Protocol: I8F-MC-GPHV

A Safety, Tolerability and Pharmacokinetic Study of Tirzepatide for the Treatment of Pediatric Participants (6 years to 11 years) with Obesity

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Approval Date: 16-Nov-2023

Title Page

Protocol Title: A Safety, Tolerability and Pharmacokinetic Study of Tirzepatide for the Treatment of Pediatric Participants (6 years to 11 years) with Obesity.

Protocol Number: I8F-MC-GPHV

Amendment Number: e

Compound: Tirzepatide (LY3298176)

Brief Title:

Safety, Tolerability and Pharmacokinetics of Tirzepatide in Pediatric Participants with Obesity.

Study Phase: 1

Acronym: GPHV

Sponsor Name: Eli Lilly and Company

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

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Medical Monitor Name and Contact Information will be provided separately

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment d	*28-July-2023*
Amendment c	*05-June-2023*
Amendment b	*19-January-2023*
Amendment a	*27-October-2022*
Original Protocol	*30-June-2022*

Amendment [e]

This amendment is considered to be substantial and was done for reducing potential safety risk of the participants while ensuring/maximizing adequacy and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:

This protocol is being amended to narrow the range of body weight in Cohort 3 in order to generate additional safety, tolerability, and PK data of tirzepatide in participants with relatively lower body weight. A lower limit was also selected for the body weight as a conservative approach, based on available adult exposure data from PK/PD modeling.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 Synopsis – treatment arms and planned duration	Updated screening body weight for Cohort 3	Participants with body weight in the range of 40 to 60 kg inclusive will be enrolled in Cohort 3: • narrow body weight range is selected to generate additional safety, tolerability, and PK data of tirzepatide in participants with relatively lower body weight • upper limit of 60 kg is selected to obtain data from participants in 50 to 60 kg range who will receive a starting dose of [redacted] mg tirzepatide in addition to data from Cohort 1 which includes participants ≥50 kg • sentinel dosing in first [redacted] participants in the body weight range of 40 to 50kg
Section 1.2 Schema	Updated schema to reflect body weight range and sentinel dosing for Cohort 3	
Section 2.3 Benefit/Risk Assessment	Deleted the text on 'lower body weight' for participants in Cohort 3	
Section 4.1 Overall Design	Updated text to include body weight range for Cohort 3 Sentinel dosing will be used for [redacted] participants in the body weight range of 40 to 50 kg in Cohort 3	
Section 4.2 Scientific Rationale for	Modified text on rationale for sentinel dosing in Cohort 3	

Section # and Name	Description of Change	Brief Rationale
Study Design		
Section 4.3 Justification for Dose	Updated text on body weight range for Cohort 3	
Section 5.1 Inclusion Criteria	Updated text on screening body weight for Cohort 3	
Section 8.3 Adverse Events, Serious Adverse Events and Product Complaints	Replaced the text on 'SAEs and AE of special interest' with all adverse events	Accurately describes what is being done in the study
Section 10.7. Appendix 7 Tanner Staging	Added the following: The assessment of sexual maturity in children should include an assessment of age, growth, and menstrual history in addition to Tanner Staging. In case of discordance between breasts or genitals vs pubic hair, the default should be breast or genitals.	Assessment of sexual maturity should be based on both pubic hair and accompanying breast/testicular changes
Section 10.12 Appendix 12	Details on amendment (d) added	

Table of Contents

1. Protocol Summary 10
1.1. Synopsis 10
1.2. Schema 13
1.3. Schedule of Activities 14

2. Introduction 18
2.1. Study Rationale 18
2.2. Background 18
2.3. Benefit/Risk Assessment 21

3. Objectives and Endpoints 22

4. Study Design 23
4.1. Overall Design 23
4.2. Scientific Rationale for Study Design 23
4.3. Justification for Dose 24
4.4. End of Study Definition 24

5. Study Population 25
5.1. Inclusion Criteria 25
5.2. Exclusion Criteria 26
5.3. Lifestyle Considerations 29
5.3.1. Intensive Behavioral Therapy (IBT) for Chronic Weight Management in Children 6-11 Years Old 29
5.3.2. Meals and Dietary Restrictions 29
5.3.3. Substance Use: Caffeine, Alcohol, and Tobacco 29
5.3.4. Activity and Vaccinations 30
5.4. Screen Failures 30

6. Study Intervention(s) and Concomitant Therapy 31
6.1. Study Intervention(s) Administered 31
6.1.1. Administration Details 31
6.1.2. Medical Devices 32
6.2. Preparation, Handling, Storage, and Accountability 32
6.3. Measures to Minimize Bias: Randomization and Blinding 33
6.4. Study Intervention Compliance 33
6.5. Dose Modification 34
6.5.1. Data Review during the Study 34
6.6. Continued Access to Study Intervention after the End of the Study 35
6.7. Treatment of Overdose 35
6.8. Concomitant Therapy 35

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 37
7.1. Discontinuation of Study Intervention 37
7.2. Participant Discontinuation/Withdrawal from the Study 37
7.3. Lost to Follow-up 38

8. Study Assessments and Procedures....39
8.1. Efficacy Assessments....39
8.2. Safety Assessments....39
8.2.1. Physical Examinations....39
8.2.2. Body Weight, Body Mass Index, Height, and Waist Circumference....39
8.2.3. Assessment of Pubertal Status - Tanner Staging....39
8.2.4. Vital Signs....39
8.2.5. Electrocardiograms....40
8.2.6. Clinical Safety Laboratory Tests....40
8.2.7. Safety Monitoring....40
8.2.8. Pregnancy Testing....44
8.3. Adverse Events, Serious Adverse Events, and Product Complaints....44
8.3.1. Timing and Mechanism for Collecting Events....45
8.3.2. Pregnancy....46
8.3.3. Adverse Events of Special Interest....47
8.4. Pharmacokinetics....49
8.4.1. Bioanalysis....49
8.5. Pharmacodynamics....49
8.5.1. Body Weight and Waist Circumference....49
8.6. Genetics....50
8.7. Biomarkers....50
8.8. Immunogenicity Assessments....50
8.9. Health Economics....50

9. Statistical Considerations....51
9.1. Statistical Hypotheses....51
9.1.1. Multiplicity Adjustment....51
9.2. Analyses Sets....51
9.3. Statistical Analyses....51
9.3.1. General Considerations....51
9.3.2. Pharmacokinetics....52
9.3.3. Safety Analyses....52
9.3.4. Evaluation of Immunogenicity....52
9.4. Interim Analysis....53
9.5. Sample Size Determination....53

10. Supporting Documentation and Operational Considerations....54
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations....54
10.1.1. Regulatory and Ethical Considerations....54
10.1.2. Informed Consent Process....55
10.1.3. Data Protection....55
10.1.4. Dissemination of Clinical Study Data....56
10.1.5. Data Quality Assurance....56
10.1.6. Source Documents....57
10.1.7. Study and Site Start and Closure....58

10.1.8. Publication Policy 58
10.1.9. Sample Retention 58
10.2. Appendix 2: Clinical Laboratory Tests 59
10.2.1. Blood Sampling Summary 61
10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 63
10.3.1. Definition of an Adverse Event 63
10.3.2. Definition of Serious Adverse Event 64
10.3.3. Definition of Product Complaints 65
10.3.4. Recording and Follow-up of Adverse Event or Serious Adverse Event and Product Complaints 66
10.3.5. Reporting of Serious Adverse Events 68
10.3.6. Regulatory Reporting Requirements 68
10.4. Appendix 4: Contraceptive and Barrier Guidance 69
10.4.1. Definitions 69
10.4.2. Contraception Guidance 69
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 69
10.6. Appendix 6: Pancreatic Monitoring 71
10.7. Appendix 7: Tanner Staging 73
10.8. Appendix 8: Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event 75
10.9. Appendix 9: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs 75
10.10. Appendix 10: Provisions for Changes in Study Conduct During Exceptional Circumstances 78
10.11. Appendix 11: Abbreviations and Definitions 82
10.12. Appendix 12: Protocol Amendment History 85

11. References 89

List of Tables

Table **Page**

Table GPHV.6.1. Treatments Administered 31

List of Figures

Figure **Page**

Figure GPHV.1.1. Illustration of enrollment and interim data review plan for Protocol I8F-MC-GPHV.....13

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Safety, Tolerability, and Pharmacokinetic Study of Tirzepatide for the Treatment of Pediatric Participants (6 years to 11 years) with Obesity.

Brief Title: Safety, Tolerability, and Pharmacokinetics of Tirzepatide in Pediatric Participants with Obesity.

Rationale:

Tirzepatide (LY3298176) is a dual glucose-dependent insulinotropic peptide receptor and glucagon-like peptide 1 receptor agonist being developed as an adjunct to diet and exercise for chronic weight management in adult patients with or without type 2 diabetes mellitus (T2DM) who have an initial body mass index of greater than equal to 30 kg/m^2 (obesity), or greater than equal to 27 kg/m^2 (overweight). The dose of tirzepatide has been defined for adults with obesity or overweight with one or more weight-related comorbidities, including T2DM, but data are lacking in pediatric participants with obesity particularly for the younger pediatric participants whose body weights are less likely to overlap with the body weights of adults with T2DM.

Study I8F-MC-GPHV will assess the safety, tolerability, and pharmacokinetic (PK) of tirzepatide administered weekly via the subcutaneous (SC) route for 8 weeks in pediatric participants (age: 6 to 11 years) with obesity partitioned according to weight (lower body weight: less than 50 kg; higher body weight: more than or equals to 50 kg).

Objectives and Endpoints:

Objectives	Endpoints
Primary • To evaluate tirzepatide safety and tolerability following SC injections of tirzepatide in pediatric participants with obesity	• Incidence of adverse events, treatment-emergent adverse events, and serious adverse events
Secondary • To evaluate the PK profile of tirzepatide following SC injections in pediatric participants with obesity	• Tirzepatide area under $AUC_{0\text{-}tau}$, C_{max} from the population PK model

Abbreviations: $AUC_{0\text{-}tau}$ = area under the concentration versus time curve from time 0 to the end of the dosing interval; C_{max} = maximum concentration; PK = pharmacokinetics; SC = subcutaneous.

Overall Design:

This is an investigator and participant blinded, randomized, placebo-controlled safety, tolerability, and PK study in up to 3 cohorts of pediatric participants with obesity.

Potential participants will be screened to assess their eligibility to enter the study within 28 days prior to Day 1. Participants will visit the clinic on Day 1 to be assessed and randomized and to establish baseline measurements.

