section 10.11
Weight (kg)				**X**		**X**	**X**	**X**	Measurements must be in kilogram. For instructions see Appendix 11, Section 10.11
Waist circumference (cm)				**X**		**X**	**X**	**X**	Measurements must be in centimeter. For instructions see Appendix 11 Section 10.11
Visual acuity checks and dilated fundoscopic examination						**X**	**X**		V19 allowable window of ±21 days. ET allowable window of +21 days. If the ET visit is scheduled within 6 months of the previous visual acuity checks and dilated fundoscopic examination, follow-up exam is not needed.

FhStudy I8F-MC-GPGV	Open-Label Period							Follow-up Period	Notes
	Phone	Clinic	Phone	Clinic	Phone	Clinic	Clinic	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**ET**	**V801**	
Week	**31**	**34**	**38**	**42**	**46**	**52**		**56**	
Allowed Visit Intervals (D)	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit						**X**	**X**		Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be adjusted upon clinical judgment of the investigator.
ECG						**X**	**X**		Vital Signs must be taken before ECG, see Section 8.2.6
Review menstrual cycle history	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	All applicable female participants.
Participant Education									
Discussion of effective contraception	**X**	**X**	**X**	**X**	**X**	**X**	**X**		For males who have reached puberty and are sexually active, and for females of childbearing potential. For contraceptive guidance see Appendix 4, Section 10.4.
Review hypoglycemic events collected	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	Includes SMBG results, hypoglycemic events, date, and exact time of every study intervention injection.
Dispense BG meter/supplies as needed		**X**		**X**					Participant or parent or guardian will be trained as needed.
Lifestyle management instruction (ie, diet and exercise)		**X**		**X**		**X**			See Section 5.3.
Participant Diary (electronic)									
e-Diary return							**X**	**X**	
Laboratory Testing									
Hematology				**X**		**X**	**X**	**X**	See Appendix 2. Section 10.2
Clinical chemistry				**X**		**X**	**X**	**X**	See Appendix 2. Section 10.2
Lipid Panel				**X**		**X**	**X**	**X**	
Serum glucose				**X**		**X**	**X**	**X**	
HbA1c				**X**		**X**	**X**	**X**	
Pancreatic amylase				**X**		**X**	**X**	**X**	

FhStudy I8F-MC-GPGV	Open-Label Period							Follow-up Period	Notes
	Phone	Clinic	Phone	Clinic	Phone	Clinic	Clinic	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**ET**	**V801**	
Week	**31**	**34**	**38**	**42**	**46**	**52**		**56**	
Allowed Visit Intervals (D)	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit						**X**	**X**		Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be adjusted upon clinical judgment of the investigator.
Lipase				**X**		**X**	**X**	**X**	
Thyroid-stimulating hormone (TSH)						**X**			
Thyroxine (T4, free)						**X**			
Calcitonin				**X**		**X**	**X**	**X**	
eGFR (CKD-EPI)				**X**		**X**	**X**	**X**	
Urinary albumin/creatinine ratio						**X**	**X**	**X**	
Serum pregnancy test				**X**			**X**		In females of childbearing potential only.
Urine pregnancy test	**X[a]**	**X**	**X*[a]**	**X**	**X[a]**	**X**	**X**		If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period. [a] If pregnancy is suspected, the participant should come to the clinic for this test. If a local urine pregnancy test is performed, collect serum pregnancy test at the same time and send to central laboratory.
Insulin						**X**	**X**		
Proinsulin, intact						**X**	**X**		
C-peptide						**X**	**X**		
Glucagon						**X**	**X**		
Adiponectin, total						**X**	**X**		
CCI [redacted]							[redacted]		

FhStudy I8F-MC-GPGV	Open-Label Period							Follow-up Period	Notes
	Phone	Clinic	Phone	Clinic	Phone	Clinic	Clinic	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**ET**	**V801**	
Week	**31**	**34**	**38**	**42**	**46**	**52**		**56**	
Allowed Visit Intervals (D)	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit						**X**	**X**		Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be adjusted upon clinical judgment of the investigator.
Immunogenicity				**X**		**X**	**X**	**X**	In the event of systemic intervention hypersensitivity reactions (immediate or nonimmediate), additional blood samples will be collected including ADA, CCI and exploratory immune safety samples. Immunogenicity samples must be taken prior to intervention administration (see Appendix 2, Section 10.2).
CCI [redacted]				[redacted]		[redacted]		[redacted]	[redacted].
Stored Samples									
Exploratory biomarker samples				**X**		**X**	**X**	**X**	

FhStudy I8F-MC-GPGV	Open-Label Period							Follow-up Period	Notes
	Phone	Clinic	Phone	Clinic	Phone	Clinic	Clinic	Clinic	Type of visit. Any phone visit may be converted to a clinic visit if deemed medically necessary by study personnel.
Visit	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**ET**	**V801**	
Week	**31**	**34**	**38**	**42**	**46**	**52**		**56**	
Allowed Visit Intervals (D)	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	
Fasting Visit						**X**	**X**		Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity. The dose of insulin on a fasting visit may be adjusted upon clinical judgment of the investigator.
Patient Reported Outcomes (PRO) Note: Complete questionnaires before any other study procedures									
EQ-5D-Y						**X**	**X**		
PedsQL Generic Core Scales						**X**	**X**		
PedsQL (3.2) Diabetes Module						**X**	**X**		
Dosing									
Distribute study intervention		**X**		**X**					
Participant returns study interventions and injection supplies		**X**		**X**		**X**	**X**	**X**	
Assess study intervention compliance		**X**	**X**	**X**	**X**	**X**	**X**		

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; BG = blood glucose; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; D = days; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; HbA1c = hemoglobin A1c; PedsQL = Pediatric Quality of Life Inventory; CCI PRO = Patient Reported Outcomes; SMBG = self-monitored blood glucose; V = visit.

2. Introduction

The state of T2DM in youth today

Type 2 diabetes mellitus is a disease that is primarily diagnosed in adults, and the risk of the disease increases with age (CDC 2020 [WWW]). However, there has been a significant relative increase of T2DM in the pediatric and adolescent population in recent years, although the absolute number of youth with T2DM remains a low portion of all diabetes in this population (Dabelea et al. 2014; Lawrence et al. 2021).

Pathophysiology of T2DM in youth

In adults and youth with T2DM, the pathophysiology of the disease is characterized by insulin resistance in the peripheral tissues and the liver and decreased insulin secretion by pancreatic β cells (D'Adamo and Caprio 2011). However, T2DM in youth is a more aggressive disease than in adults with higher insulin resistance, more rapid decline in β-cell function and higher risk of microvascular and macrovascular complications at a younger age than study participants with T1DM, and after a shorter interval than adults with T2DM (ADA 2021a; Constantino et al. 2013; RISE Consortium 2018; TODAY Study Group 2021).

Treatment options for youth with T2DM

Youth with T2DM have fewer approved glucose-lowering treatment options compared to adults with T2DM (ADA 2021a; ADA 2021b). Metformin, insulin and GLP-1 receptor agonist (RA) are the only agents approved in the US and EU for the treatment of children and adolescents with T2DM (Tamborlane et al. 2019). Metformin monotherapy is often inadequate for achieving and maintaining glycemic control in youth with T2DM (TODAY Study Group 2012; Badaru et al. 2014). The subsequent options to metformin are limited to insulin and GLP-1 RAs (liraglutide and exenatide 2 mg QW recently approved in the US) for youth with T2DM. Insulin is associated with weight gain while GLP-1 RAs are not (Tamborlane et al. 2019, 2021). Therefore, there is an important clinical need for additional approved agents to treat children and adolescents with T2DM that are safe and effective in this population with potent glycemic and weight loss effects.

Tirzepatide

Tirzepatide is a dual GIP and GLP-1 receptor agonist that is currently being investigated for its potential use in the treatment of T2DM as a QW SC injection. Tirzepatide is a single molecule based on the GIP sequence and it includes a C20 fatty diacid moiety. It has a half-life of approximately 5 days enabling once weekly administration.

This study is designed to investigate the efficacy, safety, and PK/PD of tirzepatide (5 mg and 10 mg) in the pediatric and adolescent population aged 10 years to under 18 years with T2DM who have inadequate glycemic control, despite diet and exercise, with metformin or basal insulin, or both. The double-blind period of the clinical trial will last for 30 weeks and will test placebo against tirzepatide 5 and 10 mg SC injection QW. This will be followed by the 22-week open-label period of the clinical trial where all participants will receive either tirzepatide 5 mg/week or 10 mg/week, which will be followed by a 30-day safety follow-up period.

2.1. Study Rationale

This study aims to evaluate the efficacy and safety of tirzepatide in the pediatric population. The data from this study will inform the clinical development of tirzepatide.

2.2. Background

Because of the pathophysiological similarities between T2DM in adults and youth, it is hypothesized that tirzepatide will have efficacy in the pediatric and adolescent population with a similar safety profile as in the adult population. The background therapies of diet and exercise, with metformin or basal insulin, or both, are considered appropriate, as these are approved treatments for pediatric and adolescent participants with T2DM in the US, EU, and many countries around the world.

In four Phase 3 studies in adults with T2DM, once weekly tirzepatide was associated with clinically relevant improvement in glycemia and body weight, with low risk of hypoglycemia, and a safety profile similar to approved agents from the GLP-1 RA class (Rosenstock et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Dahl et al. 2021 abstract). Of the Phase 3 studies, the two placebo-controlled studies, SURPASS-1 (Study I8F-MC-GPGK) and SURPASS-5 (Study I8F-MC-GPGI) provide the benefit/risk information for tirzepatide.

SURPASS-1 (monotherapy)

This 40-week Phase 3 study assessed the efficacy, tolerability, and safety of QW administration of 3 doses (5 mg, 10 mg, and 15 mg) of tirzepatide versus placebo in 478 adult participants with T2DM with inadequate glycemic control on diet and exercise. Baseline characteristics of the participants included a mean age of 54.1 years, diabetes duration of 4.7 years, HbA1c of 7.9% and BMI of 31.9 kg/m^2 (Rosenstock et al. 2021).

Tirzepatide 5 mg, 10 mg, and 15 mg doses significantly reduced HbA1c by 1.87%, 1.89% and 2.07% respectively compared to placebo (+0.04%) and 81% to 86% of those patients receiving tirzepatide achieved HbA1c goal≤6.5% and 31% to 52% achieved normoglycemia (HbA1c<5.7%). In addition, tirzepatide treatment led to a reduction in body weight of 7 to 9.5 kg with 31% to 47% of the patients achieving ≥ 10% weight loss goal. Similar to the GLP-1 receptor agonist class, most of the tirzepatide adverse events (AEs) were gastrointestinal (GI)-related, consisting mainly of nausea, vomiting, and diarrhea and mild to moderate in severity. Serious adverse events (SAEs) were balanced across the treatment groups and no participant from the study reported severe hypoglycemia.

SURPASS-5 (add-on to basal insulin)

This 40-week Phase 3 study assessed the efficacy, tolerability, and safety of QW administration of 3 doses (5 mg,10 mg, and 15 mg) of tirzepatide, as compared with placebo in 475 adult participants with T2DM as an add-on to titrated basal insulin glargine with or without metformin. Baseline characteristics of the participants included a mean age of 60.6 years, diabetes duration of 13.3 years, HbA1c of 8.31% and BMI of 33.4 kg/m^2 (Dahl et al. 2021 abstract).

Tirzepatide 5 mg, 10 mg, and 15 mg doses significantly reduced HbA1c by 2.23%, 2.59% and 2.59% respectively compared to placebo (-0.93%) and 80% to 95% of those receiving tirzepatide achieved HbA1c goal≤6.5% and 26% to 62% achieved normoglycemia (HbA1c>5.7%). In addition, tirzepatide treatment led to a reduction in body weight of 6.2 to 10.9 kg with 23% to 51% achieving ≥ 10% weight loss goal. Similar to the GLP-1 receptor agonist class, most of the tirzepatide AEs were GI-related, consisting mainly of nausea, vomiting, and diarrhea and mild to moderate in severity. Serious adverse events were similar across the

treatment groups and the relative rate of clinically significant hypoglycemia events (BG <54 mg/dL) was similar across all groups.

These data support development of tirzepatide as a therapy for T2DM in the pediatric and adolescent population.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Because tirzepatide is a dual GIP and GLP-1 receptor agonist, the potential risks associated with tirzepatide are expected to be similar to risks associated with currently available GLP-1 receptor agonists.

Risks associated with tirzepatide are detailed in Section 6.1 of the IB.

Adverse events of special interest (AESI), which include the risks associated with tirzepatide are described in Section 8.3.3. Each of the AESI will be monitored as described in Section 1.3 and Section 8.3.3.

Study design

To protect the safety of the participants enrolled in both the placebo and treatment arms of this study, the double-blind period is relatively short. There are also clear rescue criteria for participants with severe, persistent hyperglycemia (see Section 8.3.3.2), in addition to continuing the baseline antihyperglycemic medications such as metformin and/or basal insulin.

Gastrointestinal symptom management

The dose escalation scheme (Section 6.5) used in this study will help mitigate the GI symptoms associated with tirzepatide.

Additional guidance on the management of GI symptoms such as small meals, symptomatic medications and skipping a dose of the study intervention is described in Section 6.5.4.

Hypoglycemia

Participants with baseline HbA1c <8% and on basal insulin will be instructed to reduce the dose of basal insulin by 20% upon randomization to reduce the risk of hypoglycemia. If a hypoglycemic event occurs, insulin therapy and metformin doses may be further reduced or stopped as detailed in Section 6.5.2.

