Protocol: I8F-MC-GPIU

A Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of Tirzepatide Monotherapy Compared with Placebo in Chinese Participants with Type 2 Diabetes (SURPASS-CN-MONO)

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Approval Date: 05-Dec-2023

Title Page

Protocol Title:

A Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of Tirzepatide Monotherapy Compared with Placebo in Chinese Participants with Type 2 Diabetes (SURPASS-CN-MONO).

Protocol Number: I8F-MC-GPIU

Amendment Number: b

Compound: Tirzepatide (LY3298176)

Brief Title:

A Study to Investigate the Efficacy and Safety of Tirzepatide Monotherapy in Chinese Participants with Type 2 Diabetes.

Study Phase: 3

Acronym: SURPASS-CN-MONO

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Lilly Corporate Center, Indianapolis, Indiana 46285, USA

Regulatory Agency Identifier Number(s): Not applicable

Approval Date: Protocol Amendment (b) 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**
Original Protocol	*21-Feb-2023*
Protocol Amendment (a)	*30-Mar-2023*

Amendment [a]

Overall Rationale for the Amendment:

The overall rationale for the current protocol amendment is to update Schedule of Activities with hepatitis B and hepatitis C screening at Visit 1 and hepatitis serology tests in Appendix 2, in order to be consistent with exclusion criteria #15.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	• Added hepatitis C screening at Visit 1 and its footnote r. • Added hepatitis B screening at Visit 1 and its footnote s.	Updated SoA with hepatitis B and hepatitis C screening at Visit 1 to be consistent with exclusion criteria #15.
10.2. Appendix 2: Clinical Laboratory Tests	Added hepatitis serology tests for hepatitis C virus testing and hepatitis B virus testing.	For consistency with the update of SoA.

Amendment [b]

Overall Rationale for the Amendment:

The overall rationale for the current protocol amendment is to update Schedule of Activities, analyses sets, lab for HGRAC filing process, and the terminology of heart rate to be consistent with the operation in practice and with other series of studies.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	• "Review hypoglycemic events collected in the diaries" was checked for V99. • "Dispense BG meter/supplies as needed" was checked for V99.	• Hypoglycemic events collected in the diaries will be reviewed at V99. • BG meter/supplies will be dispensed as needed at V99.
1.3. Schedule of Activities (SoA)	Annotation d was clarified: The visit date of Visit 2 and 3 are determined based on Visit 1. The visit after Visit 3 (except visit 801) ~~The visit date~~ is determined in relation to the date of the randomization visit (± the allowed visit window).	Annotation d was clarified to make it more accurate.
1.1. Synopsis 1.3. Schedule of Activities (SoA)	"Heart rate" or "HR" was changed to "pulse rate" or "PR".	Pulse rate (PR) instead of heart rate (HR) will be tested.

Section # and Name	Description of Change	Brief Rationale
2.3.1 Risk Assessment 3. Objectives, Endpoints, and Estimands		
3. Objectives, Endpoints, and Estimands 9.1.1 Multiplicity Adjustment 9.3.1 General Consideration 9.3.3 Primary Endpoint(s) Analysis 9.3.4 Secondary Endpoints Analysis	The order of the primary and secondary estimand was switched throughout the document. The wording has also been adjusted accordingly.	Per the suggestion from health authority, treatment-regimen estimand could reflect the clinical practice, and was switched to the primary estimand.
4.1 Overall Design	"Participants will be stratified based on baseline HbA1c…" was changed to "Participants will be stratified based on HbA1c" where "baseline" was removed.	Baseline is defined for analysis purpose. The "baseline" was removed to reflect trial practice.
4.1 Overall Design	"Participants will be asked to monitor fasting blood glucose (FBG) 4 times a week and two 7-point SMBG profiles done…" was changed to "Participants will be asked to monitor fasting blood glucose (FBG) 4 times a week. Participants will also be asked to monitor two 7-point SMBG profiles done…"	One sentence was separated into two sentences to define timepoints more accurately.
9.2 Analyses Sets 9.3.2.2 Participant Characteristics 9.3.2.3 Concomitant Therapy 9.2.3.4 Treatment Compliance	• Per-protocol population was removed. • "Excluding participants discontinuing study intervention due to inadvertent enrollment." was removed from mITT population description. • Safety population was removed, and the statistical analysis on safety population were changed to be based on mITT population.	• Per-protocol population is not required after estimand framework implementation according to ICH E9 (R1). • Revision of mITT description is to comply with intent-to-treat principle. • Safety population was removed due to duplication with mITT population.
9.3.3 Primary Endpoint(s) Analysis	"…and treatment by visit interaction, any past prior use (yes or no) of any antihyperglycemic medication as fixed effects, and baseline HbA1c as a covariate." was changed to "…and treatment by visit interaction, any past prior use (yes or no) of any antihyperglycemic	Baseline-by-visit interaction term was added to make adjustment for the corresponding covariate effect.