Participants will receive 8 weekly SC injections of tirzepatide or placebo starting on Day 1, remain inpatient within the clinical research unit (CRU) until at least Day 3, and return for outpatient visits. In-clinic visits on Days 8, 29, 43, and 57 will be mandatory for all participants. For Cohort 2 participants, Days 15 and 22 will also be mandatory to be in-clinic. All other outpatient visits may either be performed remotely or in-clinic.

The final follow-up visit will occur 4 to 6 weeks after the last treatment or at least 4 weeks but up to 6 weeks upon early discontinuation.

Safety will be assessed by vital signs, electrocardiograms, safety laboratory tests, and the recording of adverse events (AEs). PK blood samples for tirzepatide and immunogenicity samples will be collected.

Treatment Arms and Planned Duration for an Individual Participant:

Participants will be randomized to receive either tirzepatide or placebo in a [redacted] ratio. The study duration for individual participants, inclusive of screening, is expected to be approximately 19 weeks, divided as follows:

- screening - up to 4 weeks prior to randomization
- treatment period - 8 weeks, and
- follow-up - 4 to 6 weeks from last dosing.

Participants enrolled will be partitioned as follows:

- Cohort 1: Higher weight cohort – screening body weight ≥50 kg
- Cohort 2: Lower weight cohort – screening body weight <50 kg, and
- Cohort 3: Screening body weight between 40 to 60 kg inclusive.

Number of Participants:

Approximately [redacted] participants aged 6 to 11 years with obesity at screening may be enrolled. This will allow PK characterization in at least [redacted] participants each, exposed to tirzepatide, for the weight categories <50 kg and ≥50 kg, respectively. Participants who do not complete all the study procedures may be replaced to target the planned number of completers specified in the sample determination section.

Statistical Analysis:

Primary safety statistical analyses will be conducted for all participants receiving the study drug whether or not they completed all protocol requirements.

Tirzepatide concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM® software. The main PK parameters for analysis will be maximum concentration and area under the concentration versus time curve from the population PK model.

Safety parameters that will be assessed include safety laboratory parameters, vital signs, AEs, treatment-emergent AEs, and serious adverse events. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data. All AEs related to study or protocol procedure will be listed, and if the frequency of events allows, they will be also summarized using descriptive methodology.

Physical examinations and electrocardiograms will be performed for safety monitoring purposes and will be presented as AEs when clinically relevant findings are reported.

Additional exploratory analyses will be performed on the effect of treatment on body mass index, body weight, and waist circumference.

Data Monitoring Committee: No.

CCI

[redacted]

1.3. Schedule of Activities

Study Schedule Protocol I8F-MC-GPHV

Visit Number	**1 Screening**	**2 Baseline and Inpatient**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 = Final Follow-up**	**Early Discontinuation**
Week	**-4 to -1**	**1**	**2**	**3**	**4**		**5**	**6**		**7**	**8**	**9**	**12 to 14**	**at least 4 weeks but up to 6 weeks from Last Dose**
Days	CCI													
Visit Interval Tolerance (Days)														
Informed consent, assent, medical history, vaccination schedule, and full date of birth collection	X													
	Comments: *The informed consent form must be signed by parents or legal guardian and the assent form (as appropriate per local requirements) must be signed by the participant before any protocol-specific tests/procedures are performed. Any vaccine which the participant is scheduled for as a part of immunization scheme must be captured in the concomitant medications pages of the CRF.*													
Review and confirm I/E criteria	X	Anytime predose												
Pregnancy test (urine) - at site for females only	X	Any time as deemed necessary by the investigator												
	Comments: *At investigator's clinical discretion (for example, there is reason to believe that the female participant is sexually active)*													
Enrolment and randomization		Day 1												
Tanner staging (females only)	X	P					P					X		X
Intensive behavioral therapy		X	X											X
	Comments: *Participant and at least one family member will be offered IBT throughout the study. Starting at baseline, participants will be able to receive approximately 24 hours of therapy sessions. The frequency of IBT sessions will be flexible and at the discretion of the investigator.*													
Inpatient visit		X												

Visit Number	**1 Screening**	**2 Baseline and Inpatient**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 = Final Follow-up**	**Early Discontinuation**
Week	**-4 to -1**	**1**	**2**	**3**	**4**		**5**	**6**		**7**	**8**	**9**	**12 to 14**	**at least 4 weeks but up to 6 weeks from Last Dose**
Days	CCI													
Visit Interval Tolerance (Days)														
	***Comments**: Participant and accompanying adult will be admitted to the inpatient unit on morning of Day 1 for medical assessments and baseline measurements prior to randomization and treatment. All participants will be closely monitored for safety and discharged earliest on Day 3. The inpatient stay may be extended by the investigator if it is necessary for the participant's clinical well-being.*													
Outpatient visit	X		X	X	X	X	X	X	X	X	X	X	X	X
	***Comments**:* *· For all participants - screening Visit 1, inpatient Visit 2 and outpatient Visits 3, 7, 10, and 12 must be performed in-clinic.* *· For all participants who discontinued early - early discontinuation visit must be performed in-clinic.* *· For Cohort 2 participants only - additionally, Visits 4 and 5 must be performed in clinic due to the necessity of tirzepatide dosing manipulations for preparing a CCI dose. This must be highlighted in the informed consent and assent forms for Cohort 2.* *· All other outpatient visits, including final follow up (but not early discontinuation) may be performed remotely such as by telemedicine or by mobile healthcare services.*													
Adverse events & concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination /medical assessment	X	P, before discharge	P				P					X	X	X
	***Comments**: Full physical examination at screening. Thereafter, assessments performed to include medical review and targeted, symptom-driven examination, as appropriate. Additional assessments may be performed at investigator's clinical discretion. P = predose measure that can be performed any time prior to dosing.*													
Height, weight, waist circumference, and body mass index	X	P					P					X	X	X
	***Comments**: Height is required only during screening, Visit 1, and Visit 12. P = predose measure that can be taken any time prior to dosing.*													

Visit Number	**1 Screening**	**2 Baseline and Inpatient**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 = Final Follow-up**	**Early Discontinuation**
Week	**-4 to -1**	**1**	**2**	**3**	**4**		**5**	**6**		**7**	**8**	**9**	**12 to 14**	**at least 4 weeks but up to 6 weeks from Last Dose**
Days	CCI													
Visit Interval Tolerance (Days)														
Supine vital signs	X	P, 8 hours	P				P			P		X	X	X
	***Comments**: Vital sign timing on Day 1 is with reference to actual time of first tirzepatide dosing (0 hours). P = predose measure that can be performed any time prior to dosing.*													
Temperature	X	P, 8 hours										X	X	X
	***Comments**: Temperature timing on Day 1 is with reference to actual time of first tirzepatide dosing (0 hours) and may be measured via the oral, aural, or rectal route according to clinic's local practice. P = predose measure that can be performed any time prior to dosing.*													
Single, safety 12-lead ECG - at site	X	P, 8 hours	P				P			P		X		X
	***Comments**: ECG timing on Day 1 is with reference to actual time of first tirzepatide dosing (0 hours). Participants must be supine for at least 3 minutes prior to procedure and remain supine but awake during ECG collection. P = predose measure that can be performed any time prior to dosing.*													
Clinical laboratory test (fasting)	X	P					P					X		X
	***Comments**: Screening performed by local laboratory and will include hormone assessments. All others by a central laboratory. Clinical laboratory test on Day 1 is for baseline purpose, and results need not be reviewed prior to tirzepatide dosing. Additional unscheduled samples may be collected and assayed by the local laboratory if necessary, at the investigator's clinical discretion. P = predose measure that can be performed any time prior to dosing.*													
Blood glucose monitoring or sampling for safety		Days 1&2												
	***Comments**: On Days 1 and 2, blood glucose should be measured before bedtime. This can be measured using a glucose analyzer on site or local lab. Additional samples may be taken at the discretion of the investigator as clinically indicated or symptom-directed.*													
Tirzepatide subcutaneous dosing to abdomen		Day 1 (0 hr)	X	X	X (0 hr)		X (Increase dose level)	X (0 hr)		X	X			

Visit Number	**1 Screening**	**2 Baseline and Inpatient**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 = Final Follow-up**	**Early Discontinuation**
Week	**-4 to -1**	**1**	**2**	**3**	**4**		**5**	**6**		**7**	**8**	**9**	**12 to 14**	**at least 4 weeks but up to 6 weeks from Last Dose**
Days	CCI													
Visit Interval Tolerance (Days)														
	***Comments**: Tirzepatide injection sites must be rotated along the 4 abdominal quadrants. Dosing may be performed by clinic staff during in-clinic visits. Self-administration by participant or parent or legal guardian is permitted after the investigator assessed them as being adequately trained. The dose increase will happen at the 5th dose as indicated in Figure GPHV.1.1*													
Tirzepatide sampling for pharmacokinetics (hrs)		12, 24		P		X: within 24 to 96 hrs postdose		P	X: within 120 to 168 hrs postdose		P	X	X	X
	***Comments**: Sampling time is relative to the latest dosing time. The actual date and time of the sampling and the most recent SC injection administered prior to collecting the sample must be recorded. Days 15, 36 and final follow-up or early discontinuation sample must be time-matched with immunogenicity sampling. No sample collection is needed if the participant discontinued before receiving tirzepatide. P = predose samples that should be collected within an hour prior to dosing.*													
Immunogenicity sampling		P		P				P					X	X
	***Comments**: Exact time of sampling must be recorded. Days 15, 36 and final follow-up or early discontinuation sample must be time-matched with pharmacokinetic sampling. No sample collection is needed if the participant discontinued before receiving tirzepatide. P = predose samples that should be collected within an hour prior to dosing.*													

Abbreviations: BMI = body mass index; CRF = case report form; ECG = electrocardiogram; hrs = hour; IBT = intensive behavioral therapy; I/E = inclusion and exclusion criteria; P = predose.

2. Introduction

Obesity is a chronic disease and its increasing prevalence is a public health concern associated with rising incidence of T2DM, increased risk for premature death, and increased risk for some cancers (AMA 2013; Council on Science and Public Health 2013; Lauby-Secretan et al. 2016). Although loss of 5% to 10% body weight through lifestyle approaches, based on caloric restriction, physical activity, and behavioral therapy, has been shown to reduce obesity-related CV risk factors, and in some cases, improve health-related quality of life (Mertens and Van Gaal 2000; Knowler et al. 2002; Jensen et al. 2014; Kolotkin and Andersen 2017), lifestyle therapies alone fail to achieve sustainable weight loss in the majority of patients with obesity (Dombrowski et al. 2014). Caloric restriction, for example, has been shown to lead to metabolic adaptive responses, including increases in hunger hormones, decreases in satiety factors (including GI peptides), increased appetitive drive and food intake, and lower energy expenditure (Leibel et al. 1995; Sumithran et al. 2011). These adaptations are thought to work in concert to cause regain and poor durability of treatment. The addition of physical activity is essential and can help maintain weight loss, but generally, maintaining lifestyle-induced weight loss is recognized as being more challenging than losing weight for individuals with obesity (Swift et al. 2018).