For complete details regarding the management of hypoglycemia risk, see Section 6.5.2.

Developmental and reproductive safety

Developmental risks in the pediatric and adolescent population will be monitored by regular height and weight measurements and Tanner staging (Section 1.3).

To mitigate possible reproductive risks, pregnant or lactating females are excluded from the study.

Effective contraception use will be discussed regularly with males who have reached puberty and are sexually active, and with females of childbearing potential (Section 10.4.2).

Menstrual cycle reviews and regular pregnancy testing (Section 8.2.4) will also occur for females of childbearing potential. For females who entered the study at prepubertal state, physical exams with Tanner

Staging, time of menarche and menstrual cycle reviews throughout the study period will help monitor for transition to childbearing potential state (Appendix 9, Section 10.9).

2.3.2. Benefit Assessment

Clinical safety and efficacy

In four Phase 3 studies in adults with T2DM, QW tirzepatide was associated with clinically relevant improvement in glycemia and body weight with low risk of hypoglycemia, and a safety profile similar to approved agents from the GLP-1 receptor agonist class (Rosenstock et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Dahl et al. 2021 abstract). Because of the pathophysiological similarities between T2DM in adults and youth, it is hypothesized that tirzepatide will also have efficacy in the pediatric and adolescent population with a similar safety profile.

Unmet therapeutic need

Youth with T2DM have fewer approved glucose-lowering treatment options compared to adults with T2DM, and T2DM in youth is a more aggressive disease than in adults with higher insulin resistance, more rapid decline in β-cell function, and higher risk of microvascular and macrovascular complications at a younger age (ADA 2021a; ADA 2021b; Constantino et al. 2013; RISE Consortium 2018; TODAY Study Group 2021). Therefore, there is an important clinical need for additional options to treat children and adolescents with T2DM that are effective with an acceptable safety profile with potent glycemic and weight loss effects.

This study will provide the participants with another treatment option for T2DM. The 1:1:1 randomization ratio of tirzepatide 5 mg QW:tirzepatide 10 mg QW:placebo QW provides participants with a better chance of receiving active intervention rather than placebo, and all participants will receive active intervention during the open-label period.

2.3.3. Overall Benefit Risk Conclusion

The overall benefit-risk assessment for this study is considered favorable. Current efficacy data provides the rationale to evaluate tirzepatide as a therapeutic option for participants in this age group with T2DM. The current safety profile of tirzepatide appears similar to the GLP-1 RA class, and measures will be taken to minimize the identified risks to participants in this study.

3. Objectives, Endpoints and Estimands

Objectives	Endpoints
Primary	
Efficacy • To demonstrate that pooled 5 mg and 10 mg tirzepatide QW is superior to placebo at 30 weeks	• Change in HbA1c from baseline
Key Secondary (controlled for type 1 error)	
Efficacy • To demonstrate that 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, is superior to placebo at 30 weeks	• Incidence of HbA1c ≤6.5% • Change in BMI standard deviation score (age- and sex-matched) from baseline • Change in fasting serum glucose (FSG) from baseline
• To demonstrate that 5 mg and 10 mg tirzepatide QW, analyzed as separate treatment arms, is superior to placebo at 30 weeks	• Change in HbA1c from baseline
Additional Secondary (not controlled for type 1 error)	
• To demonstrate that 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, is superior to placebo at 30 weeks	• Incidence of HbA1c <7.0% • Incidence of HbA1c <5.7% • Change in daily average 6-point self-monitored blood glucose profiles from baseline
• To assess the effect of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, at 52 weeks	• Change in HbA1c from baseline • Incidence of HbA1c <7.0% • Incidence of HbA1c ≤6.5% • Incidence of HbA1c <5.7% • Change in BMI standard deviation score (age- and sex-matched) from baseline • Change in FSG from baseline
• To compare 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, to placebo at 30 weeks; and to assess the effect of 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms at 52 weeks	• Change from baseline for serum lipid levels • Incidence of new or worsening of dyslipidemia

• To assess safety of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, at 30 weeks and at the end of the safety follow-up period	• Treatment-emergent adverse events (TEAEs) • Discontinuation of study intervention due to adverse events (AEs) • Adjudicated pancreatic AEs • Serum calcitonin • Incidence of allergic, hypersensitivity reactions, and injection site reactions • Incidence of treatment-emergent anti-drug antibodies to tirzepatide • Change in systolic and diastolic blood pressure and heart rate from baseline • Incidence of new or worsening of hypertension • Incidence of new or worsening of albuminuria • Occurrence of hypoglycemic events • Incidence of initiation of rescue therapy for severe-persistent hyperglycemia • Incidence of new or worsening of diabetic neuropathy
• To compare 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, to placebo at 30 weeks; and to assess the effect of 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms at 52 weeks	• Change from baseline for physical and developmental measures o Height and weight o Height SDS and weight SDS o Waist circumference, and o Tanner Staging
• To assess the safety of 5 mg and 10 mg tirzepatide QW, analyzed as separate and pooled arms, at 52 weeks for diabetic retinopathy	• Incidence of new or worsening of diabetic retinopathy or diabetic maculopathy in either eye
• Characterize the pharmacokinetics and pharmacodynamic relationships of tirzepatide	• Relationship between tirzepatide exposure and key safety and efficacy measures
• To assess the effect of 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, on patient reported outcomes at 30 and 52 weeks	• Change from baseline for o PedsQL Generic Core Scales o PedsQL (3.2) Diabetic Module from baseline
Tertiary/Exploratory	
• To compare 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, to placebo at 30 weeks; and to assess the effect of 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms at 52 weeks	• Incidence of HbA1c ≤6.5% without severe or documented symptomatic (<70 mg/dL) hypoglycemia • Incidence of HbA1c <7.0% without severe or documented symptomatic (<70 mg/dL) hypoglycemia
• To assess the effect of 5 mg, and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, on patient reported outcomes at 30 and 52 weeks	• Change from baseline for EQ-5D-Y
• To assess the effect of 5 mg, and 10 mg tirzepatide QW, separately and pooled, at	• Measures of insulin resistance, alpha cell and beta cell function, and serum adiponectin

Weeks 8, 16 and 30 on additional metabolic measures	

Abbreviations: AEs = adverse events; BMI = body mass index; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; PedsQL = Pediatric Quality of Life Inventory; QW = once weekly; SDS = standard deviation score.

Treatment-Regimen Estimand

The clinical question of interest for the "treatment-regimen estimand" is the treatment difference between tirzepatide and placebo after 30 weeks of intervention in pediatric and adolescent participants with T2DM, regardless of intervention discontinuation for any reason (excluding inadvertently enrolled participants who have discontinued study intervention for that reason) and regardless of initiation of rescue antihyperglycemic intervention.

Treatment-regimen estimand attributes

- *Population:* pediatric and adolescent participants with T2DM who meet the inclusion and exclusion criteria. Further details on participants population and inclusion/exclusion criteria can be found in Section 5.
- *Treatment condition:* the randomized treatment with or without rescue antihyperglycemic medication. Further details on study interventions and concomitant, including rescue, interventions can be found in Section 6.
- *Endpoints:* the primary and key secondary endpoints will be studied. Further details on the endpoints can be found in the Objectives and Endpoints table.
- *Population level summary:* the difference in mean change from baseline to 30 weeks will be used for continuous endpoints and the difference in proportion (absolute or relative, as appropriate) will be used for dichotomous endpoints. The population level summary will be conducted using Full Analysis Set (FAS). Further details on statistical analyses and analysis sets can be found in Section 9.
- *Intercurrent events:* the 2 intercurrent events "intervention discontinuation for any reason" and "initiation of rescue intervention" are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.
- *Rationale:* the "treatment-regimen estimand" estimates treatment effect, including the effect of intervention discontinuation and rescue medication to reflect clinical practice.

Efficacy Estimand

The clinical question of interest for the "efficacy estimand" is the treatment difference between tirzepatide and placebo after 30 weeks of intervention in pediatric and adolescent participants with T2DM, ***prior to*** intervention discontinuation for any reason and ***prior to*** the initiation of rescue antihyperglycemic intervention.

Efficacy estimand attributes

The population and endpoints attributes for the "efficacy estimand" are the same as the "treatment-regimen estimand". This describes additional attributes for the efficacy estimand.

- *Treatment condition:* the randomized treatment without rescue antihyperglycemic medication.
- *Population level summary:* the difference in mean change from baseline to 30 weeks will be used for continuous endpoints and the difference in proportion (absolute or relative, as appropriate) will be used for dichotomous endpoints. The population level summary will be conducted using Efficacy Analysis Set (EAS).

- *Intercurrent events:* the 2 intercurrent events "intervention discontinuation for any reason" and "initiation of rescue intervention" are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.
- *Rationale:* The "efficacy estimand" provides an on-treatment assessment without confounding the treatment effect from off-treatment or rescue antihyperglycemic therapy data.

4. Study Design

4.1. Overall Design

Study GPGV is a Phase 3, randomized, double-blind, placebo-controlled study in pediatric and adolescent participants with T2DM inadequately controlled with metformin or basal insulin, or both, to assess the efficacy, safety, and PK/PD of tirzepatide at 30 and at 52 weeks following a 22-week open-label extension period after Week 30.

The study will consist of 4 periods

- an approximate 4-week screening period,
- a 30-week double-blind placebo-controlled period,
- a 22-week open-label extension period on active treatment, and
- a 30-day post-treatment safety follow-up period.

4.1.1. Overview of Study Visits

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

A parent or legal guardian must accompany the participant at each visit.

For clinic visits noted in the SoA, the participant will arrive at the clinic in a fasted state, at least 8 hours without eating and drinking except for water.

Throughout the study, participant or parent or guardian should perform a self-monitored blood glucose (SMBG) in the fasted state 3 times per week, two 6-point SMBGs on nonconsecutive days prior to Visit 3 and Visit 13 as well as at any time the participant has symptoms suggestive of hypoglycemia (See Section 8.3.3.1).

This table describes the visit types.

Visit Number	Visit Type
1-3, 5-9, 12, 13, 15, 17, and 19	Clinic
4, 10, 11, 14, 16, and 18	Telephone visits
6 and 12	CCI [redacted]
Early termination (if applicable) and 801 follow-up	Clinic

Abbreviation: PK = pharmacokinetic.

Any telephone visit may be converted to a clinic visit if deemed medically necessary by study personnel.

Screening

Visit 1 Clinic Visit

The parent or legal guardian(s) will sign the informed consent form (ICF) and the participant will sign the assent form. If the participant has reached the age of majority per local country regulations, a separate assent document may not be required, as the participant will be eligible to sign the ICF. The ICF and assent must be signed before any study procedures are performed.

The purpose of screening procedures at Visit 1 and Visit 2 is to establish eligibility.

Doses of metformin and basal insulin must be stable (±15% for basal insulin) for at least 90 days prior to the screening visit.

Visit 2 Clinic Visit

Available laboratory results are reviewed, and applicable inclusion/exclusion criteria evaluated.

Concomitant medication is documented, and AEs reviewed.

The participant and parent or legal guardian will receive

- study e-diaries and instructions on how to complete them
- a glucometer, supplies, and training
- instruction on measuring two 6-point SMBGs on nonconsecutive days within two weeks prior to Visit 3, and
- diet and exercise instruction for their T2DM

If a participant qualifies for the study based on inclusion and exclusion criteria thus far, a visual acuity check and dilated fundoscopic examination will be performed by an eye care professional (ophthalmologist or optometrist) between Visit 2 and Visit 3. A previous exam ≤90 days of screening meeting study requirements by an ophthalmologist or optometrist is acceptable.

Visit 3 Randomization

The baseline dose for basal insulin will be established based on Visit 1 HbA1c. Once this dose is established, it must remain stable during the study (±15%), although it may be further decreased at any time if the participant experiences hypoglycemia. All participants with a Visit 1 HbA1c <8%, will reduce their daily dose of basal insulin by 20% at randomization to reduce the potential risk of hypoglycemia (see Management of Increased Hypoglycemia Risk, Section 6.5.2). The 6-point SMBG data will be reviewed at this visit.

The participant and parent or legal guardian will receive study intervention injection training and study intervention supply.

Prior to the conclusion of this visit, the participant, parent or guardian, or study personnel (whichever is deemed most appropriate by study personnel) will inject the participant with the first dose of study intervention, noting the date and time of injection in the study e-diary. This day is the participant's first day of study intervention administration.

Visits 4-13 Double-blind Period

Visits 4, 10 and 11 Telephone Visits

These topics will be reviewed for the previous week(s)

- AE information
- any new concomitant medications or change in metformin or insulin dose
- discussion of effective contraception for males who have reached puberty and are sexually active and for females of childbearing potential
- study e-diary entries

  - SMBG results
  - basal insulin dose, if applicable
  - hypoglycemia events
  - study intervention compliance including date and time of injections (V10 and V11), and
  - last menstrual cycle for applicable females (V10 and V11). If pregnancy is suspected, refer to Section 8.2.4 for pregnancy testing information.

The study staff will confirm that the participant tolerated the previous weeks of study intervention.