Section # and Name	Description of Change	Brief Rationale
	medication baseline HbA1c and baseline HbA1c-by-visit interaction."	
10.2. Appendix 2: Clinical Laboratory Tests	Laboratory name for hematology and HbA1c was changed from "Lilly-designated laboratory" to "Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd."	Update of assay agency is required for HGRAC filing process.
10.2. Appendix 2: Clinical Laboratory Tests	"Hematology (including blood smear) and HbA1c samples were destroyed by Shanghai Solid Waste Disposal Co., Ltd." was added as a footnote.	Addition of disposal agency is required for HGRAC filing process.
10.2. Appendix 2: Clinical Laboratory Tests	"TSH = thyroid-stimulating hormone;" was removed from "Abbreviations".	Removal of TSH from abbreviation is a correction.
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments	"Hepatic hematology samples were assayed by Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd. and were destroyed by Shanghai Solid Waste Disposal Co., Ltd." was added as a footnote.	Addition of disposal agency is for HGRAC filing process.

Table of Contents

1. Protocol Summary 9
1.1. Synopsis 9
1.2. Schema 13
1.3. Schedule of Activities (SoA) 14

2. Introduction 18
2.1. Study Rationale 18
2.2. Background 18
2.3. Benefit/Risk Assessment 19
2.3.1. Risk Assessment 19
2.3.2. Benefit Assessment 20
2.3.3. Overall Benefit Risk Conclusion 20

3. Objectives, Endpoints, and Estimands 21

4. Study Design 24
4.1. Overall Design 24
4.2. Scientific Rationale for Study Design 26
4.3. Justification for Dose 26
4.4. End of Study Definition 27

5. Study Population 28
5.1. Inclusion Criteria 28
5.2. Exclusion Criteria 29
5.3. Lifestyle Considerations 31
5.4. Screen Failures 32
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant 32

6. Study Intervention(s) and Concomitant Therapy 33
6.1. Study Intervention(s) Administered 33
6.1.1. Study intervention 33
6.1.2. Medical Devices 34
6.2. Preparation, Handling, Storage, and Accountability 34
6.3. Assignment to Study Intervention 35
6.4. Blinding 35
6.5. Study Intervention Compliance 35
6.6. Dose Modification 36
6.6.1. Tirzepatide 36
6.7. Continued Access to Study Intervention after the End of the Study 37
6.8. Treatment of Overdose 37
6.9. Concomitant Therapy 37
6.9.1. Initiation of New Antihyperglycemic Medication 38

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 39

7.1. Discontinuation of Study Intervention....39
7.1.1. Liver Chemistry Stopping Criteria....39
7.1.2. Temporary Discontinuation....40
7.2. Participant Discontinuation/Withdrawal from the Study....41
7.2.1. Discontinuation of Inadvertently Enrolled Participants....41
7.3. Lost to Follow up....41

8. Study Assessments and Procedures....43
8.1. Efficacy Assessments....43
8.1.1. Self-Monitoring of Blood Glucose (SMBG)....43
8.1.2. Patient-Reported Outcomes....44
8.2. Safety Assessments....44
8.2.1. Physical Examinations....44
8.2.2. Vital Signs....45
8.2.3. Electrocardiograms....45
8.2.4. Dilated Fundoscopic Examination....45
8.2.5. Clinical Safety Laboratory Tests....45
8.2.6. Pregnancy Testing....46
8.2.7. Safety Monitoring....46
8.3. Adverse Events, Serious Adverse Events, and Product Complaints....49
8.3.1. Timing and Mechanism for Collecting Events....49
8.3.2. Pregnancy....50
8.3.3. Serious Adverse Events....51
8.3.4. Adverse Events of Special Interest....52
8.3.5. Complaint Handling....57
8.4. Pharmacokinetics....57
8.5. Pharmacodynamics....57
8.6. Genetics....58
8.7. Biomarkers....58
8.8. Immunogenicity Assessments....58
8.9. Health Economics....58