Pharmacologic agents, in contrast to voluntary caloric restriction, can directly impact the physiology of energy balance, including the regulation of food intake and/or energy expenditure, to drive toward a lower fat mass and body weight (Heymsfield et al. 2018). Some current or previously marketed weight-management medications have had a demonstrable effect on maintaining initial weight loss over time while on treatment (James et al. 2000; Smith et al. 2010; Wadden et al. 2013). There is increasing recognition that adjunctive pharmacotherapy may be required to improve weight loss, weight maintenance, and health outcomes in individuals with obesity (AMA 2013; Apovian et al. 2015).

2.1. Study Rationale

Tirzepatide (LY3298176) is a GIP receptor and GLP-1 receptor agonist approved as an adjunct to diet and exercise in adult patients with T2DM. It is also being developed as an adjunct to diet and exercise for chronic weight management of adults who have an initial BMI of 30 kg/m^2 or greater (obesity) or 27 to 29.9 kg/m^2 (overweight, with additional health risks). The dose of tirzepatide has been defined for adults with obesity or overweight and T2DM patients, but data are lacking in pediatric participants with obesity.

Study I8F-MC-GPHV (GPHV) will assess safety, tolerability, and PK after 8 weeks of treatment with tirzepatide administered via the SC route in participants (age 6 to 11 years) with obesity partitioned according to weight (lower body weight <50kg; higher body weight ≥50 kg).

2.2. Background

Pediatric Obesity

The prevalence of obesity in the US has been captured as a part of the National Health and Nutrition Examination Survey (NHANES). The nationally representative data clearly

demonstrate that childhood and adolescent obesity continue to be a significant concern (Skinner et al. 2018).

In the US, the prevalence of obesity among pediatric patients aged 2 to 19 years has increased by approximately 1.3-fold between 1999 and 2016. The data show that the prevalence of pediatric obesity increases with age and is highest among adolescents aged 12 to 19 years (Skinner et al. 2018).

The current treatment regimens for pediatric obesity include lifestyle modification, pharmacotherapy, and bariatric surgery (Styne et al. 2017). The treatment of pediatric obesity emphasizes positive behavior change, including healthy food choices, reduction of physical inactivity, and family engagement (AAP IHCW 2015; Styne et al. 2017).

Pediatric obesity is a multifactorial disease requiring consideration of pubertal development, risk for comorbidities, psychological state, and social implications (Styne et al. 2017).

Pediatric overweight and obesity are defined based on local or regional growth charts for age- and sex-specific BMI. In the US, World Health Organization and Centers for Disease Control and Prevention growth charts are commonly used to assess BMI.

The pathophysiology of pediatric obesity is multifactorial; a combination of heritable and environmental factors leads to an imbalance between energy intake and expenditure (Crocker and Yanovski 2009). However, the exact etiology of obesity in pediatric patients is not clearly understood. Of note, pediatric obesity due to obesity syndromes or genetic conditions is infrequent and accounts for approximately 7% of patients with extreme pediatric obesity (Styne et al. 2017).

Comorbidities of pediatric obesity

Pediatric obesity is associated with an increased risk of premature death and comorbidities. The likelihood of developing adult obesity increases for pediatric patients with obesity as they approach adulthood, pointing to a need to address obesity as it presents in childhood (Krebs et al. 2007). Obesity-related comorbidities include the following (Jastreboff et al. 2019):

- cardiovascular disease (CVD)
- cerebrovascular diseases
- T2DM
- hypertension, and
- some cancers.

The comorbidities associated with obesity and overweight in adults are consistent with that of children with obesity (Styne et al. 2017). Additionally, the benefits associated with weight loss in the pediatric population with obesity are consistent with that of adults (August et al. 2008).

In pediatric patients, for every 10 kg/m^2 increase in BMI, there is an associated 34% increased risk of dyslipidemia, 46% higher risk of hypertension, and 25% increase in insulin concentration (Durkin and Desai 2017).

The risks of CVD outcomes among children and adolescents with obesity who were without obesity by adulthood appear to be similar to those who never had obesity. Such risk factors of CVD outcomes are as follows (Juonala et al. 2011):

- T2DM

- hypertension
- elevated low-density lipoprotein cholesterol
- reduced high-density lipoprotein cholesterol
- elevated triglyceride levels, and
- carotid artery atherosclerosis.

Long-term weight loss of 5% or greater as a result of lifestyle modification is associated with improvement in various metabolic and CV risk factors (Brown et al. 2016). Weight loss interventions that result in significant and durable weight loss, such as that associated with bariatric surgery, may result in multiple benefits such as

- reduced CV risk factors
- reduced risk of T2DM, and
- decreased risk of CV death and all-cause mortality (Kritchevsky et al. 2015).

Tirzepatide

Weight loss induced by GLP-1R agonists, while appearing to be centrally mediated through a combination of hormonal inputs to satiety centers (van Bloemendaal et al. 2014), has not been consistently associated with changes in mental health or with potential for addiction in long-term studies conducted to establish CV safety in patients with diabetes (Marso et al. 2016a, 2016b; Gerstein et al. 2019). Tirzepatide, which is both a GLP-1R and GIP receptor agonist, has been associated with predominantly mild-to-moderate GI adverse effects similar to currently marketed GLP-1R agonists.

Overall summary on weight loss in adult participants with obesity or overweight with or without type 2 diabetes mellitus

In adult participants with T2DM, tirzepatide 5, 10, and 15 mg demonstrated superior reductions from baseline in body weight at the primary endpoint visit (40 or 52 weeks) in all 5 global Phase 3 studies compared with placebo (that is, the management of body weight primarily by diet and exercise), semaglutide, and basal insulin (insulin degludec and insulin glargine).

The SURMOUNT-1 Phase 3 study investigated the efficacy of tirzepatide in adult participants with obesity or overweight as an adjunct to lifestyle intervention including regular lifestyle counseling sessions, delivered by a dietitian or a qualified healthcare professional, to help participants adhere to healthful, balanced meals, with a deficit of 500 calories per day, and at least 150 minutes of physical activity per week. Again, tirzepatide 5, 10, and 15 mg demonstrated superior reductions from baseline in body weight at the primary endpoint visit (72 weeks) in the SURMOUNT-1 study compared with placebo (Jastreboff et al. 2022).

Treatment guidelines suggest that patients with T2DM and obesity should target a body weight reduction of ≥5% (ADA 2021). Across all Phase 3 trials, a significantly higher proportion of tirzepatide-treated patients achieved this target in comparison to placebo and active comparators. The results of the global Phase 3 studies indicate that tirzepatide enabled significant proportions of adults with T2DM to reach the body weight goal recommended in treatment guidelines, and the results suggest that more ambitious body weight goals were feasible for many patients.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of tirzepatide is to be found in the IB.

2.3. Benefit/Risk Assessment

The risks of tirzepatide have been consistent with risks associated with other GLP-1 receptor agonists currently marketed. Potential risks include, but are not limited to, GI effects, acute pancreatitis (very rare), increases in heart rate, and hypoglycemic events (GLP-1 receptor agonist class effect).

No clinically significant safety or tolerability concerns have been identified during the clinical investigation of tirzepatide up to the single dose level of 5 mg or multiple weekly doses, when escalated up to 15 mg in adults. Based on this information, the highest starting dose of [redacted] mg and the highest dose of [redacted] mg tirzepatide to be administered in this study are reasonably anticipated to be tolerable in this group of pediatric participants with obesity.

Body weight is a known covariate affecting tirzepatide exposures based on population PK analysis in adult patients with T2DM. It is predicted that the exposure may be approximately 2-fold higher in the population with weight <50 kg compared to that in adults (weight ≥50 kg); therefore, a more conservative initial starting dose of [redacted] will be adopted for participants in the lower body weight cohort (Cohort 2). This is a mitigation approach taken to reduce the risk of safety and tolerability issues before commencing another cohort of participants on an initial [redacted]-mg dose (Cohort 3).

Based on the known pharmacology of tirzepatide, participants with obesity may benefit from clinically meaningful weight reduction after 8 weeks of treatment. Potential risks, such as GI effects, acute pancreatitis, increases in heart rate, and hypoglycemic events, are consistent with the risks associated with currently available long-acting GLP-1R agonists in adults. These risks are clinically detectable and manageable and will be monitored throughout the study.

A juvenile toxicology study in rats was conducted to assess potential effects on growth and development to support pediatric development. Rats in the study were dosed twice weekly from Postnatal Days 21 to 84, which roughly corresponds to early human pediatric (2 years of age) through late adolescence based on overall central nervous system and reproductive development across species (Rodier 1980; Bayer et al. 1993; Rice and Barone Jr 2000; Beck et al. 2006) and overlaps ages utilized in the general toxicology studies. Standard behavioral, reproductive, and pathology assessments, as well as the careful monitoring of body weight and developmental markers of sexual maturation (vaginal patency and balanopreputial separation), were included as endpoints. Consistent with adult rats, effects in juvenile rats were limited to pharmacological effects on body weight and food consumption and effects secondary to the pharmacology. These data indicate that tirzepatide does not have unique toxicities in juvenile animals and has an acceptable nonclinical safety profile to support pediatric clinical trials.

For females, use Tanner staging by physical exam, history or occurrence of menarche, and/or menses to aid in the detection of a child who is no longer Tanner 1 and may be further evaluated for childbearing potential.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of tirzepatide is to be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary • To evaluate tirzepatide safety and tolerability following the SC injections of tirzepatide in pediatric participants with obesity	• Number of treatment-emergent adverse events and serious adverse events
Secondary • To evaluate the PK profile of tirzepatide following SC injections in pediatric participants with obesity	• Tirzepatide area under the concentration versus time curve ($AUC_{0\text{-}tau}$), maximum concentration (C_{max}) from population PK model
CCI	

Abbreviations: CCI; PK = pharmacokinetics; SC = subcutaneous.