Visits 5-9 and 12 Clinic Visits

These topics will be reviewed for the previous week(s)

- AE information
- any new concomitant medications or change in metformin or insulin dose
- discussion of effective contraception for males who have reached puberty and are sexually active and for females of childbearing potential
- study e-diary entries
  - SMBG results
  - basal insulin dose, if applicable
  - hypoglycemia events
  - study intervention compliance including date and time of injections, and
  - last menstrual cycle for applicable females. If pregnancy is suspected, refer to Section 8.2.4 for pregnancy testing information.

The study staff will confirm that the participant tolerated the previous weeks of study intervention.

The participant and parent or legal guardian will receive

- glucometer supplies,
- diet and exercise instruction for their T2DM, and
- study intervention supply.
- Reminder to obtain two 6-point SMBGs on nonconsecutive days within two weeks prior to Visit 13

Visit 13 Clinic Visit

Clinic visit procedures are similar to Visits 5-9 and 12. Additionally, 6-point SMBG data will be reviewed at this visit. At the end of the double-blind period, the dose of background diabetes medication may be re-adjusted as needed (see table in Section 8.3.3.2). After the site processes the visit in the interactive web-response system (IWRS), participants will be dispensed the appropriate open-label study intervention.

Those who received placebo and basal insulin during the double-blind period may be asked, per clinical judgment of the investigator, to reduce the dose of basal insulin upon tirzepatide treatment during the open-label period.

Open-label Period

Visits 14 Telephone Visit

These topics will be reviewed for the previous week

- AE information
- any new concomitant medications or change in metformin or insulin dose
- discussion of effective contraception for males who have reached puberty and are sexually active and for females of childbearing potential
- study e-diary entries
    - SMBG results
    - basal insulin dose, if applicable, and
    - hypoglycemia events.

The study staff will confirm that the participant tolerated the previous week of study intervention.

Visit 15 Clinic Visit

Clinic visit procedures are like those in the double-blind period EXCEPT fasting is not required at this visit.

Visits 16 and 18 Telephone Visit

Telephone visit procedures are like those in the double-blind period.

Visit 17 Clinic Visit

Clinic visit procedures are like those in the double-blind period EXCEPT fasting is not required at this visit.

Visit 19 (end of open-label)

Upon completion of this visit, participants will stop taking tirzepatide and the participant's background diabetes medication should be adjusted.

Only metformin or insulin can be restarted or increased in dose as needed between Visit 19 and Visit 801.

A follow-up visual acuity check and dilated fundoscopic examination will be performed by an eye care professional (ophthalmologist or optometrist) within ± 21 days of this visit.

Early Termination and Safety Follow-up Visit

The participant will arrive at the clinic in a fasted state for Early Termination Visit. Safety Follow-up Visit is a non-fasted visit.

Participant and parent or legal guardian must return study equipment and devices (e-diary and glucometer) to the investigative site.

Participants discontinuing the study early should have the follow-up visit approximately 30 days after the early termination visit and should have a follow-up visual acuity check and dilated fundoscopic examination performed by an eye care professional (ophthalmologist or optometrist) within + 21 days of the early termination visit. If the early termination visit is scheduled within 6 months of the previous visual acuity check and dilated fundoscopic examination, a follow-up visual acuity check and dilated fundoscopic examination are not needed.

Participants who discontinue the study before randomization do not need to complete this visit.

4.2. Scientific Rationale for Study Design

This is a superiority study, the main objective of which is to compare the effects of tirzepatide 5 mg and tirzepatide 10 mg QW (pooled), with metformin or basal insulin, or both to those on placebo for glycemic control (defined as change from baseline in HbA1c) in pediatric and adolescent population with T2DM over a 30-week period, followed by a 22-week open-label extension.

The efficacy measure, HbA1c, was chosen as the primary objective because it is an accepted endpoint in glycemic studies in pediatric and adolescent participants with T2DM.

The use of placebo for 30 weeks during the double-blind portion of the study is considered appropriate, as Phase 3 studies with tirzepatide have not been conducted to date in the pediatric and adolescent population. Thus, a placebo comparator is necessary to understand tirzepatide's true safety and efficacy. To protect the safety of the participants enrolled across all arms of this study, the double-blind period is relatively short, there are clear rescue criteria for participants with severe, persistent hyperglycemia (see Section 8.3.3.2) and participants are allowed to decrease basal insulin and/ or metformin as needed if hypoglycemia occurs (for the definition of hypoglycemia, see Section 8.3.3.1).

The doses of tirzepatide for this study were based on efficacy, safety and PK/PD data from two placebo-controlled studies in adults with T2DM, SURPASS-1 (GPGK), monotherapy study versus placebo and SURPASS-5 (GPGI), add-on to basal insulin vs placebo.

To mitigate the occurrence of GI AEs and permit time for the development of tolerance to GI effects, a dose escalation scheme will be used that starts at a low dose of 2.5 mg QW for 4 weeks and then escalates 2.5 mg increments every 4 weeks (Section 6.5.1). Therefore, it will take 4 weeks of dosing to reach a maintenance dose of 5 mg and 12 weeks to reach a maintenance dose of 10 mg.

The background therapies of diet and exercise, with metformin or basal insulin or both, are considered appropriate, as these are approved treatments for pediatric and adolescent participants with T2DM in the US, EU, and many countries around the world.

In adults, tirzepatide has been shown to be effective in lowering HbA1c with consistent safety in the monotherapy setting (diet and exercise only) and when added to metformin and other oral anti-diabetes agents and/or basal insulin. The decision not to maximize the doses of metformin and basal insulin was considered appropriate, as metformin at a dose of ≥1000 mg/day is considered an effective dose in pediatric participants. For participants using basal insulin, up-titration of insulin during the double-blind period would reduce the study's ability to perceive a difference between the placebo and tirzepatide treatment arms and therefore is not allowed beyond ± 15% of the baseline dose (see Section 6.8.1). Temporary increases in insulin dose are allowed during the study and appropriate rescue methods exist in the protocol to ensure that participants do not continue in the double-blind portion of the study with poor glycemic control. Participants may decrease doses of background diabetes medications at any time if hypoglycemia is noted.

According to the visit schedule, participants will be seen by physicians in the clinic during tirzepatide dose escalation approximately every month until maintenance dose is achieved, and with telephone visits approximately every month in between the clinic visits. This is considered appropriate, as pediatric and adolescent participants with T2DM are usually seen in the clinic every 3 months.

To optimize statistical power to detect a meaningful treatment difference, there will be treatment group comparisons at the 30-week primary endpoint based on the pooled tirzepatide arms compared to placebo.

4.3. Justification for Dose

The dose levels proposed for Study GPGV are maintenance dose levels of 5 mg and 10 mg.

Data from the Phase 3 studies SURPASS-1 and SURPASS-5 in adult patients with T2DM, was used along with existing Phase 1 and Phase 2 data to justify the dose and escalation scheme proposed for Study GPGV.

Following completion of Phase 3 studies SURPASS-1 and SURPASS-5, the PK model was updated to incorporate up-to-date tirzepatide PK information. This model was used to simulate exposures in the pediatric population accounting for body weight effects on PK parameters. The median body weight in adult patients with T2DM was about 88 kg.

Simulations showed that tirzepatide average steady-state exposure (Css,avg) increased 1.5% per kg decrease in body weight.

The exposures from SURPASS-1 and SURPASS-5 were stratified by baseline body weight into 3 categories: [1]< 75 kg [2] 75-100 kg, and[3] > 100 kg. Model predicted tirzepatide exposure following the 10-mg dose in the weight range of <75kg was comparable to exposure following the 15-mg dose in the weight range of 75-100kg. These exposures correspond to a near maximum HbA1c lowering effect (EC90-EC95).

Study GPGV plans to enroll adolescent and pediatric patients with at least 50 kg in body weight and meeting a body mass index (BMI) threshold of >85th percentile at Visit 1. Based on the PK/PD data, benefit/risk assessment from the Phase 3 studies in adults with T2DM, tirzepatide doses of 5 and 10 mg QW are expected to be efficacious with an acceptable tolerability and safety profile in an adolescent and pediatric population for T2DM treatment.

4.4. End of Study Definition

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

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

5. Study Population

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 10 to <18 years of age, at the time of signing the informed consent/assent.

Type of Participant and Disease Characteristics

For T2DM diagnosis criteria see Appendix 8, Section 10.8.

2. Participants have T2DM treated at the time of randomization with lifestyle measures (standardized diet and exercise program), and
    a. Metformin, or
    b. Basal insulin, or
    c. Metformin and basal insulin.

    If metformin is used, the dose must be ≥1000 mg/day and not more than the locally approved dose

    a. Doses of metformin and basal insulin must have been stable (±15% for basal insulin) for at least 90 days prior to Visit 1 and until Visit 3
3. Have HbA1c >6.5% to ≤11% at screening visit (determined by central laboratory)
4. Body weight ≥50 kg and BMI of >85th percentile of the general age and gender-matched population for that country or region

Sex

5. Male or female
   Contraceptive use by men or women of childbearing potential should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. See Appendix 4, Section 10.4 for guidance.

    a. Male participants who have reached puberty are required to use contraception, if sexually active, in compliance with specific local government study requirements (see Appendix 4, Section 10.4 for contraceptive requirements)
    b. Female participants:

    - Are not of childbearing potential, defined as not having reached puberty (see Appendix 4, Section 10.4)

    OR

    - Are of childbearing potential (see Appendix 4, Section 10.4):
        - Are not breastfeeding.

- Must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at Visit 1, followed by a negative urine pregnancy test within 24 hours prior to study intervention exposure.
- If sexually active, there must be agreement to use two effective contraceptive methods that include one highly effective method (less than 1% failure rate) for the entirety of the study plus 30 days.

Informed Consent

6. Capable of giving signed informed consent or assent as described in Appendix 1 Section 10.1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

7. Have T1DM.
8. AFTER the diagnosis of T2DM, have a history of diabetic ketoacidosis or hyperosmolar syndrome.
9. Have diabetes-associated autoantibodies (GAD65 and/or IA2), historically or at Visit 1.
10. Have had ≥1 episode of severe hypoglycemia and/or ≥1 episode of hypoglycemic unawareness within the last 6 months.
11. Have history of:
    - proliferative diabetic retinopathy, or
    - diabetic macular edema, or
    - nonproliferative diabetic retinopathy that requires acute treatment.

    Note: A dilated fundoscopic examination, evaluated by an eye care professional (ophthalmologist or optometrist) or a previous exam ≤90 days of Visit 1 meeting study requirements is acceptable to confirm eligibility.
12. Have blood pressure above the 99th percentile for age and gender OR systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mmHg at screening.
13. Have family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2).
14. Had chronic or acute pancreatitis any time prior to study entry (Visit 1).
15. Are chronically taking drugs that directly affect GI motility, or have a known clinically significant gastric emptying abnormality, such as severe diabetic gastroparesis or gastric outlet obstruction, or have undergone or plan to undergo weight loss procedure during the study, such as
    1) a gastric bypass (bariatric) surgery
    2) sleeve gastrectomy, or
    3) restrictive bariatric surgery, such as Lap-Band® gastric banding.

16. Have evidence of a significant, uncontrolled endocrine abnormality, in the opinion of the investigator.

    Examples: thyrotoxicosis or adrenal crises

17. Known or suspected hypersensitivity to study intervention or related products.
18. Have evidence of a significant, active autoimmune abnormality that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 15 months.

    Examples: lupus or rheumatoid arthritis

19. Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant.
20. Have an active or previously treated malignancy.
21. Have a history of any other condition that, in the opinion of the investigator, may preclude the participant from following and completing the protocol.

    Examples: known drug or alcohol abuse, eating disorder or psychiatric disorder

22. Female participants who are pregnant or breast feeding or intending to become pregnant.

Prior/Concomitant Therapy

23. Treatment with any glucose-lowering agent other than stated in the inclusion criteria 2 in a period of 90 days prior to Visit 1 and use of any other glucose-lowering medication except basal insulin and metformin (≥1000 mg/day), between Visit 1 and randomization (Visit 3).

    Note: Participants must not have received bolus insulin within 45 days of Visit 1, except as rescue treatment for management of acute medical conditions for a maximum of 14 days.

24. Have been treated with prescription drugs or over-the-counter medications that promote weight loss within 90 days prior to Visit 1 and/or between study entry (Visit 1) and randomization (Visit 3).

    Examples: Saxenda® [liraglutide 3.0 mg], Xenical® [orlistat], and phentermine.

25. Are receiving chronic (greater than 2 weeks or 14 days consecutively) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, or inhaled preparations) or have received such therapy within 1 month prior to Visit 1 or between Visit 1 and Visit 3.

Prior/Concurrent Clinical Study Experience

26. Are currently enrolled in any other clinical study involving an intervention or any other type of medical research judged not to be scientifically or medically compatible with this study.
27. Have participated, within the last 30 days in a clinical study involving an intervention. If the previous intervention has a long half-life, 5 half-lives or 30 days (whichever is longer) must have passed.
28. Have previously completed or discontinued from this study or any other study investigating tirzepatide.

Diagnostic assessments

29. Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than Nonalcoholic fatty liver disease (NAFLD), or ALT or AST level >5.0 times the upper limit of the age-adjusted reference range, or Total bilirubin ≥ 1.5 times the upper limit of the age-adjusted reference range (except

in the case of Gilbert's syndrome) as determined by the central laboratory at study entry; participants with NAFLD are eligible for participation in this study only if their ALT and AST levels are ≤5.0 times the ULN for the reference range and Total bilirubin level is < 1.5 times the ULN at screening.