9. Statistical Considerations....59
9.1. Statistical Hypotheses....59
9.1.1. Multiplicity Adjustment....59
9.2. Analyses Sets....59
9.3. Statistical Analyses....60
9.3.1. General Considerations....60
9.3.2. Treatment Group Comparability....61
9.3.3. Primary Endpoint(s) Analysis....62
9.3.4. Secondary Endpoints Analysis....62
CCI [redacted]
9.3.6. Safety Analyses....63
9.3.7. Other Analyses....64
9.4. Interim Analysis....64
9.5. Sample Size Determination....64

10. Supporting Documentation and Operational Considerations 66
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 66
10.1.1. Regulatory and Ethical Considerations 66
10.1.2. Financial Disclosure 66
10.1.3. Informed Consent Process 67
10.1.4. Data Protection 67
10.1.5. Committees Structure 67
10.1.6. Dissemination of Clinical Study Data 67
10.1.7. Data Quality Assurance 68
10.1.8. Source Documents 69
10.1.9. Study and Site Start and Closure 70
10.1.10. Publication Policy 70
10.1.11. Investigator Information 70
10.2. Appendix 2: Clinical Laboratory Tests 71
10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event 73
10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 75
10.3.1. Definition of AE 75
10.3.2. Definition of SAE 76
10.3.3. Definition of Product Complaints 77
10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints 77
10.3.5. Reporting of SAEs 79
10.3.6. Regulatory Reporting Requirements 79
10.4. Appendix 4: Contraceptive and Barrier Guidance 81
10.4.1. Definitions 81
10.4.2. Contraception Guidance 81
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 84
10.6. Appendix 6: World Health Organization Classification of Diabetes and Diagnostic Criteria 86
10.7. Appendix 7: Protocol GPIU Standardized Protocols for the Measurement of Height, Weight and Waist Circumference 87
10.8. Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances 89
10.9. Appendix 9: Abbreviations and Definitions 93

11. References 97

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of Tirzepatide Monotherapy Compared with Placebo in Chinese Participants with Type 2 Diabetes (SURPASS-CN-MONO).

Brief Title:

A Study to Investigate the Efficacy and Safety of Tirzepatide Monotherapy in Chinese Participants with Type 2 Diabetes.

Regulatory Agency Identifier Number(s):

Not applicable.

Rationale:

Diabetes is a global health issue that affects approximately 536.6 million adults (20 to 79 years) worldwide, with type 2 diabetes mellitus (T2DM) accounting for over 90% of all diabetes worldwide (IDF 2021). In China, based on International Diabetes Federation (IDF) 2021, there are 140.9 million people (20 to 79 years) living with diabetes, which accounts for 1 in 4 of all adults living with diabetes worldwide (IDF 2021). Type 2 diabetes mellitus is associated with a higher risk for macrovascular and microvascular complications. The results of UK Prospective Diabetes Study published in 2021 suggest that intensive glucose control from the time of diagnosis is essential to maximize reduction of the long-term risk of the complications (Lind et al. 2021).

In the study GPGK (also known as SURPASS-1), tirzepatide demonstrated superior improvements as monotherapy in comparison to placebo in glycemic control and body weight reduction without increased risk of hypoglycemia. However, there is limited tirzepatide monotherapy evidence in Chinese patients with T2DM in early phase.

Study I8F-MC-GPIU (GPIU, monotherapy) is a Phase 3, multicenter, randomized, double-blind, parallel, placebo-controlled, 40-week study that investigates the efficacy and safety of 3 doses of tirzepatide compared with placebo in Chinese participants with T2DM, inadequately controlled with diet and exercise alone, and have not been treated with any antihyperglycemic medication during the 90 days preceding the start of the study. This study aims to provide evidence of the tirzepatide as monotherapy for the treatment of Chinese patients with T2DM in early phase.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To demonstrate that tirzepatide QW 5 mg, and/or 10 mg, and/or 15 mg are superior to placebo QW in HbA1c change from baseline to Week 40	• Change in HbA1c from baseline
Key Secondary (controlled for type 1 error)	
• To demonstrate superiority of tirzepatide QW 5 mg, and/or 10 mg, and/or 15 mg to placebo QW at Week 40 for:	• Proportion of participants with HbA1c target values of <7.0% (<53 mmol/mol) • Change in fasting serum glucose (central laboratory) from baseline • Proportion of participants with HbA1c target values of ≤6.5% (≤48 mmol/mol) • Change in body weight from baseline • Proportion of participants with HbA1c target values of <5.7% (<39 mmol/mol)
Additional Secondary (not controlled for type 1 error)	
• To compare tirzepatide QW 5 mg, 10 mg, and 15 mg to placebo QW at Week 40 for:	• Change in daily average 7-point self-monitored blood glucose profiles from baseline • Proportion of participants who achieved weight loss of ≥5%, ≥10%, and ≥15%
Safety	
• To compare the safety of tirzepatide QW 5 mg, 10 mg, and 15 mg to placebo QW for:	• Incidence of treatment-emergent adverse events • Incidence of early discontinuation of study intervention due to AEs • Incidence of adjudicated pancreatic AEs • Change in serum calcitonin from baseline • Incidence of allergic and hypersensitivity reactions • Change in systolic blood pressure, diastolic blood pressure and pulse rate from baseline • Occurrence of hypoglycemic episodes • Time to initiation of rescue therapy for severe persistent hyperglycemia