4. Study Design

4.1. Overall Design

This is a randomized, placebo-controlled, participant and investigator blinded, 8-week treatment Phase 1 study in pediatric participants with obesity who do not have diabetes mellitus. Potential pediatric participants will be screened to assess their eligibility to enter the study within 28 days prior to Day 1. Participants enrolled will be partitioned as follows:

- Cohort 1: Higher weight cohort – screening body weight ≥50 kg
- Cohort 2: Lower weight cohort – screening body weight <50 kg, and
- Cohort 3: Screening body weight between 40 to 60 kg, inclusive.

The schematic of the study is shown in Figure GPHV.1.1. Initially, [redacted] participants are planned to be enrolled into the higher body weight (Cohort 1). Participants will be randomized on Day 1 to tirzepatide or placebo ([redacted] ratio) after the confirmation of eligibility. Placebo is included as the control in a blinded manner for investigator, site staff, and participants to allow an unbiased assessment of the safety and tolerability data generated, which will allow a more robust comparison between tirzepatide and placebo. In-clinic outpatient visits are planned as detailed in the SoA.

Safety and tolerability data will be reviewed by the unblinded sponsor CP, CRP/CRS, and blinded investigator. Decisions for commencing dosing in Cohort 2 (lower body weight participants) will be made based on the following:

- the completion of at least 5 treatment doses from at least [redacted] participants in Cohort 1, and
- the review of safety/tolerability data through Day 36, including safety clinical laboratory.

Likewise, the dosing of Cohort 3 participants (body weight 40 to 60 kg inclusive) will proceed only after the satisfactory review of safety and tolerability data from at least [redacted] participants who received at least 5 treatment doses in Cohort 2 as shown in Figure GPHV.1.1. PK samples will be collected, and exposure data for tirzepatide will be analyzed during the study to support dose-escalation decisions where possible. Sentinel dosing will be used for [redacted] participants in the specific body weight range of 40 to 50 kg in Cohort 3 [redacted]. If safety and tolerability after at least 1 week are acceptable in the [redacted] sentinel participants, as clinically assessed by the investigator, the remainder of the participants in Cohort 3 ([redacted] tirzepatide and [redacted] placebo) in the 40 to 60 kg range can be randomized and dosed.

A final follow-up visit will occur within 4 to 6 weeks after last treatment or at least 4 weeks but up to 6 weeks for participants who discontinued prematurely.

Starting at Visit 2 (baseline visit), all participants will be offered intensive behavioral therapy (IBT) sessions (Section 5.3.1) which will continue through the study period and until the final follow up.

4.2. Scientific Rationale for Study Design

This study is designed to assess the safety, tolerability, and PK profile of tirzepatide administered SC in participants aged 6 to 11 years with obesity.

The dose justification for tirzepatide is provided in Section 4.3.

The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK and is not powered on the basis of any a priori statistical hypothesis testing for efficacy. The rationale for the sample size is provided in Section 9.5.

Placebo is included as a control, in a blinded manner for investigators, site staff, and participants, to allow an unbiased assessment of the data generated, which will allow a more robust comparison of safety, tolerability, and PD data.

Sentinel dosing design will be used in Cohort 3 because this cohort has a higher starting dose compared to Cohort 2, while allowing participants with body weight below 50 kg. Cohort 1 will include participants ≥50 kg at a starting dose of [redacted] mg. Cohort 3 will include participants in the range of 40 to 60 kg at a starting dose of [redacted] mg. Hence, sentinel dosing will be used in [redacted] participants in the body weight range of 40 to 50 kg in Cohort 3, as this weight range is not included in Cohort 1. Sentinel dosing design is included to assess the tolerability or safety profiles due to increased starting dose in participants with obesity receiving tirzepatide.

4.3. Justification for Dose

A starting dose of [redacted] mg accompanied by dose titration of [redacted] mg increments every 4 weeks (up to a maximum dose of 15 mg) was shown safe and well tolerated in adults with T2DM. The body weight of the pediatric participants in the higher body weight cohort (Cohort 1) in this study will overlap with the weight of adults studied in the T2DM program (weight around or higher than 50 kg). Thus, a starting dose of [redacted] mg for 4 weeks, followed by [redacted] mg for 4 weeks, is planned for this pediatric population with body weight more than or equal to 50 kg.

The exposure in pediatric participants with weight <50 kg is anticipated to be up to 2-fold higher than the exposure in adults (weight range in Phase 3 studies in adults with T2DM: 43.1 to 227 kg), given that body weight was identified as a covariate on tirzepatide exposures in adults. Thus, a lower starting dose of [redacted] mg in this pediatric population with weight below 50 kg will be evaluated for tolerability and safety in Cohort 2. If the starting dose of [redacted] mg is well-tolerated, a starting dose of [redacted] mg will also be tested in Cohort 3 within a narrower weight range (40 to 60 kg, inclusive).

4.4. End of Study Definition

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

A participant is considered to have completed the study if the participant has completed the last scheduled procedure shown in the SoA.

5. Study Population

The eligibility of participants for the study will be largely based on the results of medical history, physical examination, vital signs, clinical laboratory tests, and 12-lead ECG.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days prior to Day 1. If the investigator decides not to administer the dose to a participant or not to enroll a participant on a particular day, the participant's visit may be rescheduled, and any assessments or procedures performed up to that point may be repeated to confirm their eligibility.

The 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 for inclusion in the study if they meet all of the following criteria at screening:

Participant Characteristics

1. Are male and female participants with obesity determined by medical history
    a. between the ages of 6 and 11 years, inclusive
    b. have BMI ≥ the 95th percentile for age and sex
2. Have a screening body weight of
    - Participants to be enrolled into Cohort 1: ≥50 kg
    - Participants to be enrolled into Cohort 2: <50 kg
    - Participants to be enrolled into Cohort 3: Between 40 to 60 kg, inclusive
3. Have failed to achieve adequate weight loss through lifestyle modification in the investigator's opinion
4. Have adequate immunization according to local / national requirement as assessed by the investigator
5. Not be sexually active and remain so throughout the duration of the study
6. Have safety laboratory test results within normal reference range or with abnormalities deemed clinically insignificant by the investigator
7. Have venous access sufficient to allow for blood sampling as per the protocol
8. Female participants with obesity only: Determined as prepubertal Tanner Stage 1. See Appendix 7 (Section 10.7) for further details on Tanner Staging.

Informed Consent

9. Both child and parent or legal guardian are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures
10. Both child and parent or legal guardian are willing and able to commit to the inpatient stays and procedures per study requirement
11. Both the child and a parent or legal guardian are able to understand and fully participate in the activities of the clinical trial and sign their assent and consent, respectively

5.2. Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions - General

12. A self-reported (or by parent(s)/legally acceptable representative where applicable) change in body weight above 5 kg (11 lbs) within 90 days before screening irrespective of medical records
13. Have a history or current CV (for example, acute myocardial infarction, congestive heart failure, unstable angina, uncontrolled hypertension [systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥ 100 mmHg], cerebrovascular accident [including transient ischemic attack], venous thromboembolism, and so on), respiratory, hepatic, renal, GI, endocrine, hematological (including history of thrombocytopenia), or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the IP; or may interfere with the interpretation of data
14. Have obesity induced by other endocrinologic disorders (for example, Cushing syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome)
15. Have acute or chronic pancreatitis or a history of acute idiopathic pancreatitis; or have other GI disorders (for example, relevant esophageal reflux or gall bladder disease) that could be aggravated by GLP-1 analogs; participants who had cholecystolithiasis (gall stones) or cholecystectomy (removal of gall bladder) in the past, with no long-term complications, are eligible for participation

16. Have a known clinically significant gastric emptying abnormality (for example, gastric outlet obstruction), have undergone weight loss surgery such as gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or have endoscopic or device-based therapy for obesity or have had device removal within the last 6 months (for example, mucosal ablation, gastric artery embolization, intragastric balloon, and duodenal-jejunal bypass sleeve)
17. Have a personal or family history of medullary thyroid carcinoma, have multiple endocrine neoplasia syndrome type 2, or calcitonin ≥20 pg/mL at screening
18. Have confirmed type 1 or type 2 diabetes mellitus or a history of ketoacidosis, or hyperosmolar state/coma
19. Have findings in the 12-lead ECG at screening that, in the opinion of the investigator, may increase the risks of potentially clinically relevant worsening associated with participation in the study
20. Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for <5 years prior to screening
21. Have evidence of human immunodeficiency virus or positive human immunodeficiency virus antibodies at screening
22. Have evidence of hepatitis B or positive hepatitis B surface antigen or evidence of HCV or hepatitis C antibody with confirmed presence of HCV RNA at screening (a positive HCV antibody at screening will need an additional HCV RNA assay - detectable HCV RNA means a participant will meet exclusion criteria)

    - Participants with a previous diagnosis of HCV who have been treated with antiviral therapy and achieved a sustained virological response may be eligible for inclusion in the study, provided they have no detectable HCV RNA on the screening HCV polymerase chain reaction test. A sustained virological response is defined as an undetectable HCV RNA level 24 weeks after the completion of a full, documented course of an approved antiviral therapy for HCV.
    - Participants who have spontaneously cleared HCV infection, defined as (a) a positive HCV antibody test and (b) a negative HCV RNA test, with no history of anti-HCV treatment, may be eligible for inclusion in the study, provided they have no detectable HCV RNA on screening for this study.

23. Have serum AST or ALT >2.0× the ULN or TBL >1.5 × ULN (except for participants with Gilbert's syndrome, which can be enrolled with TBL <2.0× ULN), or alkaline phosphatase (ALP) >1.5× ULN
    - Participants with nonalcoholic fatty liver disease are allowed to participate.
24. Have any lifetime history of a suicide attempt
25. Have had a blood transfusion or severe blood loss within the last 3 months, or have known hemoglobinopathy, hemolytic anemia, and sickle cell anemia, or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females) or any other condition known to interfere with safety laboratory measurements
26. Have a history of atopy or clinically significant multiple or severe drug allergies, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)
27. Impaired renal eGFR of <60 mL/min/1.73 m^2 calculated by Bedside Schwartz Equation recommended by the National Kidney Foundation. One retest may be performed in case of an initial borderline eGFR result of <60 mL/min/1.73 m^2. The highest eGFR value from the 2 tests will be accepted
28. Have an accompanying parent or legal guardian who is unable or unwilling to stop alcohol or nicotine consumption from admission to the CRU and until discharge from the study or completion of all study procedures at the CRU

Prior/Concomitant Therapy - General

29. Have been treated with prescription drugs that promote weight loss (for example, sibutramine, mazindol, phentermine, naltrexone or bupropion, or liraglutide) or similar other weight-loss medications, including over-the-counter medications (for example, Alli®) within 6 months prior to screening
30. Have received chronic (lasting >14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-articular, and inhaled preparations) within 1 month before screening
31. Have been treated with any glucose-lowering agent during the last 3 months prior to screening
32. Have received treatment with a drug that has not received regulatory approval for any indication within 30 days or 5 half-lives (whichever is longer) of screening
33. Have previously completed or withdrawn from this study

34. Have previous exposure or known allergies to tirzepatide or related compounds
35. Are currently enrolled in a clinical study involving a study intervention or any other type of medical research judged not to be scientifically or medically compatible with this study
36. Have parent or legal guardian who are investigative site or study management sponsor personnel directly affiliated with this study or their immediate families. Immediate family is defined as a parent, grandparent, or sibling, whether biological or legally adopted
37. Have parent or legal guardian who are Eli Lilly and Company employees, and
38. Are deemed unsuitable by the investigator for any other reason or have parent or legal guardian who are deemed unsuitable by the investigator for any other reason.