30. Have an estimated glomerular filtration rate <45 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory at Visit 1.
31. Have a serum calcitonin level ≥ 35 ng/L, as determined by central laboratory at Visit 1.
32. Have had a blood transfusion or severe blood loss within 90 days prior to Visit 1 or have known hematological conditions that may interfere with HbA1c measurement.

    Examples: hemolytic anemias, sickle cell disease

Other Exclusions

33. 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.
34. Parent or legal guardians are Lilly employees.
35. Are unwilling or unable to comply with all aspects of the protocol including the use of an e-diary to directly record data from the participant.

5.3. Lifestyle Considerations

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 treatment of hypoglycemia, should it occur.

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

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 or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened one time. The interval between re-screening must be at least 8 weeks. If re-screening is performed, the parent or legal guardian must sign a new ICF and the participant a new assent. They will be assigned a new identification number.

In addition, participants with nonproliferative diabetic retinopathy requiring acute treatment may be eligible for one-time re-screening after treatment and meet requirements in the opinion of the investigator. The study site/investigator must receive prior sponsor approval prior to re-screening.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable for this study. All entry criteria must be met within the specified visit intervals in the SoA.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

Study intervention will be self-administered by the participant or administered to the participant by the parent/caregiver.

This table describes the interventions administered in this study.

Intervention Name	Tirzepatide (LY3298176)	Placebo
Type	Intervention	Intervention
Dose Formulation	Single dose pen (SDP)	SDP
Unit Dose Strength(s)	2.5 mg, 5 mg, 7.5 mg, 10 mg	Not applicable
Dosage Level(s)	5 mg, 10 mg	Not applicable
Dose Volume	0.5 mL	0.5 mL
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor and dispensed by IWRS	
Packaging and Labeling	Study intervention will be provided in single dose pens and packaged in cartons to be dispensed. Clinical study materials will be labeled according to country regulatory requirements.	

Abbreviations: IMP = investigational medicinal product; IWRS = interactive web-response system; NIMP = non-investigational medicinal product; SC = subcutaneous; SDP = single dose pen.

6.1.1. Timing of Doses and Dosing Site

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.

The actual date and time of all dose administrations will be recorded by the participant or parent or guardian. If a dose of study intervention is missed, the participant must take it as soon as possible unless it is within 72 hours of the next dose, in which case, that dose must be skipped and the next dose must be taken at the

appropriate time. The day of weekly administration can be changed if necessary, as long as the last dose was administered 72 or more hours before.

All participants will inject study intervention subcutaneously in the abdomen or thigh using the SDPs provided; a caregiver may administer the injection in the participant's upper arm. A new SDP will be used for each injection. If study intervention is to always be injected in the same body region, participants should be advised to use a different injection site each week.

6.1.2. Medical Devices

The combination products provided for use in the study is the tirzepatide SDP and placebo SDP.

All Product Complaints (PCs; including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation and appropriately managed by the sponsor (see Section 10.3.3).

6.2. Preparation, Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or dispense 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 (i.e., receipt, reconciliation, and final disposition records).

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

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an IWRS. Participants will be randomized in a 1:1:1 ratio to tirzepatide 5 mg QW:tirzepatide 10 mg QW:placebo QW.

Participant stratification factors are:

- age (≤ 14 years of age, >14 years of age), and
- baseline antihyperglycemic medication use of
    - metformin only, or
    - basal insulin only, or
    - metformin and basal insulin.

Double-blind period

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

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' treatment assignment is warranted for medical management of the event. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

If an investigator, site personnel performing assessments, or participant is unblinded during the double-blind period, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor medical monitor for the participant to continue in the study.

Open-label period

During this part, study intervention will be assigned using an IWRS.

6.4. Study Intervention Compliance

Study intervention administration data will be recorded by the participant or parent or guardian throughout the study.

The investigator will assess study intervention compliance at each visit by reviewing

- participant's recorded administration data
- adherence to the visit schedule
- completion of study diaries, and
- any other parameters the investigator considers necessary.

The participant and parent or guardian will be instructed to return any unused study intervention and/or empty cartons at the next visit to the study site for the purpose of performing drug accountability.

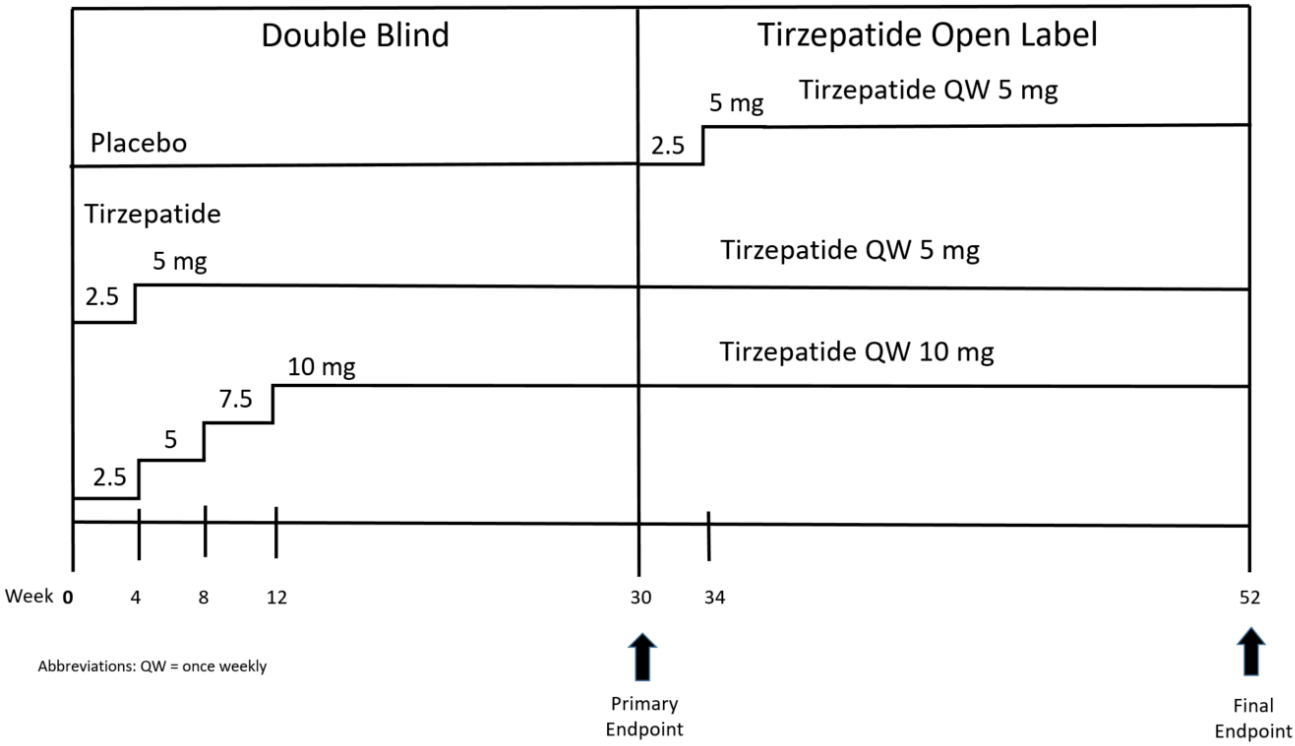
Participants considered poorly compliant with their medication and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol.

6.5. Dose Modification

6.5.1. Tirzepatide Dose Escalation

The dose escalation scheme consists of a starting dose of 2.5 mg QW accompanied by a dose escalation of 2.5 mg increments every 4 weeks until the desired dose level is reached and maintained for the duration of the study.

This figure illustrates the tirzepatide dose escalation regimen.



6.5.2. Management of Increased Hypoglycemia Risk

What the participant should do if they experience a hypoglycemic event

Study participant and parent or guardian will be instructed on recognizing symptoms of hypoglycemia and how to treat it. If a hypoglycemic event requires treatment assistance, then the participant or parent or guardian should call the investigative site as soon as it is safe to do so.

If safe to do so during the symptoms of hypoglycemia, the participant or parent or guardian must record in the study e-diary

- the blood glucose (BG) level measured prior to administration of treatment, if taken
- associated symptoms, and
- treatment administered.

What the investigator should do if the participant experiences a hypoglycemic event

If a participant experiences a hypoglycemic event the investigator should

- use definitions and criteria provided in Section 8.3.3.1 to diagnose hypoglycemia,
- properly categorize the suspected or confirmed event,
- assess the effect and timing of the intervention(s),
- evaluate the frequency of the event(s),
- establish the role of dietary changes in the development of the event,
- establish the role of physical exercise, or any other contributing factor, in the development of the event, and
- provide participant additional education, if deemed appropriate.

Investigators should pay close attention as to whether the basal insulin dose needs to be reduced in participants on basal insulin, especially those who are in good glycemic control (HbA1c <7.0%).

Investigators are responsible for their participant's management and well-being. Therefore, it is their responsibility to implement these generally recommended measures, or to modify them, taking into account clinical and other relevant criteria.

Management of antihyperglycemic medications to reduce the risk of hypoglycemia

For participants using basal insulin who experienced hypoglycemia without an obvious cause, such as dietary or physical activity changes, the daily dose of basal insulin should be adjusted first per the clinical judgment of the investigator.

This table shows a suggested scheme for adjusting basal insulin in response to hypoglycemia and/or to reduce the risk of hypoglycemia.

If, within one week, a participant has 2 FBG results of…	Then…
≤50 mg/dL (<2.8 mmol/L)	Decrease the basal insulin by 8 units
>51-70 mg/dL (>2.8-3.9 mmol/L)	Decrease the basal insulin by 6 units
>70-80 mg/dL (>3.9-4.4 mmol/L)	Decrease the basal insulin by 4 units
>80 mg/dL (>4.4 mmol/L)	No adjustment needed

Abbreviation: FPG = fasting plasma glucose

In case of repeated hypoglycemic events with a low basal insulin dose, that is, less than 10 units/day, and despite basal insulin dose decreases per the titration algorithm, administration of daily basal insulin may be temporarily or permanently discontinued.

If the hypoglycemia persists despite discontinuing basal insulin and the participant takes metformin, the metformin dose may be reduced or discontinued.

6.5.3. Tirzepatide Dose Modifications

Dose modification for tirzepatide is not permitted.

6.5.4. Management of Gastrointestinal Symptoms

During the double-blind dose escalation period, every effort must be made by the investigator to maintain participants on the dose assigned by IWRS.

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

STEP 1	Advise participants to eat smaller meals, for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full.
STEP 2	Continue STEP 1 + Prescribe symptomatic medication, for example, anti-emetic or anti-diarrheal medication, per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the eCRF.
STEP 3	Continue STEP 1 + STEP 2 + Temporarily interrupt tirzepatide; omit 1 dose, the participant will take 3 of 4 doses at that dose level. After the interruption, the investigator should restart the dose 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.
STEP 4	If intolerable GI symptoms or events persist despite the above measures, the investigator may decide to discontinue study intervention permanently. Participants who stop study intervention permanently will intensify insulin treatment and/or receive another glucose-lowering intervention (Section 7.1) and will continue participating in the study according to the protocol to collect all planned efficacy and safety measurements. The new glucose-lowering intervention will be recorded on the eCRF for collecting anti-hyperglycemic medications.

Note: De-escalation of study intervention will not be allowed.
Abbreviations: eCRF = electronic case report form; GI = gastrointestinal.

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

Study intervention, tirzepatide, will not be made available to participants after the conclusion of the study. Participants may continue treatment with metformin available locally and/or basal insulin at investigator discretion.

6.7. Treatment of Overdose

During this study, any dose of tirzepatide/placebo greater than the assigned dose within 72 h will be considered an overdose.

In the event of an overdose, the investigator must:

1. Contact the medical monitor immediately
2. Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities
4. Ensure appropriate supportive treatment is initiated according to the participant's condition and symptoms

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

In the event of overdose, refer to the IB for tirzepatide.

6.8. Concomitant Therapy

Any medication, including over-the-counter drugs, such as paracetamol or aspirin, or vaccine that the participant is receiving at the time of enrollment or receives during the study must be documented in the concomitant medications CRF. All non-diabetes concomitant therapies that are part of routine medical care that the participant requires are allowed and can be used during the study, except prescription and over-the-counter weight loss medications.

High dose inhaled or oral steroids should be used only as medically necessary.

Psychiatric medication should remain stable.

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

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

6.8.1. Rescue Therapy

In any situation that, in the investigator's opinion, may require an intervention that is not consistent with the requirements provided in this section, he or she must also consult the Lilly medical monitor before such intervention is implemented, except when an immediate adjustment of the treatment regimen is medically required.

Insulin therapy and metformin can be used as rescue therapy.

Rescue treatment with GLP-1 RAs or DPP-4 inhibitors are not allowed.

Definition of rescue therapy

These definitions assume that a participant has not previously received rescue therapy.

Rescue therapy is defined as any of the following changes in glucose-lowering regimen in response to persistent hyperglycemia:

- A participant treated with metformin + study intervention at baseline receives an increased dose of ≥500 mg metformin and/or insulin at any dose for more than 2 weeks
- A participant treated with metformin + basal insulin + study intervention at baseline receives an increased dose of ≥500 mg metformin and/or any increased dose of >15% basal insulin and/or adding another type of insulin at any dose for more than 2 weeks, or
- A participant treated with basal insulin + study intervention at baseline receives treatment with any increased dose of >15% basal insulin and/or adding another type of insulin at any dose for more than 2 weeks.