Abbreviations: AE = adverse event; HbA1c = hemoglobin A1c; QW = once weekly.

Overall Design

Study GPIU is a multicenter, randomized, double-blind, parallel, placebo-controlled, Phase 3 study which will investigate the efficacy and safety of three doses of tirzepatide as monotherapy compared with placebo in Chinese participants with T2DM.

Brief Summary:

The study will consist of 3 periods:

- Period I: approximately CCI screening/lead-in period
- Period II: CCI treatment period, and
- Period III: CCI safety follow-up period.

Study Population:

Key inclusion and exclusion criteria are listed as follow.

To be eligible for the study, participants must

- be ≥18 years old
- have been diagnosed with T2DM and have not been treated with any antihyperglycemic medication during the 90 days preceding Visit 1
- have hemoglobin A1c（HbA1c) of ≥7.0% (≥53 mmol/mol) to ≤9.5% (≤80 mmol/mol) despite diet and exercise treatment at Visit 1
- have a stable weight (±5%) for 90 days prior to Visit 1
- have a body mass index (BMI) of at least 23.0 kg/m^2 at Visit 1.

To be eligible for the study, participants must <u>not</u>

- have type 1 diabetes mellitus (T1DM)
- have been treated with insulin 1 year preceding Visit 1 and between Visit 1 and Visit 3; or have been treated with any antihyperglycemic medication 90 days preceding Visit 1 and between Visit 1 and Visit 3
  Note: An exception is for the use of insulin for gestational diabetes or short-term use (≤14 days) for certain clinical situations such as acute illness, hospitalization, or elective surgery
- have history of chronic or acute pancreatitis prior to Visit 1
- be currently requiring or receiving treatment for diabetic retinopathy and/or macular edema
- have been treated with prescription drugs or similar other body weight loss medications including over-the-counter (OTC) medications that promote weight loss within 90 days prior to Visit 1 and/or between Visit 1 and Visit 3
- have been receiving chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, or inhaled preparations) or had received such therapy within 30 days of Visit 1 or between Visits 1 and 3.

Number of Participants:

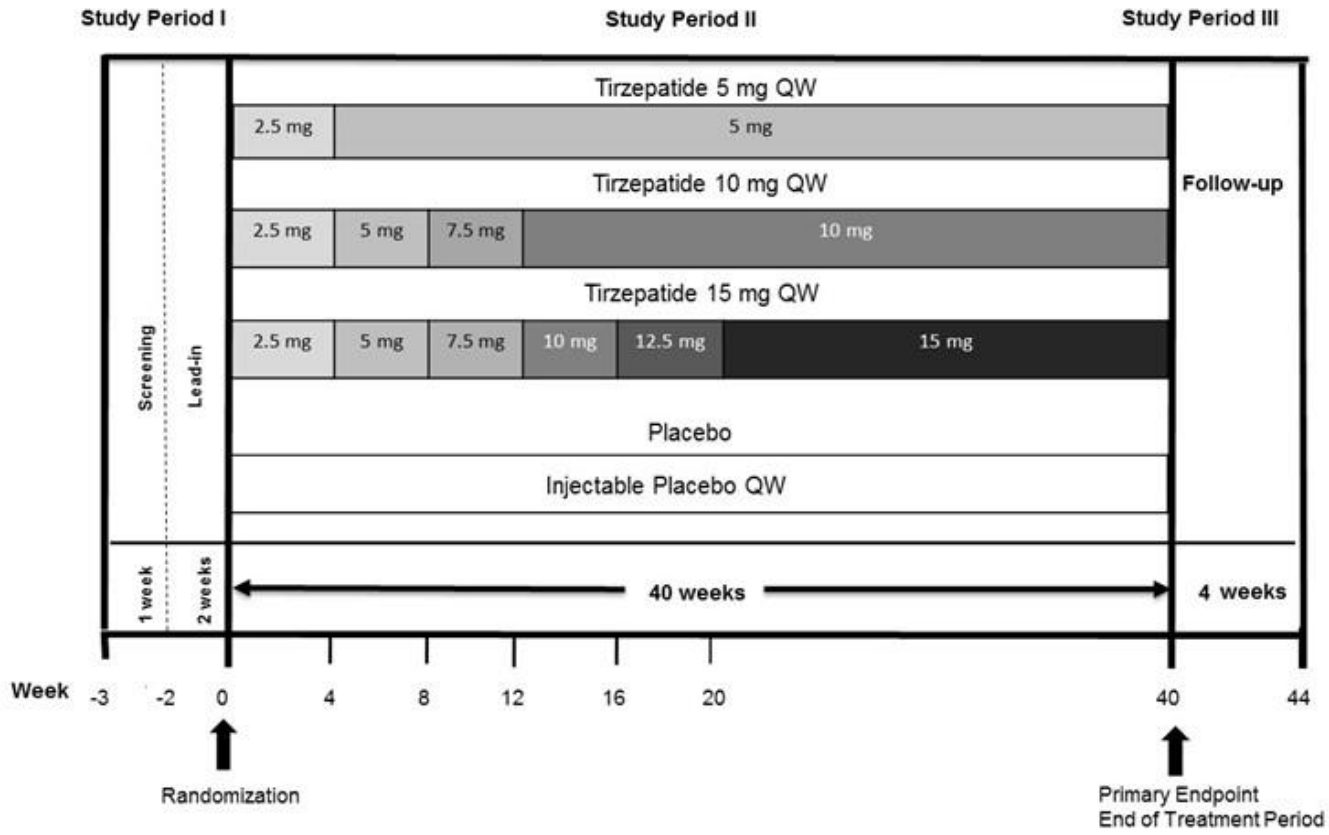
Approximately 200 participants (50 participants per arm) will be randomized in a CCI ratio (tirzepatide 5 mg once weekly [QW], tirzepatide 10 mg QW, tirzepatide 15 mg QW, and placebo QW).

Ethical Considerations of Benefit/Risk:

Considering the data that are available to date from previous clinical studies, and the measures taken to ensure the safety of the participants in this study, the potential risks related with tirzepatide are justified by the anticipated benefits a participant with T2DM may experience in the study.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: QW = once weekly.

1.3. Schedule of Activities (SoA)

The Schedule of Activities (SoA) described below should be followed for all participants enrolled in Study GPIU. However, for those participants whose participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Section 10.8 for additional guidance.

	Study Period I		Study Period II											Study Period III
	Screening/ Lead in		Treatment Period											Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**99[b]**	**ET[c]**	**801**
Week of Treatment	CCI													
Allowable Deviation (days)[d]														
Fasting Visit[e]			X	X	X	X	X	X	X	X	X	X	X	X
Informed consent	X													
Randomization			X											
Clinical Assessments														
Medical history[f]	X													
Physical	X										X		X	X
Height	X													
Weight[g]	X		X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference			X	X	X	X	X	X	X	X	X		X	X
12-lead ECG (local)			X								X		X	X
Vital signs (2 sitting BP and PR)	X		X	X	X	X	X	X	X	X	X		X	X
Dilated fundoscopic Examination[h]		X												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review hypoglycemic events collected in the diaries			X	X	X	X	X	X	X	X	X	X	X	X
Participant Education														
Diabetes education[i,j]		X												
BG meter, SMBG training[j]		X												