5.3. Lifestyle Considerations

Throughout the study, participants may undergo medical assessments and review of compliance with requirements before continuing in the study.

5.3.1. Intensive Behavioral Therapy (IBT) for Chronic Weight Management in Children 6-11 Years Old

All participants will be offered IBT that meets current practice guidelines and recommendations (APA 2018; Barlow 2007; USPSTF 2017). The IBT will include individual and family-based sessions for all study participants, including participants assigned to placebo (Farris et al. 2011; Mayr et al. 2020). After completing the follow-up visit, participants may have the option to receive 1-hour follow-up sessions once a month for up to 3 months. The total hours of IBT can be approximately 27 hours over the study duration and for 3 months following completion of the study.

5.3.2. Meals and Dietary Restrictions

Participants will be required to fast overnight when clinical laboratory test samples are taken. During the inpatient stay, participants may not consume any food other than that provided by the clinic, although water may be consumed freely.

5.3.3. Substance Use: Caffeine, Alcohol, and Tobacco

No alcohol and nicotine use will be permitted for participants and accompanying parent or legal guardian resident in the CRU.

Participants will be allowed to maintain their regular caffeine consumption throughout the study period (except during specific fasting time periods).

5.3.4. Activity and Vaccinations

Intense physical activity should be avoided 48 hours prior to tirzepatide dosing on Day 1 until the completion of all study procedures.

Participants should continue on their current vaccination and immunization schedule as per local or national requirement.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study.

Screening tests such as clinical laboratory tests and vital signs/ECGs may be repeated at the discretion of the investigator. Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened. Participant numbers are assigned earliest on Day 1 to ensure that only eligible participants enter the study.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

Participants will receive the SC doses of tirzepatide or placebo SC weekly. Matching placebo and tirzepatide [redacted] mg and [redacted] mg in prefilled syringes will be provided. For participants in Cohort 2 who are initiated on [redacted] mg dose, detailed instructions will be provided by the sponsor to clinical sites for preparing the required dose from the [redacted]-mg prefilled syringe and for placebo. As such, participants in Cohort 2 and their parents or legal guardian will have to be in-clinic (that is, remote visits will not be permitted) for Visits 2 to 5 for safety as well as for treatment preparation reasons.

Participants and legal guardians will receive a paper diary for the collection of study intervention details during remote visits. Paper diaries should be returned at the next site visit.

Table GPHV.6.1 shows the treatments administered.

Table GPHV.6.1. Treatments Administered

Intervention name	**Tirzepatide**	**Placebo**
Dosage formulation	Prefilled syringe or dosing syringe	Prefilled syringe or dosing syringe
Dosage Level(s)	[redacted] mg [redacted] mL [redacted] mg [redacted] mL [redacted] mg [redacted] mL	Injections with the volume matching the investigational drug at each dose level
Route of administration	Subcutaneous	Subcutaneous

Packaging and labeling

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

6.1.1. Administration Details

When performed during on-site visits, study drug administration for each participant should be carried out by a limited number of site personnel for consistency. The participant (or parent or legal guardian) will be permitted to perform self-administration on other dosing occasions after being trained by the investigator or designee according to administration instructions provided by

the sponsor. On occasions where the visit is performed remotely, the visiting nurse will be permitted to administer the scheduled dose.

All injections will be administered into the SC tissue of the abdominal wall, with injection sites alternated weekly between 4 sites, that is, right and left upper quadrants and right and left lower quadrants. Dosing will ideally occur at approximately the same time of day in all dose cohorts. The actual time of dosing will be recorded in the patient's eCRF.

Participants will receive tirzepatide or placebo SC starting on Day 1.

The investigator or designee is responsible for

- explaining the correct use of the study intervention to the site personnel
- verifying that instructions are followed properly
- maintaining the accurate records of study intervention dispensing and collection, and
- returning all unused medication to the sponsor or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.1.2. Medical Devices

The combination products provided for use in the study are the tirzepatide prefilled syringe and placebo prefilled syringe.

Product complaints (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 that appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before the use of the study intervention.

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

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

All used or unused study drugs may only be destroyed by the site at the end of the study upon complete reconciliation and receipt of written authorization by the sponsor or its designee.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a participant- and investigator-blinded study. To preserve the blinding of the study for tirzepatide and placebo, all study site personnel, except staff who prepare and dispense study intervention, will be blinded to treatment allocation.

All participants will be centrally assigned to randomized study intervention using an Interactive Web Response System. Before the study is initiated, the log-in information and directions for the Interactive Web Response System will be provided to each site.

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

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

If a participant's study treatment assignment is unblinded, the participant must be discontinued from the study, unless the investigator obtains specific approval from a sponsor CP or CRP for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

In case of an emergency, the investigator has the sole responsibility for determining if the unblinding of a participant's treatment assignment is warranted for the medical management of the event. The participant's safety must always be the first consideration in making such a determination. Where feasible and when timing of the emergent situation permits, the investigator should attempt to contact the Lilly medical monitor before unblinding a participant's treatment assignment. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify the sponsor as soon as possible.

Upon the completion of the study, all codes must be returned to the sponsor or its designee.

6.4. Study Intervention Compliance

When participants are dosed during outpatient visits at the CRU, study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in source documents and will be provided to the sponsor as requested.

Self-administration by a participant or parent or legal guardian is permitted after the investigator has assessed them as being adequately trained. When administered at home, dosing information will be recorded in study dosing records provided by the investigator and compliance with study intervention will be assessed at each visit via review of dosing records and returned used prefilled syringes. Compliance will be further assessed by direct questioning and documented in the source documents and CRF.

A record of the number of study intervention prefilled syringes dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, will also be recorded in the CRF.

6.5. Dose Modification

Dose modification other than that defined per protocol is not permitted in this study.

In certain situations, after randomization, for example, if GI tolerability AEs occur, the investigator may need to temporarily interrupt treatment. Investigators should preferably consult with and notify the sponsor CP/CRP, if treatment needs to be interrupted. Every effort should be made by the investigator to maintain participants on treatment and to restart treatment after temporary interruption, as soon as it is assessed as safe to do so. The participant should resume study treatment administration at the scheduled dose level per protocol.

If any of the following scenarios occur, dosing at the current level and further dosing will be stopped for the participant who will be discontinued:

1. The SAE is considered at least possibly related to the study intervention.
2. A severe non-serious AE occurs and is considered at least possibly related to the study intervention occurring in the participant.
3. The participant experiences intolerable GI events that require further dose interruptions, and the investigator or designee determines that it is unsafe to resume continued treatment.

If any of the following scenarios occur, an additional safety review will be initiated and new enrollment will be paused until the safety review is complete:

1. One or more participants in the cohort on active drug experience SAE considered to be related to tirzepatide.
2. One or more participants on active drug experience 2 clinically significant severe AEs considered to be related to tirzepatide.
3. Two or more participants in the cohort experience
    a. drug-related GI effects (for example, emesis and diarrhea) assessed to be severe treatment-emergent AEs causing significant distress or requiring urgent medical interventions beyond routine symptomatic treatment, and
    b. symptomatic hypoglycemic episodes with blood glucose levels of <3.0 mmol/L (54 mg/dL).

6.5.1. Data Review during the Study

Data will be analyzed while the trial is ongoing. An assessment committee will not be formed. Safety data will be reviewed by sponsor on a regular basis while participants are enrolled in the study.

Two safety data reviews are planned to occur during the Study GPHV. Such an interim safety review will not be considered as formal interim analyses. This review will be used to support dose decisions for subsequent cohorts to be enrolled. The interim data reviews will include the following:

- *Cohort 1 safety and tolerability data review*- all available safety and tolerability data up to at least Day 36 from at least [redacted] participants with obesity in Cohort 1 who received and completed at least 5 weeks of treatment, and
- *Cohort 2 safety and tolerability data review*- all available safety and tolerability data up to at least Day 36 from at least [redacted] participants with obesity in Cohort 2 who received and

completed at least 5 weeks of treatment and all available safety and tolerability data from Cohort 1 participants.

At the time of safety reviews, any available PK data may also be reviewed by sponsor.

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

Not applicable.

6.7. Treatment of Overdose

For this study, any dose of study intervention greater than [redacted] mg will be considered an overdose in Cohorts 1 and 3. Likewise for Cohort 2, doses above [redacted] mg will be considered an overdose.

In the event of an overdose, the investigator should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, if additional tests and treatment will be required
- closely monitor the participant for any AE/SAE and laboratory abnormalities until the participant is clinically stable or recovering
- obtain an unscheduled plasma sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis), and
- document the quantity of the excess dose in the CRF.

6.8. Concomitant Therapy

Prior to therapeutic intervention, an investigator must review the study participant's vaccine record to evaluate the risk of under-immunization to the pediatric study participant.

In general, concomitant medication should be avoided. If the need for concomitant medication arises (for example, to treat an AE), inclusion or continuation of the participant may be at the discretion of the investigator, preferably after consultation with a sponsor CP or CRP/CRS or designee. Any medication used during the course of the study must be documented.

All participants on stable concomitant medication at the time of study entry, other than those that are prohibited, should continue their usual dose throughout the study unless deemed clinically necessary.

To mitigate potential GI symptoms due to tirzepatide and manage participants with poorly tolerated GI AEs, the investigator

- should advise the child to eat slowly or offer smaller meals, for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full, and
- may prescribe symptomatic medication (for example, approved anti-emetic or antidiarrheal medication for children).

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

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

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

Participants must abstain from starting any new prescription or nonprescription drugs after screening unless, in the opinion of the investigator in consultation with the sponsor CP or CRP/CRS, the medication is assessed as clinically necessary or is deemed unlikely to interfere with the study outcome.