If a participant is experiencing severe, persistent hyperglycemia as outlined in section 8.3.3.2, the participant should be considered for rescue. If they are rescued, they will continue in the study and will continue to take study intervention unless the investigator determines that they should not.

6.8.2. Allowed Acute Diabetes Therapies

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, or
- during the safety follow-up period.

Short-term insulin use for up to 14 days is allowed for certain clinical situations (for example, elective surgery, during hospitalization, hyperosmolar states) and must be differentiated from insulin use as rescue therapy when reported in the electronic case report form (eCRF).

6.8.3. Allowed Chronic Diabetes Therapies

The only allowed concomitant chronic diabetes therapies are metformin and basal insulin.

Use of metformin

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

- In the event of a hypoglycemic episode(s) (clinical symptoms of hypoglycemia and/or fasting blood glucose [FBG]-confirmed symptomatic hypoglycemia of glucose concentration <3.0 mmol/L [54 mg/dL]), participants should first reduce or discontinue basal insulin (if applicable) and then may reduce or discontinue the dose of metformin only after discontinuing basal insulin (if applicable).
- In certain situations that require short-term discontinuation in line with the product(s) labeling for each respective country, for example, for severe dehydration, elective surgery, or need for radiologic examination involving intravenous (IV) iodinated contrast dye. Once the situation that led to temporary discontinuation is resolved, treatment should be restarted at investigator discretion.
- If a participant develops contraindications to metformin such that the use of the drug is contraindicated according to the country-specific label.
- If a participant meets the criteria for severe, persistent hyperglycemia (Section 8.3.3.2) or discontinues study intervention, then the metformin dose may be increased according to country-specific label.

A participant will be considered noncompliant with the protocol (protocol deviation) if he or she changes the dose or discontinues metformin for reasons other than those described here. Dose reduction/discontinuation of metformin during the study must be properly documented and recorded on the appropriate eCRF.

Use of basal insulin

The type of basal insulin must remain the same throughout the study, if possible.

In case of hypoglycemic episode(s), please refer to Section 6.5.2.

If the participant experiences acute illness with hyperglycemia, unlimited insulin therapy may be used for up to 2 weeks. After that time, the participant's basal insulin dose should be at the baseline dose (including up to ±15% of baseline dose) and other insulins (if used) should be stopped. This does not constitute rescue.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1, Section 10.1.

7.1. Discontinuation of the Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study and complete all study visits and procedures as outlined in the SoA (Section 1.3).

This list describes circumstances in which participants will be discontinued from the intervention:

- If participants develop confirmed pancreatitis (if not confirmed, study intervention may be restarted) (see Section 8.3.3.3)
- If a participant is diagnosed with MTC or C-cell hyperplasia after randomization or has calcitonin value ≥35 ng/L that has increased at least 50% over baseline after randomization
- If a participant is diagnosed with an active malignancy or if a previously treated malignancy becomes known after randomization
- If a participant becomes pregnant
- If a participant is diagnosed with T1DM
- Any significant study intervention-related hypersensitivity reaction
- Any other treatment-emergent adverse events (TEAE), SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken, or
- If a participant requests to discontinue intervention.

Participants who stop the study intervention permanently will receive another glucose-lowering medication, if needed per clinical judgment of investigator, and will continue participating in the study according to the protocol to collect all planned efficacy and safety measurements per Section 1.3 (SoA), Section 8.3 (Adverse Events), and Section 8.2 (Safety Assessments) of this protocol. The new glucose-lowering medication will be recorded on the eCRF for antihyperglycemic medications.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation due to a hepatic event or liver test abnormality

Participants who are discontinued from intervention due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.

The study intervention should be interrupted or discontinued if one or more of these conditions occur.

Participants with Normal or Near Normal Baseline ALT and AST (<1.5x ULN) at Visit 1	**Participants with Elevated Baseline ALT and AST (≥1.5x ULN) at Visit 1**
ALT or AST >5x ULN	ALT or AST >3x baseline at Visit 1
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5 (Except for participants with Gilbert's syndrome)[a]	ALT or AST >2x baseline at Visit 1 and either TBL >2x ULN or INR >1.5 (Except for participants with Gilbert's syndrome)[a]
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	ALT or AST >2x baseline at Visit 1 with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
All participants	
ALP >3x ULN (when the source of increased ALP is the liver)	
ALP >2.5x ULN and TBL > 2x ULN (Except for participants with Gilbert's syndrome)[a]	
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; TBL = total bilirubin; ULN = upper limit of normal. [a] In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL>2x ULN.	

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

See Section 8.2.8 (Hepatic Monitoring) and Appendix 6, Section 10.6 (Liver Safety: Suggested Action and Follow-Up Assessments) for further guidance on Hepatic monitoring.

7.1.2. Temporary Discontinuation

In certain situations, the investigator may need to temporarily interrupt study intervention. 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.

The data related to temporary interruption of study intervention will be documented in source documents.

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

If the number of missed study treatment 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.

Abbreviations: IWRS = interactive web-response system.

If the study treatment interruption is due to intolerable persistent GI AE, such as nausea, vomiting, or diarrhea, the participant should be treated as suggested in Section 6.5.4.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrollment in any other clinical study involving an intervention or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, or
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

If a participant is found to be pregnant or breastfeeding during the study, they will be discontinued from the study.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

During the ET visit, the participant will not initiate any new glucose-lowering therapy. Between ET visit and Visit 801, only metformin or insulin can be restarted or increased in dose as needed.

Visit 801 (safety follow-up visit) should be performed approximately 4 weeks after the ET visit as the final study visit.

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

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

Immediate safety concerns must 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

HbA1c, fasting serum glucose and BMI standard deviation score (SDS) will be used to characterize the efficacy of tirzepatide.

8.1.1. Patient Reported Outcomes Assessments

The self-reported questionnaires will be translated into the native language of the region and linguistically validated.

The questionnaires should be completed before the participant has discussed their medical condition or progress in the study with the investigator and/or site staff.

The questionnaires should be completed before any other study procedures.

8.1.1.1. EQ-5D-Y (Youth)

The youth-friendly EQ-5D-Y version consists of 2 pages, the EQ-5D-Y descriptive system and the EQ visual analogue scale (VAS) (EuroQol Research Foundation, 2020).

Each participant will complete this version of the EQ-5D.

The EQ-5D-Y descriptive system

The descriptive system comprises the same 5 dimensions as the EQ-5D 3 level (EQ-5D-3L) but using a youth-friendly wording. The 5 dimensions are

- mobility,
- looking after myself,
- doing usual activities,
- having pain or discomfort, and
- feeling worried, sad or unhappy.

Each dimension has 3 levels: no problems, some problems, or a lot of problems.

The EQ-5D-Y descriptive system will be converted into a single index value by applying a formula that attaches value (also called weights) to each of the levels in each dimension. The index value is a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years that are used to inform economic evaluations of healthcare interventions.

The EQ-5D-Y VAS

The EQ VAS records the respondent's self-rated health on a vertical scale, from, "The best health you can imagine," to, "The worst health you can imagine." This VAS information can be used as a quantitative measure of health outcome as judged by the individual.

Scoring

Details about scoring are available in the EQ-5D-Y User Guide at EuroQol Research Foundation, EQ-5D-Y User Guide, 2020, available from: https://euroqol.org/publications/user-guides.

8.1.1.2. Pediatric Quality of Life Health Inventory (PedsQL)

The PedsQL is a health-related quality-of-life instrument that can be used in healthy children and adolescents and those with acute and chronic health conditions (Varni et al. 2019).

Different versions of the PedsQL (3.2) Diabetes Module and the PedsQL Generic Core Scales are available for children of different ages.

The PedsQL Scoring Manual provides instructions to appropriately score all the dimensions, subscales, and total scores.

PedsQL (3.2) Diabetes Module

The PedsQL (3.2) Diabetes Module comprises 33 items for ages 13 years and older, and 32 items (1 less item for the Worry Scale) for ages 2 to 12 years.

This table describes the 5 dimensions of the PedsQL (3.2) Diabetes Module for both age groups.

Dimension	Items per dimension
diabetes symptoms	15
treatment barriers	5
treatment adherence	6
worry	2 (3 for teens and adults)
communication	4

Scores are calculated for each dimension and a total score is available. Higher scores indicate less problems.

PedsQL Generic Core Scales

The 23-item PedsQL Generic Core Scales were designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning.

This table describes the scales in the generic scale and the summary scores.

Multidimensional Scale	**Items per Scale**
Physical Functioning	8
Emotional Functioning	5
Social Functioning	5
School Functioning	5
Summary Scores	**Items per Summary Score**
Psychosocial	15
Physical Health	8
Total	23

Higher scores indicate better health related quality of life.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Height, weight, and waist circumference will be measured and recorded, per Appendix 11, Section 10.11.

Physical exams during in-clinic visits will be performed by a physician.

A complete physical examination at Visits 3, 13, 19, V801 (and ET if applicable) will include, at a minimum, assessments of

- skin
- cardiovascular (CV)
- respiratory
- GI
- neurological systems
- thyroid exam, and
- foot exam including evaluation for diabetic neuropathy.

8.2.2. Body Weight, Body Mass Index, Height, and Waist Circumference

Body weight, height, and waist circumference will be measured at prespecified time points. Each participant's weight, height, and waist circumference must be measured according to standardized guidelines (Appendix 11, Section 10.11). Body mass index will be computed from the participant's weight and height.

8.2.3. Assessment of Pubertal Progression – Tanner Staging

Participants' pubertal progression will be assessed throughout the study. Tanner staging will be performed at baseline, Week 16, Week 30 and Week 52. Participants who have reached Tanner stage 5 will not be evaluated again. (see Appendix 9, Section 10.9 for Tanner Stages).

8.2.4. Pregnancy Testing

Pregnancy testing will occur for females of childbearing potential according to the SoA (Section 1.3).

A local urine pregnancy test must be performed at Visit 3 with the result available prior to randomization and first injection of study intervention.

If pregnancy is suspected at any time in females of childbearing potential, a local urine pregnancy test will be performed and a serum pregnancy test will be sent to the central laboratory. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period. If the participant is pregnant, she must be permanently discontinued from study intervention and the study.

8.2.5. Vital Signs

Vital sign measurements should be taken before collection of blood samples for laboratory testing, at visits where required. For study-specific recommendations, see Appendix 11, Section 10.11.

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

8.2.6. Electrocardiograms

For each participant, a single 12-lead digital electrocardiogram (ECG) will be collected according to the SoA. The ECGs should be performed after vital signs are collected and prior to the collection of blood samples for laboratory testing if the participant is not adversely affected by the fasting condition.

Participants should be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.

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

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly.

A cardiologist at the central ECG laboratory will then conduct a full overread on the ECG. A report based on data from this overread will be issued to the investigative site.

All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

If there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate subject management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of ECG printed at the time of collection, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

8.2.7. Clinical Safety Laboratory Tests

See Appendix 2, Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

Due to blood volume considerations, frequency of blood draws and blood volumes have been limited.

One of the following measures will be offered to reduce pain associated with venipuncture: anesthetic creams, anesthetic patches, or high pressure anesthetic delivery system immediately before venipuncture.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, Section 10.2 must be conducted in accordance with the SoA (Section 1.3), standard collection requirements, and laboratory manual.

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

8.2.8. Hepatic Monitoring

Close hepatic monitoring

Laboratory tests (Appendix 6, Section 10.6), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin (D. Bil), gamma-glutamyl transferase (GGT), and creatine kinase (CK), 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 Visit 1 results of ...	develops the following elevations:
ALT or AST <1.5X ULN	ALT or AST ≥3X ULN
ALP <1.5X ULN	ALP ≥2X ULN
TBL <1.5X ULN	TBL ≥2X ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5X ULN	ALT or AST ≥2X baseline at Visit 1
ALP ≥1.5X ULN	ALP ≥2X baseline at Visit 1

* All ULN values should be age adjusted (AAULN)

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

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, 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 lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels. Special care should be taken to minimize the volume of blood taken during hepatic monitoring.

Comprehensive hepatic evaluation*

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 Visit 1 results of...	**develops the following elevations:**
ALT or AST <1.5X ULN	ALT or AST ≥3X ULN with hepatic signs/symptoms**, or ALT or AST ≥5X ULN
ALP <1.5X ULN	ALP ≥3X ULN
TBL <1.5X ULN	TBL ≥2X ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5X ULN	ALT or AST ≥2X baseline at Visit 1 with hepatic signs/symptoms**, or ALT or AST ≥3X baseline at Visit 1
ALP ≥1.5X ULN	ALP ≥2X baseline at Visit 1

* All ULN values should be age and gender adjusted (AAULN)

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

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR and direct bilirubin, if total bilirubin was elevated.

Based on the participant's age, medical history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for viral hepatitis A, B, C, E; autoimmune hepatitis; or an abdominal imaging study (for example, ultrasound, magnetic resonance imaging [MRI], or computerized tomography [CT] scan). Consider additional tests, based on the medical history and clinical picture, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol.

Special care should be taken to prioritize more pertinent blood tests and minimize the volume of blood taken during hepatic evaluation. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a pediatric hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy as deemed appropriate for the clinical condition and participant's age.

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 case report forms (CRFs) should be performed in study participants who meet 1 or more of the following 5 conditions:

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

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

All ULN values should be age and gender adjusted (AAULN) as applicable.

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
- 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 and/or study (see Section 7).

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (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 Appendix 3, Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	signing of the informed consent form (ICF)	participation in study has ended	as soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention and deemed reasonably possibly related with study procedures	signing of the informed consent form (ICF)	start of intervention	within 24 hours of site awareness	SAE eCRF	SAE paper form
SAE and SAE updates – after start of study intervention	start of intervention	participation in study has ended	within 24 hours of site awareness	SAE eCRF	SAE paper form
SAE* – after participant's study participation has ended and the investigator becomes aware	after participant's study participation has ended	N/A	promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	after the start of study intervention	four months after the last injection for female partners of male participants and 2 months after the last injection for female participants	within 24 hours	pregnancy paper form	pregnancy paper form
Product Complaints (PC)					
PC associated with an SAE or might have led to an SAE	start of study intervention	end of study intervention	within 24 hours of site 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 site awareness	Product Complaint form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Updated PC information	—	—	as soon as possible upon site awareness	originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	participation in study has ended	N/A	promptly	Product Complaint form	N/A

8.3.2. Pregnancy

Female participants who become pregnant

For a female participant who becomes pregnant, this information will be shared with the study participant's legally acceptable representative, parent(s), or legal guardian if the participant's age is <18 years as required by local regulations.

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.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

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

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. 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 discontinued 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.

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 and for 90 days after the end of the study.

After obtaining the necessary signed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

8.3.3. Adverse Events of Special Interest

8.3.3.1. Hypoglycemia

Authorized study personnel will train participant and parent or guardian about signs and symptoms of hypoglycemia and how to treat hypoglycemia. Participant or parent or guardian will collect information on each episode of hypoglycemia in the e-diary.

A hypoglycemic episode must be noted as having occurred any time a participant feels that (s)he is experiencing a sign or symptom associated with hypoglycemia AND/OR has a BG level <70 mg/dL (3.9 mmol/L), even if asymptomatic.

For each hypoglycemic episode, participant or parent or guardian should record the participant's BG level (if available) and treatment in the study diaries provided.

The time and date of all SMBG readings should be recorded in the study diaries as well as the date and time of weekly study intervention administration.

Definitions and criteria for diagnosing hypoglycemia

Investigators must use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (ADA 2021b). The BG values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips which are provided to the participant by the study sponsor.

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).

In each case of suspected or confirmed hypoglycemia, it is important that the event be properly categorized, the effect of the intervention be assessed, and the frequency of hypoglycemia be evaluated. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established. The participant and parent or guardian should receive additional education, if deemed appropriate. Please refer to Section 6.5.2 for guidance on Management of Increased Hypoglycemia Risk.

Level 1 hypoglycemia - Glucose <70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L)

Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers must continue to counsel participant and parent or guardian to treat hypoglycemia at this glucose alert value.

This table defines Level 1 Glucose Alerts.

Level 1 Glucose Alerts	**Definition**
Documented symptomatic hypoglycemia	Any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of <70 mg/dL (3.9 mmol/L).
Documented asymptomatic hypoglycemia	Any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG <70 mg/dL (3.9 mmol/L).
Documented unspecified hypoglycemia	Any event with no information about symptoms of hypoglycemia available, but with a measured BG <70 mg/dL (3.9 mmol/L).

Abbreviations: BG = blood glucose.

Level 2 hypoglycemia - Glucose <54 mg/dL (3.0 mmol/L)

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

This table defines Level 2 Clinically Significant Hypoglycemia.

Level 2 Clinically Significant Hypoglycemia	**Definition**
Documented symptomatic hypoglycemia	Any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of <54 mg/dL (3.0 mmol/L).
Documented asymptomatic hypoglycemia	Any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG <54 mg/dL (3.0 mmol/L).
Documented unspecified hypoglycemia	Any event with no information about symptoms of hypoglycemia available, but with a measured BG <54 mg/dL (3.0 mmol/L).

Abbreviations: BG = blood glucose.

Level 3 hypoglycemia - Severe hypoglycemia

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

The determination of a hypoglycemic event as 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 based on the report of a participant simply having received assistance.

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

Nocturnal hypoglycemia

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

8.3.3.2. Severe, Persistent Hyperglycemia

Severe, persistent hyperglycemia will be collected during the study to assess 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.

Rescue medication as outlined in Section 6.8.1 will be prescribed as an add-on to randomized treatment in the absence of intercurrent cause of the hyperglycemia if the average FBG value of at least 3 values of FBG per week, over 2 consecutive weeks, exceeds these values

- >270 mg/dL (>15.0 mmol/L) from baseline to Week 6
- >240 mg/dL (>13.3 mmol/L) from Week 7 to Week 16, or
- >200 mg/dL (>11.1 mmol/L) from Week 17 to end of study.

Investigators must first confirm that the participant is fully compliant with the assigned therapeutic regimen and that they do not have an acute condition causing severe hyperglycemia.

If applicable, determine if the participant has appropriately titrated the dose for basal insulin prior to deciding if severe, persistent hyperglycemia criteria has been met. Basal insulin should be titrated first before adding any rescue therapy.

Protocol allowed rescue therapies may be added for participants who meet the severe, persistent hyperglycemia criteria, at the discretion of investigator, in accordance with American Diabetes Association/European Association for the Study of Diabetes guidance (ADA 2021c). Rescue medication will be prescribed as add-on to study intervention, and participants will continue to follow the protocol-specified visit schedule.

8.3.3.3. Pancreatitis

Diagnosis of acute pancreatitis

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

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

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal MRI, and

- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone/gall bladder disease, hypertriglyceridemia, and concomitant medications.

Discontinuation for acute pancreatitis

If acute pancreatitis is suspected, the participant must discontinue study intervention. If acute pancreatitis is confirmed, study intervention should not be restarted.

Case adjudication and data entry

An independent clinical endpoint committee (CEC) will adjudicate all suspected cases of acute or chronic pancreatitis. In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from pediatric and adolescent participants with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed eCRF page by study site. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

Asymptomatic elevation of serum amylase and/or lipase

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

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

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

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 tirzepatide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms. These data will be captured in specific eCRFs.

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.

8.3.3.5. Arrythmias and Cardiac Conduction Disorders

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 / corrected QT 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).

8.3.3.6. Diabetic Retinopathy Complications

Visual acuity evaluation will be performed as part of the ophthalmology assessments prior to dilation. The results from this exam will be recorded on a specific eCRF. 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 exam ≤90 days of screening meeting study requirements. The results from this examination will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy.

Additional visual acuity checks and 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 eCRF.

A follow-up visual acuity check and dilated fundoscopic examination occur for all randomized participants at Visit 19 (Week 52).

8.3.3.7. Hypersensitivity Reactions

Many drugs, but 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 eCRF.

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 10, Section 10.10. Laboratory results are provided to the sponsor via the central laboratory.

If the investigator, after consultation with the sponsor-designated 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 sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

8.3.3.8. Injection Site Reactions

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

If an ISR is reported by a participant or parent or guardian 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 bodies (ADAs) and tirzepatide concentration

8.3.3.9. Anti-Drug Antibodies

The occurrence of anti-drug antibody formation will be assessed as outlined in Section 8.8.

8.3.3.10. Hepatobiliary Disorders

All events of treatment-emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.2.8.

8.3.3.11. Severe Gastrointestinal Adverse Event

Tirzepatide may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the eCRF/AE form.

For detailed information concerning the management of GI AEs, refer to Section 6.5.4.

8.3.3.12. Acute Renal Events

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

8.3.3.13. Major Depressive Disorder/Suicidal Ideation

The prevalence of depressive symptoms and disorders is increased in patients with T1DM or T2DM (ADA 2019). Any AE of major depressive disorder or suicidal ideation should be reported.

8.3.3.14. Metabolic Acidosis, Including Diabetic Ketoacidosis

Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been reported occasionally in participants with T2DM. Participants who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting BG levels, as ketoacidosis may be present even if BG levels are less than 250 mg/dL.

If ketoacidosis is suspected, participant should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

Lactic acidosis has been reported rarely in participants with T2DM associated with use of metformin, excessive alcohol intake, and decreased renal function. Routine bicarbonate assessment will be performed during the course of the study. If lactic acidosis is suspected, metformin, if used, should be temporarily discontinued until the resolution of the event.

8.4. Pharmacokinetics

Characterization of PK properties of tirzepatide in pediatric and adolescent participants will be supported by collection of CCI PK blood samples per participant according to the SoA (Section 1.3).

CCI [redacted]

The date and time of the most recent SC injection administered prior to collecting the sample must be recorded in the e-diary. The actual date and time at which each sample was drawn must be recorded on the laboratory requisition form. Instructions for the collection and handling of blood samples will be provided by the sponsor. The date and time of the most recent SC injection administered prior to collecting the sample must be recorded in the source document. The actual date and time at which each sample was drawn must be recorded on the laboratory requisition form. Instructions for the collection and handling of blood samples will be provided by the sponsor.

The number and timing of PK samples are expected to be adequate in enabling comprehensive population PK and exposure-response modeling analyses within this special population.

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry method. Bioanalytical samples collected to measure tirzepatide concentrations will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, and/or bioanalytical method cross-validation.

8.5. Pharmacodynamics

Blood samples for fasting insulin, C-peptide, proinsulin, glucose, and adiponectin will be taken to assess the effect of tirzepatide on insulin resistance, alpha cell and beta cell function.

8.6. Genetics

A whole blood sample will be collected for genetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

See Appendix 5, Section 10.5 for information regarding genetic research and Appendix 1, Section 10.1.12 for details about sample retention and custody.

8.7. Biomarkers

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

Samples for biomarker research will be collected at the times specified in the SoA (Section 1.3.) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to tirzepatide, pathways associated with T2DM, mechanism of action of tirzepatide, and/or research method or in validating diagnostic tools or assay(s) related to T2DM.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel. Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the course of the development and commercialization of intervention.

All exploratory biomarker storage samples should be preferable taken in fasting state and before dose of study intervention, if applicable.

In addition, samples will be stored, and analysis may be performed on immunogenicity along with a paired sample for PK analysis (see Section 8.8), and biomarker variants thought to play a role in T2DM including, but not limited to, serum/plasma analytes to evaluate their association with observed clinical responses to tirzepatide.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected for analysis to determine antibody production against tirzepatide using a validated assay method. ADA may be further characterized for cross-reactive binding to native GIP and GLP-1, their ability to neutralize the activity of tirzepatide and neutralizing antibodies to endogenous counterparts. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of tirzepatide. All samples for immunogenicity must be taken predose when applicable and possible. Treatment-emergent ADA are defined in Section 9.3.6.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to tirzepatide. Samples may also be used for development and control of an immunogenicity assay.

8.9. Medical Resource Utilization and Health Economics

Health economics and medical resource utilization parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The hypotheses relative to the primary and key second endpoints are whether there is a difference in tirzepatide 5 mg and 10 mg (pooled or separate) versus placebo at 30 weeks with changes in the diabetic measures outlined in Section 3.

9.2. Analyses Sets

The following populations are defined:

Population	Description
Screened Participants	All participants who sign the ICF.
Randomized participants	All participants who are randomly assigned to a treatment arm.
Modified Intent-to-Treat (mITT) population	All randomly assigned participants who are exposed to at least 1 dose of study intervention (that is tirzepatide or placebo), excluding inadvertently enrolled participants who have discontinued study intervention for that reason.
EAS	Data obtained during Double-Blinded Period from the mITT population, excluding data after initiating rescue antihyperglycemic medication or stopping study intervention.
FAS	Data obtained during Double-Blinded Period from the mITT population, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.
SS1	Data obtained during Double-Blinded Period from all randomly assigned participants who are exposed to at least 1 dose of study intervention, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.
SS2	Data obtained during Double-Blinded Period, Open-Label Period and Safety Follow-up Period from all randomly assigned participants who are exposed to at least 1 dose of study intervention, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.

Abbreviations: EAS = Efficacy Analysis Set; FAS = Full Analysis Set; ICF = informed consent form; mITT = modified Intend-to-Treat; SS = Safety Analysis Set.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of sponsor 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 and the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05/1-sided alpha level of .025, unless otherwise stated, and all confidence intervals (CIs) will be given at a 2-sided [95%] level. In statistical summaries and analyses, all data, including those collected during the open-label period, will be analyzed by randomized treatment assignment. In the event of a treatment error, participants will be analyzed according to the treatment they were randomly assigned to.

Estimands

There will be 2 estimands of interest in comparing efficacy of tirzepatide doses with placebo. First estimand, the "efficacy" estimand, represents efficacy prior to discontinuation of study intervention without confounding effects of antihyperglycemic rescue therapy. Second estimand, the "treatment-regimen" estimand, represents the efficacy irrespective of adherence to study intervention or initiation of rescue antidiabetic drugs.

The primary efficacy assessment, guided by the "efficacy" estimand, will be conducted using the EAS. The primary efficacy assessment, guided by the "treatment-regimen" estimand, will be conducted using the full analysis set.

Since analysis aligned to efficacy and treatment-regimen estimands are intended for different purposes, primary and key secondary efficacy assessments relative to efficacy and treatment-regimen estimands will be conducted separately at a family-wise type 1 error rate of 0.05. Additional details, including analysis methods for key secondary endpoints and a strategy for controlling the overall family-wise type 1 error rate at an alpha of 0.05 for primary and key secondary endpoint evaluation will be provided in the SAP.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of each treatment group, irrespective of adherence to study intervention or initiation of antihyperglycemic rescue therapy. Thus, the safety analysis will be conducted using the safety analysis set (SS). Selected safety analysis (for example, hypoglycemia) may be conducted excluding data after introducing another antihyperglycemic therapy.