If acetaminophen treatment is needed for pain management, the maximal allowed dose will be the amount as stipulated in the package insert for the body weight and age of the participant.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The discontinuation of specific sites or of the study as a whole is handled as a part of Appendix 1 (Section 10.1).

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant, must complete early discontinuation procedures as shown in the SoA.

7.1. Discontinuation of Study Intervention

A participant may not receive study intervention if

- the participant (females only) exhibits signs and symptoms of puberty, and
- in the opinion of the investigator, the participant should not receive study intervention for safety reasons.

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.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an IP, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, and
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be clinically effective for the treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

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

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

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits or if permitted remote visits cannot be scheduled or is unable to be contacted by the study site staff. Site personnel or designee are expected to make diligent attempts to contact participants and their parents or legal guardian who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

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

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

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

8.1. Efficacy Assessments

Although this study is primarily a safety and tolerability study, weight loss is a potential benefit for children with obesity. Body weight will be assessed as a part of safety and also potential efficacy measure according to the SoA.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, the assessments of CV, respiratory, GI and neurological systems. Height and weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, CV system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to signs and symptoms of puberty.

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 (Section 10.9 [Appendix 9]). BMI will be computed from the participant's weight and height.

8.2.3. Assessment of Pubertal Status - Tanner Staging

Female participants' pubertal status will be assessed using Tanner Staging performed at screening and other scheduled time points per protocol (see also Section 10.7 [Appendix 7] for Tanner Stages). This study will only include female participants that are at Tanner Stage 1.

8.2.4. Vital Signs

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

Blood pressure and pulse rate should be measured after at least 3 minutes supine.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes. If the participant feels unable to stand, supine vital signs only will be recorded.

8.2.5. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3). ECGs may be obtained at additional times, when deemed clinically necessary.

8.2.6. Clinical Safety Laboratory Tests

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

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

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

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

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

8.2.7. Safety Monitoring

Hepatic Safety

Close hepatic monitoring[a]

Laboratory tests (Appendix 2), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm

the abnormality and to determine if it is increasing or decreasing, if one or more of following conditions occur:

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

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

[a] All ULN values should be age-adjusted (AAULN).

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 sponsor-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, the 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. The 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]

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

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

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

[a] All ULN values should be age-adjusted (AAULN).

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR 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 Sponsor-designated medical monitor, including tests for viral hepatitis A, B, C, E, as well as autoimmune hepatitis; or an abdominal imaging study (for example, ultrasound, MRI, or CT scan). Consider additional tests, based on the medical history and clinical picture, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. 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, endoscopic retrograde cholangiopancreatography, 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 CRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

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

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

Pancreatic Safety

Diagnosis of acute pancreatitis

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

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

If acute pancreatitis is suspected, the investigator should

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

Discontinuation for acute pancreatitis

If acute pancreatitis is diagnosed, the participant must discontinue the use of IPs.

Asymptomatic elevation of serum amylase and lipase

The 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 the asymptomatic elevation of pancreatic enzymes (lipase 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.

8.2.8. Pregnancy Testing

All female participants will undergo urine pregnancy tests at screening.

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

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

- AEs
- SAEs, and
- PCs.

These events will be reported by the participant or parent(s), 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 (see Section 7).

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events 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 or causality. Further information on follow-up procedures is provided in Section 10.3 (Appendix 3).

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting the sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

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
AE					
AE	Signing of the ICF and assent as applicable	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
SAE					
SAE and SAE updates - prior to the start of study intervention and deemed reasonably possibly related to study procedures	Signing of the ICF and assent as applicable	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates - after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE[a] - after participant's study participation has ended and the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants	After the start of study intervention	2 months after the last injection of TZP	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
PCs					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	-	-	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	N/A

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

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

8.3.2. Pregnancy

Because of the pediatric population (Tanner Stage 1) in the rare event of pregnancy, pregnancy information will be collected as follows:

Collection of pregnancy information

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any 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. 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.

Prior to the continuation of study intervention following pregnancy, the following must occur:

- The sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and the participant's offspring.

8.3.3. Adverse Events of Special Interest

8.3.3.1. 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 8 (Section 10.8). Laboratory results are provided to the sponsor via the central laboratory.

8.3.3.2. 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 the measurement of tirzepatide antidrug antibodies and tirzepatide concentration.

8.3.3.3. Hypoglycemia Reporting

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia.

Investigators should use the following classification of hypoglycemia:

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 should continue to counsel participants to treat hypoglycemia at this glucose alert value.

Level 2 hypoglycemia:

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

Level 3 hypoglycemia:

Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example,

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

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

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

Nocturnal hypoglycemia:

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

8.3.3.4. Nausea and Vomiting

Nausea and vomiting events are considered AEs of interest and will be recorded as AEs in the CRF. For each event assessment of severity, duration and investigator's opinion of relatedness to the study drug and protocol procedure will be captured.

8.3.3.5. Elevated Lipase or Amylase

Serum amylase and lipase measurements will be collected as a part of the clinical laboratory testing at time points specified in the SoA (Section 1.3). Additional measurements may be performed at the investigator's discretion. Further diagnostic assessments will be recommended whenever lipase or amylase is confirmed to be ≥3X ULN at any visit post randomization, even if the participant is asymptomatic (as per the algorithm refer for the monitoring of pancreatic events in Appendix 6, Section 10.6).

8.4. Pharmacokinetics

The characterization of the PK properties of tirzepatide in pediatric participants will be supported by collection of both predose and postdose PK blood samples per participant according to the SoA (Section 1.3).

At Visit 2 (Days 1 to 3), the sample is collected at 12 hours and 24 hours after the first dose during inpatient visit. At Visit 6 (Days 23 to 25), each participant will have PK sample collected at window of 24 to 96 hours post Day 22 dose. At Visit 9 (Days 41 and 42), each participant will have PK sample collected at window of 120 to 168 hours post Day 36 dose. For Visits 4, 8, and 11 (Days 15, 36, and 50), PK samples are collected prior to the intervention administration. Participants may be required to come to the site for PK-specific visits depending on sample window.

The actual date and time of the most recent SC injection administered prior to collecting the sample must be recorded. 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.

8.4.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry method. The analyses of samples collected from placebo-treated participants are not planned.

Bioanalytical samples collected to measure study intervention 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, protein binding, or bioanalytical method cross-validation.

8.5. Pharmacodynamics

The PD exploratory analyses include treatment comparison based on the following variables:

- body weight
- BMI, and
- waist circumference.

8.5.1. Body Weight and Waist Circumference

Weight and waist circumference will be measured as indicated in the SoA (Section 1.3). Wherever possible, the same scale will be used for all weight measurements throughout the study and the scale will not be moved or recalibrated.

Refer to Section 10.9 for guidance on the standardized protocols for weight and waist circumference measurements.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine antibody production against tirzepatide. Samples with detected tirzepatide ADA will be titered and evaluated for their ability to neutralize tirzepatide activity on the GIP and GLP-1 receptors. Antibodies may be further characterized for cross-reactive binding to native GIP and GLP-1 and, if such is detected, then for cross-reactive neutralizing antibodies against native GIP and GLP-1. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points after predose visit (Day 1) to determine the serum concentrations of tirzepatide. Detailed instructions for the sample collections and handling will be provided by the sponsor. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of tirzepatide at a laboratory approved by the sponsor.

Treatment-emergent ADAs (TE ADA) are defined in Section 9.3.4.

If the immunogenicity sample at the last scheduled assessment or discontinuation visit indicates TE ADA, the sponsor may request for additional samples to be taken until the signal returns to baseline (that is, no longer indicates TE ADA) or for up to 1 year after last dose, as a part of safety measures. The requirement for possible additional, unscheduled ADA safety follow-up must be included in the ICF.

Refer to Appendix 1 (Section 10.1.9) for details on sample retention.

8.9. Health Economics

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

9. Statistical Considerations

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

9.1. Statistical Hypotheses

Not applicable.

9.1.1. Multiplicity Adjustment

Not applicable. No formal statistical analysis will be performed.

9.2. Analyses Sets

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

Participant Analysis Set	Description
Full analysis set	All *enrolled participants. Participants will be included in the analyses according to the planned intervention.*
Safety analysis set	All participants who are exposed to study intervention. Participants will be *analyzed according to the intervention they actually received.*

The full analysis set will be used to summarize disposition and demographic characteristics.

The safety analysis set will be used for safety evaluation.

9.3. Statistical Analyses

9.3.1. General Considerations

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

PK analyses will be conducted on data from all participants who receive at least 1 dose of the study intervention and have evaluable PK.

Safety analyses will be conducted for all enrolled participants who were administered study intervention, whether or not they completed all protocol requirements.

A detailed description of participant disposition will be provided at the end of the study. All participants who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

The demographic characteristics of enrolled participants (including but not limited to age, sex, and race) will be summarized. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.3.2. Pharmacokinetics

9.3.2.1. Pharmacokinetic Analyses

All tirzepatide concentration data will be listed and summarized using descriptive analysis. Tirzepatide concentration may also be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM® software to determine the C_{max} and $AUC_{0\text{-}tau}$ of tirzepatide by each dose and cohort.

9.3.2.2. Pharmacokinetic Statistical Inference

No formal statistical analysis will be performed.

9.3.3. Safety Analyses

9.3.3.1. Clinical Evaluation of Safety

All study intervention and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of AEs will be presented by severity and by association with study intervention as perceived by the investigator. AEs reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

The number of study intervention-related SAEs will be reported.

9.3.3.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs (including blood pressure and pulse rate), body weight and BMI, and ECG parameters. Continuous safety variables will be summarized using descriptive statistics. Categorical safety variables will be summarized using count and percentage.

Additional analysis will be performed if warranted upon review of the data.

9.3.4. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADAs, ADAs at any time postbaseline, and TE ADA+ to tirzepatide may be tabulated. TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution (1:10) of the ADA assay 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 the TE ADA+ participants, the distribution of maximum titers may be described. The frequency of neutralizing antibodies, if assessed, and cross-reactivity to native GIP and GLP-1 may also be tabulated in TE ADA+ participants.

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

9.4. Interim Analysis

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

For further information on the review of safety and tolerability data during the study, refer to Section 6.5.1.

9.5. Sample Size Determination

Approximately CCI participants may be enrolled. This will allow PK characterization in at least CCI participants each, exposed to tirzepatide, for the weight categories <50 kg and ≥50 kg, respectively. Evaluable participants are participants who receive at least 1 dose of the study intervention and have at least 1 evaluable PK sample. The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK, and is not powered on the basis of any a priori statistical hypothesis testing for efficacy.

Participants who do not complete all the study procedures may be replaced to achieve the planned number of completers.