Summary statistics

Summary statistics for continuous measures will include sample size, mean, standard deviation (SD), median, minimum, and maximum. The analysis model to make comparisons among treatment arms relative to continuous measurements assessed over time will be an mixed model for repeated measures (MMRM), with terms of treatment, visit and treatment-by-visit interaction, age group (10 to 14 years versus 15 to <18 years), baseline antihyperglycemic medication use (metformin only, or basal insulin only, or metformin and basal insulin), and baseline measurement as a covariate. An unstructured covariance matrix 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. Summary statistics for discrete count measures will include sample size, mean, SD, median, minimum, and maximum. The negative binomial regression model will be used for the treatment comparison of discrete count measures.

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

9.3.2. Treatment Arm Comparability

9.3.2.1. Participant Disposition

Frequency counts and percentages of all participants screened, randomized, and receiving at least 1 dose of study intervention, will be presented by treatment arm. Of the participants in the modified intent-to-treat (mITT) population, frequency, counts and percentages of participants completing the study, prematurely discontinuing the study, including the reason for premature discontinuation, will be presented by treatment arm.

9.3.2.2. Participant Characteristics

Demographics, medical history, and concomitant illness will be summarized by treatment arm using the mITT population.

9.3.2.3. Concomitant Therapy

Stratification will be used to ensure a balance across treatment arms of participants using metformin and/or basal insulin as a background therapy. These stratification factors will be included in all analysis models to further adjust the treatment effect estimates for background usage of metformin and/or basal insulin usage.

Concomitant medications, including previous therapy for diabetes, will be summarized by anatomical therapeutic chemical classification and treatment arm using the mITT population. The incidence of rescue therapy for severe, persistent hyperglycemia will be analyzed as an additional secondary safety endpoint.

9.3.2.4. Treatment Compliance

Treatment compliance will be summarized by all treatment arms, by study period, and overall. The compliance calculation will be detailed in the SAP.

9.3.3. Efficacy Analyses

9.3.3.1. Primary Endpoints

There will be 2 primary efficacy analyses conducted to establish superiority of pooled tirzepatide 5 mg and 10 mg to placebo relative to mean change in HbA1c from baseline to the 30 week visit.

Primary efficacy analysis will be guided by the “treatment-regimen estimand”, using an analysis of covariance (ANCOVA) of all available data up to Week 30.

The ANCOVA model will include

- treatment (tirzepatide 5 mg, 10 mg or placebo)
- age group (10 to 14 years versus 15 to <18 years)
- baseline antihyperglycemic medication use (metformin only, or basal insulin only, or metformin and basal insulin), and
- baseline HbA1c as a covariate.

A linear contrast, averaging estimates from the individual tirzepatide doses, will be used to estimate the treatment effect of pooled tirzepatide arms compared with placebo. Analysis will be conducted with multiple imputations of missing HbA1c data at the 30-week visit with statistical inference over multiple imputations guided by the method proposed by Rubin (1987). Missing HbA1c value imputation will be based on observed HbA1c data from subjects in the same treatment arm who had their HbA1c measured at the Week 30 visit after early discontinuation of study intervention (retrieved dropouts). In cases where there are not enough retrieved dropouts to provide a reliable imputation model, the missing data in an endpoint from each treatment group are imputed using observed endpoint data from the placebo arm.

For all other purposes, the primary efficacy analysis will be guided by the "efficacy" estimand defined in Section 9.3.1. This assessment will be conducted using EAS.

The primary analysis model for HbA1c measurements over time will be a MMRM. The response variable of the MMRM will be change in HbA1c from baseline values obtained at each scheduled postbaseline visit. The independent variables of the MMRM model are

- treatment (tirzepatide 5mg, 10mg or placebo)
- visit
- treatment-by-visit interaction
- age group
- baseline antihyperglycemic medication (metformin only, or basal insulin only, or metformin and basal insulin) as fixed effects, and
- baseline HbA1c as a covariate.

A linear contrast, averaging estimates from the individual tirzepatide doses, will be used to estimate the treatment effect of pooled tirzepatide arms compared with placebo.

9.3.3.2. Secondary Endpoint(s)

The secondary study objectives subject to Type I Error rate control are as follows:

- Superiority of tirzepatide QW (5 mg and 10 mg, pooled) to placebo at 30 weeks in pediatric and adolescent participants for
  - change in BMI SDS from baseline
  - incidence of HbA1c ≤6.5%
  - change in fasting serum glucose from baseline
- Superiority of each tirzepatide dose to placebo at 30 weeks in pediatric and adolescent participants for
  - change in BMI SDS from baseline
  - incidence of HbA1c ≤6.5%
  - change in fasting serum glucose from baseline, and
  - change in HbA1c from baseline.

Analysis of change from baseline in BMI SDS/fasting serum glucose at the 30-week visit will be conducted in a manner similar to the primary efficacy analyses with change in BMI SDS/fasting serum glucose from baseline as the response variable, baseline BMI SDS/fasting serum glucose as a covariate.

Comparisons among treatments relative to the proportion of participants achieving the HbA1c target value of ≤6.5% (48 mmol/mol) at the 30-week visit will be conducted using a logistic regression analysis with terms of treatment, country, metformin use (Yes or No), and baseline HbA1c as a covariate.

In the analysis of participants achieving the HbA1c target value relative to the "efficacy" estimand, missing values at the 30-week visit will be imputed from an MMRM model and then dichotomized.

In the analysis of participants achieving the HbA1c target value relative to the "treatment-regimen" estimand, missing values at the 30-week visit will be imputed based on observed data at respective visits from participants in the same treatment arm who had their efficacy assessed after early discontinuation of study intervention and/or initiation of rescue medication. The analysis will be conducted with multiple imputations and statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

9.3.3.3. Tertiary/Exploratory Endpoint(s)

Details of tertiary and exploratory analysis will be provided in the SAP.

9.3.4. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses with placebo irrespective of adherence to study intervention or initiation of rescue therapy. Safety analyses for the double-blind period will be conducted using the SS1. For overall study safety (including double-blind period, open-label period and safety follow-up period), summary statistics will be provided using the SS2. Selected safety analyses may be conducted excluding data after the introduction of another antihyperglycemic therapy.

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

9.3.4.1. Hypoglycemic Events

Incidence of documented symptomatic hypoglycemia events and severe hypoglycemia in each category will be compared between tirzepatide doses and placebo using negative binomial regression analysis.

9.3.4.2. Gastrointestinal Events

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

9.3.4.3. Central Laboratory Measures, Vital Signs and Electrocardiograms

Values and change from baseline to postbaseline values of central laboratory measures, vital signs, and selected ECG parameters will be summarized at each scheduled visit. The analysis model to make comparisons among treatment groups, relative to continuous change from baseline values assessed over time will be an MMRM similar to the primary efficacy analysis and with baseline measurement as a covariate. An unstructured covariance structure will model the relationship of within-patient errors.

The percentages of participants with Treatment-emergent (TE) abnormal, high, or low laboratory measures at any time will be summarized and compared between treatment groups by using Fisher's exact test. A TE abnormal value is defined as a change from normal value at baseline to a value greater than the high limit at any time during double-blind period, open-label period and safety follow-up. A TE 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 double-blind period, open-label period and safety follow-up. High and low laboratory limits will be determined by the central laboratory reference ranges.

9.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Tirzepatide concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software. The relationships between tirzepatide dose and/or concentration and efficacy, tolerability, and safety endpoints will be characterized.

If ADA titers are detected from immunogenicity testing, then the impact of immunogenicity titers on tirzepatide PK or any relevant PD parameters may also be examined.

9.3.6. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA, with TE ADA and with neutralizing TE ADA to tirzepatide may be tabulated by tirzepatide dose. Treatment-emergent ADA are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution (MRD) if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For TE ADA participants, the distribution of maximum titers may be described. The frequency of neutralizing antibodies to tirzepatide and/or cross-reactive and neutralizing antibodies to endogenous counterparts may be tabulated in participants with TE ADA.

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

9.3.7. Other Analyse(s)

9.3.7.1. Patient Reported Outcomes

Analyses of actual and change from baseline in patient reported outcomes (PRO) scores will be conducted using linear models with baseline PRO scores, treatment, and other factors that may be considered relevant. These variables will be specified in the SAP.

9.3.7.2. Subgroup Analyses

The following subgroup analyses of mean change in HbA1c from baseline to Week 30 will be considered (but not limited to):

- age group (≤14 years old, >14 years old),
- race,
- ethnicity,
- region (US and non-US),
- gender,
- duration of diabetes (<median and ≥median),
- baseline BMI (<median and ≥median),
- baseline body weight (<median and ≥median),

- baseline metformin use,
- baseline insulin usage, and
- baseline HbA1c (≤8.0% or >8.0% [≤64, >64 mmol/mol]).

Other analyses may include analyses of assessments, which are not defined as endpoints, that need to be pre-specified and not necessarily be reported in the CSR such as, but not limited to, immunogenicity, biomarkers, population PK, health care utilization endpoints and health technology assessment related endpoints.

9.4. Interim Analyses

No interim analyses of efficacy for early termination are planned for this study. An external DMC will have the responsibility to review unblinded interim analyses results to monitor the safety of the participants in the study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

9.5. Sample Size Determination

The statistical power calculation assumes that the evaluation of superiority of pooled tirzepatide 5 mg and 10 mg QW against placebo will be conducted at a 2-sided significance level of 0.05, relative to the primary endpoint (change in HbA1c from baseline at 30 weeks) in an analysis utilizing all data, on or off intervention. Additionally, it assumes a 1.1% greater mean reduction in HbA1c (placebo adjusted) for pooled tirzepatide (5 mg and 10 mg) at Week 30 visit, and a common SD of 1.5% from change in HbA1c at Week 30 visit (accounting for increase in SD due to the inclusion of data on rescue medications and after premature treatment discontinuation and imputation of missing data).

Based on these assumptions, randomizing at least 90 participants in a 1:1:1 ratio to each study arm until an expected accrual of 90 evaluable participants will provide 90% power to demonstrate superiority of the pooled tirzepatide 5 mg and 10 mg to placebo. Evaluable participants are those who have been randomized and exposed to at least one dose of study treatment with HbA1c measurements at baseline and at the Week 30 visit.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF/assent, IB, and other relevant documents (for example, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (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 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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

Participants must be informed that their participation is voluntary. Participants or their legally acceptable representative, parent(s), or legal guardian will be required to provide a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that legally acceptable representative, parent(s), or legal guardian) consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained before the participant was enrolled in the study and the date the written consent was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICF was the participant's legally acceptable representative, parent(s), or legal guardian). The acceptable person obtaining the informed consent must also sign the ICF.

Participants and their legally acceptable representative, parent(s), or legal guardian must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.

Minor participants must be re-consented if they reach the age of majority during the course of the study, to continue participating.

A copy of the ICF(s) must be provided to the participant or the participant's legally acceptable representative, parent(s), or legal guardian

10.1.4. Data Protection

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

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

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

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

Rationale for collection of full date of birth

This study includes children, adolescents, and young adults. Within this age range, participants' expected height and weight, as well as normal ranges for laboratory tests, vary by both age and sex. Therefore, it is necessary to collect the full date of birth (day, month, year) for all pediatric and adolescent participants to appropriately analyze and interpret changes in growth and laboratory parameters.

In countries where local regulations do not permit collection of the full date of birth, if the supporting regulatory/ethics documentation is available, at a minimum, the month and year of birth must be collected on the eCRF.

10.1.5. Committee Structure

An external DMC will have the responsibility to review unblinded interim analyses results to monitor the safety of the participants in the study until the last participant completes the Week 52 visit. More details will be included in the DMC charter.

Study sites will receive information about interim results ONLY if deemed necessary for the safety of the participants.

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.

Data

The sponsor provides access to all individual participant data collected during the study, after anonymization, with the exception of PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, CSR, 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 CRF 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.

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 (e.g., contract research organizations).

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

Records retention and audits

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

In addition, the 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 the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

Electronic data capture system

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

Clinical outcome assessments (COA)

Some of the clinician-administered questionnaire data will be collected by the study personnel via a paper source document and will be transcribed by the study personnel into the EDC system.

Patient reported and clinician-administered questionnaires, other than those collected via paper, will be directly recorded by the participant and study personnel into an instrument (for example, hand-held smart phone or tablet). The electronic clinical outcome assessment (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 system(s) will be stored at third-parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture

system(s). Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

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

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

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

10.1.9. Study and Site Start and Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

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

10.1.10. Publication Policy

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

10.1.11. Investigator Information

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

10.1.12. Sample Retention

Sample retention enables the use of new technologies, response to regulatory questions, and investigation of results that may not be observed until later in the development.

Sample Type	Custodian	Retention Period After Last Patient Visit*
Pharmacokinetic	Sponsor or Designee	1 year
Exploratory Biomarker Samples	Sponsor or Designee	15 years
Genetics	Sponsor or Designee	15 years
Immunogenicity	Sponsor or Designee	15 years

*Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory unless specified otherwise.

Local laboratory results are only required if 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.

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.

Pregnancy Testing will be performed as detailed in SoA, Section 1.3.

One of the following measures will be offered to reduce pain associated with venipuncture: anesthetic creams, anesthetic patches, or high pressure anesthetic delivery system immediately before venipuncture.

Investigators must document their review of the laboratory results.