Note: Enrolled means a participant's parent or their legally acceptable representative's, agreement to participate in a clinical study following the completion of the informed consent process and assent where applicable and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled. A participant will be considered as enrolled if the informed consent is not withdrawn prior to participating in any study activity after the screening 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 International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP Guidelines, and
- applicable laws and regulations.

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

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

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

The investigator will be responsible for the following:

- providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, and
- providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (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. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or the participant's legally authorized representative, defined as either a parent or a legal guardian and answer all questions regarding the study.

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

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

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

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

10.1.3. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant, parent or legal guardian 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, parent or legal guardian identifiable, will not be transferred.

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

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

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

Rationale for collection of full date of birth

This study includes children. 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, and year) for all 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.

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by The sponsor to all investigators (for example, by phone or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by The sponsor personnel prior to any further planned dosing. If a dose is planned imminently, The sponsor personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

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 does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case by case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.5. Data Quality Assurance

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

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

Source data may include laboratory tests, medical records, and clinical notes.

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

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

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

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

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

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

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

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

Data Capture System

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

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

Data collected via the sponsor-provided data capture system 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 will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.6. Source Documents

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

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

Definition of what constitutes source data can be found in Section 10.1.5.

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

for study termination:

- discontinuation of further study intervention development

for site termination:

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

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

10.1.8. 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 if the results are deemed to be of significant medical importance.

10.1.9. Sample Retention

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

Sample Type	Custodian	Retention Period After Last Patient Visit[a]
Pharmacokinetics	Sponsor or designee	1 year
Immunogenicity	Sponsor or designee	15 years

[a] 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.

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

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

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

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

Investigators must document their review of the laboratory safety results.

Safety Laboratory Tests

Hematology[a]	Clinical chemistry (fasting)[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Glucose
Leukocytes (WBC)	Blood urea nitrogen
	Total protein
Absolute counts of[a]:	Albumin
Neutrophils	Total bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Aspartate aminotransferase
Eosinophils	Alanine aminotransferase
Basophils	Creatinine
Platelets	Amylase
	Lipase
Pubertal hormone[a]: Testosterone (male participants only) Estradiol (female participant only)	Uric acid Phosphorous Calcitonin[c] Insulin
Urinalysis[a] Specific gravity	Lipid panel (fasting)[a,b]
pH	Triglycerides
Protein	Total cholesterol
Glucose	LDL
Ketones	HDL
Bilirubin	Hepatitis C antibody, hepatitis C RNA[c,d]
Urobilinogen	HIV[c,d]
Blood	Hepatitis B surface antigen[c,d]
Nitrite	Urine pregnancy test[e]
Microscopic examination of sediment[f]	

Abbreviations: LDL = low-density lipoprotein; HIV = human immunodeficiency virus; HDL = high-density lipoprotein; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cells.

[a] Performed by central laboratory except at screening, which will be by local laboratory. Results will be validated by the laboratory at the time of initial testing.

[b] Performed at screening (by local laboratory), Visit 2 (central laboratory), and Visit 12 or at early discontinuation visit (central laboratory).

[c] Performed by local laboratory at screening only.

[d] Tests may be waived if they have been performed within 6 months before screening with reports available for review.

[e] Only applicable to female participants whom the investigator suspects to be sexually active.

[f] Test only if dipstick result is abnormal (that is, positive for blood, protein, or nitrites).

10.2.1. Blood Sampling Summary

The table below summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. The number of samples in parenthesis assumes 3 additional unscheduled samples, which may be taken for safety purposes.

To ease discomfort associated with venipunctures, the following options are allowed in the study per local practice and prescribing information:

- local anesthetic creams, for example, EMLA® or ELA-max®
- needleless devices for injecting local anesthetics, for example, a J-tip, and
- local vibration devices, for example, a buzzy.

Protocol I8F-MC-GPHV Overall Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a,b]	20	1	20
Safety laboratory tests[a,c]	12	3	36
Tirzepatide pharmacokinetics[c]	2	9	18
Immunogenicity[c]	10	4	40
Blood glucose[a,b]	2	2	4
Total			118
Total for clinical purposes			120

[a] Additional samples may be drawn if needed for safety purposes. Safety laboratory tests will be inclusive of lipid panels on days when they are performed.

[b] Performed on site or in a local laboratory.

[c] Performed at a central or referral laboratory approved by the sponsor.

10.2.1.1. Rationale for Blood Draws and Required Blood Volume

Careful consideration was given to collect the necessary information to address the key scientific objectives of this pediatric study while also minimizing invasive procedures and overall patient burden.

As PK profiling is a secondary objective of this study, the number of bioanalytical samples proposed is the minimum required to be able to derive a concentration-time profile for tirzepatide in children, based on an anticipated half-life of about 5 to 6 days. The blood volume for each PK sampling has been capped at 2 mL, which is the smallest volume of K3EDTA collection tube available.

Safety laboratory tests and BG had been limited to only the minimal number of samples to ensure safety of participants. The volume of blood required for safety clinical laboratory tests have been defined based on the analyte requirement in Appendix 2, which includes the monitoring of prepubertal hormones as part of pediatric monitoring.

The 10-mL blood volume for the immunogenicity sample is required to generate 5 to 7 mL serum divided into 6 aliquots due to the need to test for ADA and neutralizing antibodies using 4

aliquots (approximately 1 mL serum per aliquot) of serum in the event that the ADA sample is positive. A sample is required every 4 to 5 weeks, and another sample will also be drawn 2 weeks after initial treatment commencement to monitor IgM ADA as is often explicitly requested by FDA from experience.

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

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.2 for the list of sponsor medical devices.

10.3.1. Definition of an Adverse Event

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, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency or intensity of the condition. New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. 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 overdoses should be reported regardless of sequelae.

Events not meeting the AE definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

Medical or surgical procedure (for example, endoscopy and appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social or convenience admission to a hospital).

Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of Serious Adverse Event

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation 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 the elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability or incapacity

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

e. Is a congenital anomaly or birth defect

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

f. Other situations

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

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 trials are collected in order to ensure the safety of participants, monitor quality, and facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.

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

10.3.4. Recording and Follow-up of Adverse Event or Serious Adverse Event and Product Complaints

AE, SAE, and product complaint recording

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

The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page, and PC information is reported on the PC form.

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

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the CRF page for AE/SAE and the PC 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, 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 arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

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

The investigator will also consult the IB in their assessment.

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

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

The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is 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 or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature 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 healthcare professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of Serious Adverse Events

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

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Women of Childbearing Potential

Females less than 18 years of age are considered women of childbearing potential if they have

- had at least 1 cycle of menses, or
- Tanner Stage 4 breast development (see Tanner Staging, Section 10.7 [Appendix 7]).

Any amount of spotting should be considered menarche.

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

Not applicable.

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

Hepatic Evaluation Testing

See protocol Section 8.2.6 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.

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

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

Abbreviations: CMV= cytomegalovirus; EBV = Epstein-Barr virus; HAV = hepatitis A virus; HBV = hepatis B virus; HCV = hepatis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus; HSV = herpes simplex virus; IgA; IgG; IgM; INR; PT-INR; RBC = red blood cells; WBC = white blood cells.

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

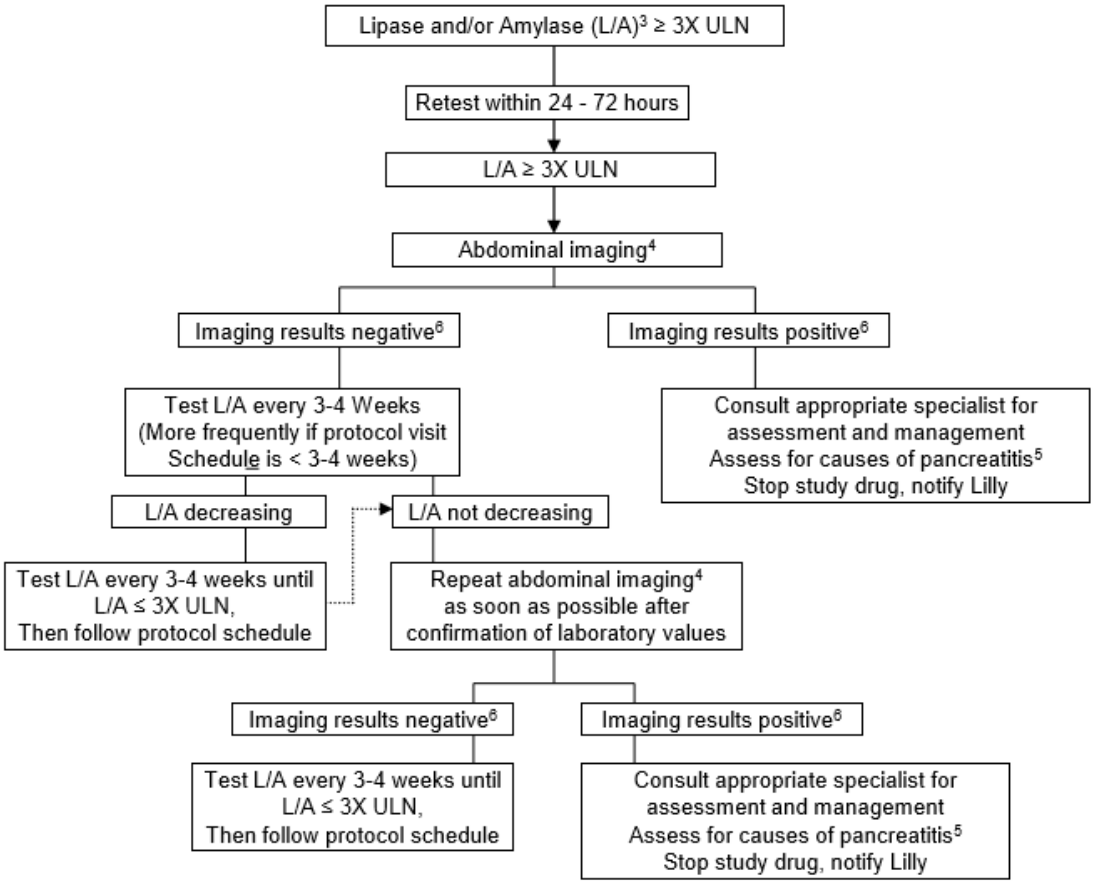
[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

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

10.6. Appendix 6: Pancreatic Monitoring

Pancreatic Enzymes: Safety Monitoring Algorithm for Subjects/Patients without Symptoms of Pancreatitis[1,2]

Follow this algorithm when the value(s) for serum lipase and/or amylase are ≥ 3X ULN.



1. Symptomatic – related primarily to abdominal pain consistent with pancreatitis; however, severe nausea, vomiting and other symptoms may be considered by the investigator as symptomatic as well.

2. If, at any time, in the opinion of the investigator, patient/subject has symptoms of acute pancreatitis irrespective of L/A results:
   (a) Consult appropriate specialist for assessment and management
   (b) Assess for causes of pancreatitis
   (c) Stop study drug
   (d) Notify Lilly

3. L/A = Lipase and/or amylase. Either or both enzymes can be measured and either or both can be used to meet the algorithm criteria.

4. Abdominal imaging is most valuable when performed at the time of elevated enzyme values. If in the opinion of the radiologist or investigator, it is safe for the patient/subject to receive contrast, an enhanced abdominal CT is preferred. MRI is also an acceptable imaging modality.

5. As minimum, test hepatic analytes, triglycerides, and calcium, and record all concomitant medications

6. Imaging results positive or negative for signs of acute pancreatitis

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; ULN = upper limit of normal.

Participants diagnosed with pancreatitis will be discontinued from the study. Investigators will be responsible for following, through an appropriate healthcare option, these pancreatitis AEs until the events resolve or are explained. AEs that meet the diagnostic criteria of acute pancreatitis will be captured as SAEs. For all other pancreatic AEs (such as idiopathic or asymptomatic pancreatic enzyme abnormalities), the investigator will be responsible for determining the seriousness of the event (AE or SAE) and the relatedness of the event to study drug.

10.7. Appendix 7: 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 the 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”)

Note: The assessment of sexual maturity in children should include an assessment of age, growth, and menstrual history in addition to Tanner Staging. In case of discordance between breasts or genitals vs pubic hair, the default should be breast or genitals.

10.8. Appendix 8: 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	Preferred Sample Type [a]	Laboratory Test [b]
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 Sample type may be different depending on local requirements.

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

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

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

Measuring Height

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

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

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

Step 4. Ask the participant to breathe in and stand tall. 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 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 to 1 decimal place.
- All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.
- Participants should be lightly clothed but not wearing shoes while their weight is measured.
- Body weight must be measured in fasting state. If the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting body weight measured.

Step 1. Ask the participant to remove their footwear, outerwear (coat, jacket, and so on), 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 to the nearest one-tenth kg.

Measuring Waist Circumference

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.

- Waist circumference should be measured in the horizontal plane and at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.
- Measurements should be taken at the end of a normal expiration using a nonstretchable measuring tape. The tape should lie flat against the skin without compressing the soft tissue.
- The waist circumference should be measured twice, rounded to the nearest 0.5 cm. The measuring tape should be removed between the 2 measurements. Both measurements will be recorded in the eCRF. If the difference between the 2 measurements exceeds 1 cm, this set of measurements should be discarded and the 2 measurements repeated.

Vital Sign Measurements (blood pressure and heart rate)

- Vital sign measurements 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.
- The participant should be supine for at least 3 minutes before vital sign measurements are taken.

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

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

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon the 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 and assent where applicable from the participant will be obtained, if required, for

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

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, concomitant medications, AE data capture, and self-performed body weight and height measures.

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site allowed per protocol (refer to the SoA in Section 1.3 for visits that are permitted to be conducted remotely). Other than visits permitted per protocol, written approval must be provided by the sponsor for remote visits when participants cannot travel to the site due to an exceptional circumstance. Procedures performed at such visits include, but are not limited to, AE documentation, concomitant medications, collection of blood samples, collection of ECG and vital sign parameters, physical assessments, administration of study intervention, and collection of health information.

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing for unscheduled events or as stipulated in Section 10.2. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

When a participant's parent or legal guardian 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 the 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 the delivery of study supplies.

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

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

- Only authorized study personnel may supply, prepare, or administer study intervention.
- The mobile healthcare team must be able to handle and store study interventions in accordance to the requirements specified on the label.

Screening period guidance

To ensure the safety of study participants, laboratory values and other eligibility assessments taken at screening visit are 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 28 days from Visit 2, the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 28 days from first screening.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 28 days from Visit 2, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure.

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.11. Appendix 11: Abbreviations and Definitions

Term	Definition
ADA	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{0\text{-}tau}$	area under the concentration versus time curve from time 0 to the end of the dosing interval
blinding	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.
BG	blood glucose
BMI	body mass index
C_{max}	maximum concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CP	clinical pharmacologist
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRS	clinical research scientist
CRU	clinical research unit
CV	cardiovascular
CVD	cardiovascular disease
CT	computed tomography
ECG	electrocardiogram
eCRF	electronic case report form

Term	Definition
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide 1
GLP-1R	glucagon-like peptide 1 receptor
HCV	hepatitis C virus
IB	Investigator's Brochure
IBT	Intensive behavioral therapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IgM	Immunoglobulin M
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
ISR	injection site reaction
MRI	magnetic resonance imaging

Term	Definition
participant	equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SoA	schedule of activities
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.
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TE ADA	treatment-emergent ADA
TE ADA+	treatment-emergent ADA positive
ULN	upper limit of normal

10.12. Appendix 12: Protocol Amendment History

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

Amendment [d]:

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

This protocol was amended to delete inconsistencies in protocol text regarding vital sign measurements and other minor changes for clarity.

Section # and Name	Description of Change	Brief Rationale
10.9. Appendix 9: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs	Step 2 and Step 3 vital sign measurement instructions have been removed.	Step 2 and Step 3 vital sign measurement instructions require 3 measurements to be recorded in the eCRF. Triplicate recordings are not required as standard for this study and have been removed.

Amendment [c]: 05 June 2023

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

This protocol was amended to update the equation used for the exclusion criterion on renal impairment and other minor changes for clarity.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Clarified that the dose increase will occur at the fifth dose of TZP on Day 29 Week 5 and referenced Figure GPHV.1.1.	To provide information in the Schedule of Activities about when the TZP dose administered will increase to the next dose level.
Section 2.3 Benefit/Risk Assessment	Clarified that female participants will be monitored for changes in Tanner stage.	To provide consistency throughout the protocol.
Section 5.2 Exclusion Criteria	Updated the calculation used in Exclusion criterion #27 from Chronic Kidney Disease Epidemiology to Bedside Schwartz Equation recommended by National Kidney Foundation	Bedside Schwartz Equation is more appropriate on this age group
Section 6.5 Dose Modification	Replaced stopping dosing and dose escalation with the initiation of a safety review and putting a pause on new enrollment until the safety review is complete.	Initiating a safety review instead of stopping dosing at current and further levels provides a mechanism to make specific decisions based on the criteria.

Section # and Name	Description of Change	Brief Rationale
Section 10.5 Appendix 5: Liver Safety: Suggested Actions and Follow up Assessments	Moved the acetaminophen protein adduct test from local laboratory table to the central laboratory table.	Acetaminophen protein adduct test will be provided by the central labs
Section 10.9 Appendix 9: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs	Clarified that for each measurement of pulse and blood pressure, the participant will be supine and not sitting.	To provide consistency throughout the protocol

Amendment [b]: 19 January 2023

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

This protocol was amended to update the timing of the final follow-up visit and the early discontinuation visit and other minor changes for clarity.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Changed the occurrence of the final follow-up visit from 2 to 4 weeks after last treatment or within 4 weeks after early discontinuation to 4 to 6 weeks after last treatment or at least 4 weeks but up to 6 weeks after early discontinuation	In response to feedback during European Union (EU) Paediatric Investigational Plan (PIP) review stating that the safety follow-up must be planned for at least 4 weeks.
1.1 Synopsis	Added language on replacing participants who do not complete the study	To maintain consistency with later sections of the protocol
1.3 Schedule of Activities	Updated final follow-up visit to occur between Week 12 Day 78 and Week 14 Day 92	In response to feedback during EU PIP review stating that the safety follow-up must be planned for at least 4 weeks.
1.3 Schedule of Activities	Updated Early Discontinuation visit to occur at least 4 weeks but up to 6 weeks from the last dose	
1.3 Schedule of Activities	Updated height measurement to be taken at screening, Visit 1, and Visit 12 only.	To clarify the timing of the height measurements
4.1 Overall Design	Changed the final follow-up visit to occur with 4 to 6 weeks following the last treatment or at least 4 weeks but up to 6 weeks for participants that discontinue early, and IBT from starting at screening to starting at baseline.	To clarify the timing of the follow-up visit and the starting point of offering participants IBT
5.2 Exclusion Criteria	Updated [18] to include type 1 and type 2 diabetes mellitus	To clarify that participants with either type 1 or type 2 diabetes will be excluded from this study.
5.3.1. Intensive Behavioral Therapy (IBT) for Chronic Weight Management in Children 6-11 Years Old	Changed the total hours of IBT from approximately 26 hours to approximately 27 hours	To clarify the total amount of hours IBT will be offered to participants

Section # and Name	Description of Change	Brief Rationale
6.1 Study Intervention(s) Administered	Added language on the paper diaries used during remote visits and removed the dosing instructions row from Table GPHV.6.1	To provide details on paper diaries and to remove redundancy between the table and the text within this section.
9.5 Sample Size Determination	Specified that participants who do not complete the study may be replaced	To clarify that participants may be replaced if they do not complete the study
10.9 Appendix 9: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs	Clarified that participants should be supine for at least 3 minutes before measuring blood pressure and heart rate	To maintain consistency in the measurement of vital signs throughout the protocol

Amendment [a]: (27-October-2022)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment

This protocol was amended to change the definition of obesity in children of age 6 to 9 years.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis and 9.5 Sample Size Determination	Added language to clarify the sample size of 6 evaluable participants for weight category >50 kg and 12 evaluable participants for weight category <50 kg	In response to feedback from the FDA to breakdown the overall sample size by each cohort for clarity.
1.3 Schedule of Activities	Added a row for the intensive behavioral therapy during the study	To capture timing and frequency of the intensive behavioral therapy
4.1 Overall Design	Added intensive behavioral therapy content	To capture intensive behavioral therapy in the overall study design
5. Study Population	Changed Inclusion Criterion [1] to define consistently the BMI that characterizes children with obesity for both younger (6 to 9 years, inclusive) and older age groups (10 to 11 years, inclusive).	In response to feedback from the European Medical Agency and for consistent alignment with intended definition for Phase 3 studies.
5.3.1 Intensive Behavioral Therapy (IBT) for Chronic Weight	Added intensive behavioral therapy	To enhance study intervention and further increase the prospect of direct benefit to participants

Management in Children 6-11 Years Old		given diet and exercise are critical elements in treating obesity

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