Clinical Laboratory Tests

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Differential:	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Uric acid	
Calcium	

Glucose	
Special Chemistry	Assayed by Lilly-designated laboratory
HbA1c	
Insulin	Results will not be provided to the investigative sites
C-peptide	Results will not be provided to the investigative sites
Calcitonin	
Thyroid-stimulating hormone (TSH)	
Thyroxine (T4, free)	
Biomarkers	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Adiponectin, total	
Proinsulin, intact	
Glucagon	
Lipid Panel	Assayed by Lilly-designated laboratory
Total cholesterol	
Low density lipoprotein (LDL)	Value will be calculated. If triglycerides are >400mg/dL, the direct LDL will be assayed
High density lipoprotein (HDL)	
Very low density lipoprotein (VLDL)	
Triglycerides	
Hormones (female)	
Serum pregnancy	Assayed by Lilly-designated laboratory
Urine pregnancy	Evaluated locally at study site
Urine Chemistry	Assayed by Lilly-designated laboratory
Albumin	
Creatinine	
Pancreas (Exocrine panel)	Assayed by Lilly-designated laboratory
Pancreatic amylase	
Lipase	
Calculations	Will be calculated by the central laboratory and included in laboratory result reports

eGFR (CKD-EPI)	
Urinary albumin/creatinine ratio	
Pharmacokinetic Samples for Tirzepatide	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Genetics Sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Exploratory Biomarker Stored Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Serum	
Plasma (EDTA)	
Plasma (P800)	
Immunogenicity Samples	Assayed by Lilly-designated laboratory
Islet Cell Antibody 2 (IA2)	
GAD65	
Tirzepatide anti-drug antibody	Results will not be provided to the investigative sites
Tirzepatide PK sample for immunogenicity	Results will not be provided to the investigative sites

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

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization (ISO) 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (See Section 6.1.2 for the list of sponsor medical devices).

10.3.1. Definition of AE

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

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose must be reported regardless of sequelae. “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or

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

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. Medical or surgical procedure (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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

A 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 pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (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/birth defect

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

Medical or scientific judgment should be exercised 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.

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

10.3.3. Definition of Product Complaints

Product Complaint

A 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 studies are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participant and parent or guardian 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 must be reported as both a PC and as an AE/SAE.

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

AE, SAE, and PC Recording

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

The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate (e)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 must 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 (e)CRF page for AE/SAE and the Product Complaint Form for PCs.

There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.

The investigator may change his/her opinion of causality in light of follow-up information and send a 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 a SAE paper form (see next section) or by telephone.

Contacts for SAE reporting can be found in the site training documents.

SAE Reporting via Paper Form (back-up)

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor or sponsor's 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 documents.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

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

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

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the 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

Women of Childbearing Potential (WOCBP)

Females are considered a woman of childbearing potential (WOCBP) if

- Menarche has occurred (any amount of bleeding, even just spotting, can be considered menarche), OR
- They have breast development Tanner 2 or more (see Tanner Staging, Appendix 9., Section 10.9).

Women not of Childbearing Potential

Females are considered women not of childbearing potential if

- they have breast development Tanner 1, or
- they have a congenital anomaly such as Mullerian agenesis, or
- they are infertile due to surgical sterilization.

Examples of surgical sterilization include hysterectomy, bilateral oophorectomy, and tubal ligation.

10.4.2. Contraception Guidance

Contraception Requirements for Females of Childbearing Potential

All participants of childbearing potential must follow the contraception guidance in the tables below for the entirety of the study and for 30 days thereafter.

Females of childbearing potential who are completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle…	
Must…	**Must not…**

agree to either remain abstinent, or	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or

stay in a same sex relationship without sexual relationships with males	• use the withdrawal method

This table describes guidance for females of childbearing potential who are NOT completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle.

Topic	**Condition**
Pregnancy testing	Negative serum result at screening and a negative urine result at Visit 3 prior to treatment exposure.
	Note: follow pregnancy testing schedule in the Schedule of Activities, Section 1.3.
Contraception	Agree to use 2 forms of effective contraception, where at least one form must be highly effective (less than 1% failure rate).

Contraception Requirements for Male Participants

Male participants who have reached puberty and are sexually active,

- are required to use contraception in compliance with specific local government study requirements
- must refrain from sperm donation and
- must follow contraception guidance for the duration of the study and until their tirzepatide plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days after the end of study.

The table below describes contraception guidance for all men.

Topic	Guidance
For all men	Do not donate sperm for the duration of the study and for 90 days after the end of study.
Contraception for men with partners of childbearing potential	• either remain abstinent, if this is their preferred and usual lifestyle OR • must use condoms during intercourse for the duration of the study, and • for 90 days after the end of the study.
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception.

Forms of Contraception

This table describes the different forms of contraception.

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: The barrier method must include use of a spermicide to be considered effective, for example, condom with spermicide, diaphragm with spermicide, female condom with spermicide.
Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • post coital douche • lactational amenorrhea

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to tirzepatide or T2DM and related diseases. They may also be used to develop tests/assays including diagnostic tests related to tirzepatide and/or interventions of this drug class and T2DM. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome, as appropriate.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to tirzepatide or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on tirzepatide and/or interventions of this drug class continues but no longer than 15 years or other period as per local requirements.

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

See protocol Section 8.2.7 for guidance on appropriate test selection.

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

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

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

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

HBV DNA[b]	Anti-actin antibody[c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[b]	EBV DNA[b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[b]	HSV (Type 1 and 2) DNA[b]
Microbiology[d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.
[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.
[c] Not required if anti-smooth muscle antibody (ASMA) is tested.
[d] Assayed ONLY by investigator-designated local laboratory, no central testing available.

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

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

10.8. Appendix 8: Criteria for the Diagnosis of Diabetes

Criteria for the diagnosis of diabetes mellitus[a] (ADA 2021b; IDF Guideline, 2018)

1. Symptoms of diabetes plus random plasma glucose concentration ≥11.1 mmol/L (200 mg/dL).

   Random is defined as any time of day without regard to time since last meal.

or

2. Fasting plasma glucose ≥7.0 mmol/L (≥ 126 mg/dL)[a].

   Fasting is defined as no caloric intake for at least 8 hours.

or

3. 2-hour postload glucose ≥11.1 mmol/L (≥200 mg/dL) during an oral glucose tolerance test (OGTT).

   The test should be performed as described by World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g.

4. HbA1c ≥ 6.5% (48 mmol/mol).

   However, there are difficulties with assay standardization and individual variation in the relationship between BG and HbA1c, which may outweigh the convenience of this test.

[a] In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples (ADA 2021b).

10.9. Appendix 9: Tanner Staging

Tanner Stages guidelines for measurement of pubescence (Marshall and Tanner 1969, 1970).

Boys: Development of external genitalia

Stage 1:	Prepubertal
Stage 2:	Enlargement of scrotum and testes; scrotum skin reddens and changes in texture
Stage 3:	Enlargement of penis; further growth of testes
Stage 4:	Increased size of penis; testes and scrotum larger, scrotum skin darker
Stage 5:	Adult genitalia

Girls: Breast development

Stage 1:	Prepubertal (no glandular tissue: areola follows the skin contours of the chest)
Stage 2:	Breast bud stage with enlargement of areola (breast bud forms, with small area of surrounding glandular tissue; areola begins to widen)
Stage 3:	Further enlargement of breast and areola (breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast)
Stage 4:	Areola and papilla form a mound (increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast)
Stage 5:	Mature stage (breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla)

Boys and girls: Pubic hair

Stage 1:	Prepubertal (no pubic hair at all; can see vellus hair similar to abdominal wall)
Stage 2:	Sparse growth of long, slightly pigmented hair, straight or curled (small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum [males] or on the labia majora [females])
Stage 3:	Darker, coarser and more curled hair, spreading sparsely over junction of pubes
Stage 4:	Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
Stage 5:	Adult in type and quantity, with horizontal distribution ("feminine")

10.10. Appendix 1 0: Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

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

When to collect samples after a systemic hypersensitivity event occurs

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

Obtain follow-up pre-dose 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 minutes to 4 hours after the start of the event. ● Note: The optimal collection time is from 1 to 2 hours after the start of event.	Serum	total tryptase
	Serum	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 hours after the start of the event.	Serum	Tirzepatide anti-drug antibodies (ADA)
	Serum/plasma	Tirzepatide concentration

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

Abbreviations: ADA = anti-drug antibodies; IL = interleukin.

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.

10.11. Appendix 11: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, Vital Signs

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

Measuring Height

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

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

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

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

Measuring Weight

- Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilogram.
- All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.
- 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.

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 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 eCRF.

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.

10.12. Appendix 12: 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 ERBs, 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/assent from the participant will be obtained for the below items, as required by ERB's and local regulations:

- participation in remote visits, as defined below 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.

Minor participants must be re-consented if they reach the age of majority during the course of study, to continue participating.

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to a review of

- concomitant medications
- study participant e-diary (including study drug compliance)
- contraception as applicable, and
- last menstrual cycle, as applicable.

Mobile healthcare:

Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to

- height, weight and waist measurements
- physical assessments
- vital signs
- review of patient reported outcome measures
- collection of blood samples, and
- collection of health information.

Other alternative locations:

Laboratory draws may be done at an alternate location in exceptional circumstances except for PK, immunogenicity, genetics and exploratory biomarker samples.

Data capture

In source documents and the CRF, the study site must 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 must 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 with sponsor approval. The local laboratory must be qualified in accordance with applicable local regulations. However, central laboratory testing must be retained for PK, immunogenicity, genetics, intact proinsulin, adiponectin and exploratory biomarker samples.

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken:

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

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at the screening visit are valid for a maximum of 60 days, with the exception of the serum pregnancy test which is valid for a maximum of 28 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances.

If screening is paused for less than 60 days from the start date of screening, the participant will proceed to the next study visit per the usual SoA, provided that the randomization visit is conducted within 60 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 or assent and document this confirmation in the source documentation.

If screening is paused for more than 60 days from the start of the 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 the randomization visit.

Adjustments to visit windows

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

This table describes the allowed adjustments to visit windows.

Visit Number	Acceptable Tolerance (instead of what is mentioned in the Schedule of Activities)
Visit 4, Visit 14	-3 to +7 days
Visit 5, Visit 7 to Visit 11	± 10 days
Visit 13 (primary endpoint visit)	±14 days (i.e. the visit may be brought forward no sooner than 14 days [Week 28] or extended up to 14 days [Week 32])
Visit 15 and Visit 17	±14 days
Visit 16 and Visit 18	± 10 days
Visit 19	±28 days (i.e. the visit may be brought forward no sooner than 28 days [Week 48] or extended up to 28 days [Week 56])
Visit 801	-7 to +14 days

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

Documentation

Changes to study conduct will be documented

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

10.13. Appendix 13: Abbreviations and Definitions

Term	Definition
ADA	American Diabetes Association
AE	adverse event: Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	Adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ACR	albumin/creatinine ratio
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some ethical review boards [ERBs]).
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
CI	confidence interval
CEC	Clinical Endpoint Committee
CIOMS	Council for International Organizations of Medical Sciences
COA	clinical outcome assessment

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 efficacy, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSR	clinical study report
CT	computed tomography scan
CV	cardiovascular
DBP	diastolic blood pressure
Device deficiencies	Equivalent to product complaint
DMC	data monitoring committee. A DMC, 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-IV inhibitor	dipeptidyl peptidase-IV inhibitor: A class of oral hypoglycemic drugs used to treat participants with T2DM.
DSMT	Developmental Safety Management Team
DSST	Developmental Safety Surveillance Team
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EDC	electronic data capture system
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate: A measure of kidney function.
efficacy	The ability of a treatment to achieve a beneficial intended result under controlled conditions.

EMA	European Medicines Agency
end of study (trial)	The date of the last visit or last scheduled procedure shown in the Study Schedule for the last participant.
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.
ERB	ethical review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the participants participating in a clinical study are protected.
ET	Early termination
EU	European Union
FAS	Full Analysis Set
FBG	fasting blood glucose
FSG	fasting serum glucose
GAD65	glutamic acid decarboxylase 65 autoantibodies: A marker of type 1 diabetes mellitus (T1DM).
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist: A class of injectable hypoglycemic drugs approved to treat adult participants with T2DM.
HbA1c	glycated hemoglobin A1c
HF	human factor
HR	heart rate
IA2	tyrosine phosphatase-like insulinoma antigen 2 autoantibodies: A marker of T1DM.
IB	Investigator’s Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

IMP	Investigational Medicinal Product
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Intervention	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.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study.
MEN2	multiple endocrine neoplasia syndrome type 2
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MTC	medullary thyroid carcinoma
NAFLD	Nonalcoholic fatty liver disease
NIMP	Non-investigational Medicinal Product
NOAEL	no-observed-adverse-effect level
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
p-amylase	pancreatic amylase
PC	product complaint

PedsQL	Pediatric Quality of Life Inventory
PK/PD	pharmacokinetics/pharmacodynamics
PND	postnatal delay
PPS	per-protocol set: The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PRO/ePRO	participant-reported outcomes/electronic participant-reported outcomes
QTc	corrected QT interval
QW	once weekly
RA	receptor agonist
randomize	The process of assigning participants to an experimental group on a random basis.
RISE	Restoring Insulin Secretion
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDP	single dose pen
SDS	standard deviation score
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.
SMBG	self-monitored blood glucose
SoA	schedule of activities
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
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 limits of normal

US	United States

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