	Study Period I		Study Period II											Study Period III
	Screening/ Lead in		Treatment Period											Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**99[b]**	**ET[c]**	**801**
Week of Treatment	CCI													
Allowable Deviation (days)[d]														
Fasting Visit[e]			X	X	X	X	X	X	X	X	X	X	X	X
Dispense BG meter/supplies as needed		X	X	X	X	X	X	X	X	X	X	X	X	
Study intervention injection training with demo device[j]			X											
Hand out diaries, instruct in use[j]		X	X	X	X	X	X	X	X	X	X	X	X	
Remind participants about 7-point SMBG[k]		X						X		X				
Review 7-point SMBG values collected in the diaries			X						X		X			
Dispense study intervention			X	X	X	X	X	X	X	X				
Observe participant administer study intervention[l]			X											
Participant returns study interventions and injection supplies				X	X	X	X	X	X	X	X		X	
Assess study intervention compliance				X	X	X	X	X	X	X	X		X	
Laboratory Tests														
Serum pregnancy test[m]	X													
Urine pregnancy test[n]			X			X			X		X			
FSH[o]	X													
Chemistry panel	X[p]					X			X		X		X	X
Serum glucose			X	X	X	X	X	X	X	X	X	X	X	X
Insulin			X		X		X		X		X			X
C-peptide			X		X		X		X		X			X
Lipid panel			X		X		X		X		X		X	X

	Study Period I		Study Period II											Study Period III
	Screening/ Lead in		Treatment Period											Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**99[b]**	**ET[c]**	**801**
Week of Treatment	CCI													
Allowable Deviation (days)[d]														
Fasting Visit[e]			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Urinary albumin/creatinine ratio	X[p]										X		X	X
eGFR (CKD-EPI 2021)[q]	X[p]					X			X		X		X	X
Calcitonin	X[p]					X			X		X		X	X
Hematology	X[p]					X			X		X		X	X
HbA1c	X		X	X	X	X	X	X	X	X	X	X	X	X
Pancreatic amylase	X[p]					X			X		X		X	X
Lipase	X[p]					X			X		X		X	X
Hepatitis C Screening[r]	X													
Hepatitis B Screening[s]	X													
Patient-Reported Outcomes[t]														
EQ-5D-5L			X								X		X	
IWQOL-Lite-CT			X								X		X	

Abbreviations: BG = blood glucose; BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life-dimensions; ET = early termination; FSH = Follicle-stimulating hormone; F/U = follow-up; HbA1c = hemoglobin A1c; PR = pulse rate; IWQOL-Lite-CT= Impact of Weight on Quality of Life-Lite Clinical Trials Version; PRO = patient-reported outcome; SMBG = self-monitoring of blood glucose; Tx = treatment.

[a] Baseline assessments must be completed before processing in the interactive web-response system.

[b] Visit 99 is only applicable to participants who discontinue the study treatment prematurely before Week 40 and decline to complete the remaining study visits but are willing to return for Visit 99 at Week 40 after randomization for the purpose of HbA1c, body weight and FSG collection, assessment of adverse events, concomitant medications.

[c] Participants who are unable or unwilling to continue in the study for any reason and decline to return for Visit 99 will perform an ET visit. If the participant is discontinuing during an unscheduled visit, that visit should be performed as the ET visit. If the participant is discontinuing during a scheduled visit, that visit should be performed as an ET visit. Visit 801 (safety follow-up visit) should be performed 4 weeks after the ET visit as the final study visit.

[d] The visit date of Visit 2 and 3 are determined based on Visit 1. The visit after Visit 3 (except visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).

[e] Participants should be reminded to report to the site from Visit 3 in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or any significant physical activity and before taking study intervention.

[f] Medical history includes assessment of preexisting conditions (including history of gall bladder disease, cardiovascular disease, thyroid conditions, and medullary thyroid carcinoma) and substance usage (such as alcohol and tobacco).

[g] Weight measurements must be in kilograms.

[h] A dilated fundoscopic examination will be performed by an ophthalmologist or optometrist for all participants between Visit 2 and Visit 3 to confirm eligibility. A previous examination ≤90 days meeting study requirements from Visit 1 is acceptable to confirm eligibility.

[i] Includes counseling on diet and exercise, symptoms and management of hypoglycemia and hyperglycemia, etc.

[j] All training should be repeated as needed to ensure participant compliance.

[k] Participant is required to collect two 7-point SMBGs on nonconsecutive days prior to the next visit. A 7-point SMBG consists of measurements before and 2 hours after each of 3 main meals within the same day and at bedtime. These SMBG profiles will be collected by the participant within 2 weeks prior to the assigned visits. If more than 2 SMBG profiles are available, the 2 most recent nonconsecutive profiles should be used.

[l] Participants should administer their first dose of study intervention at the end of this visit, after other study procedures and randomization.

[m] A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only.

[n] A local urine pregnancy test must be performed at Visit 3 with the result available prior to randomization and first injection of study intervention(s) for women of childbearing potential only. Additional pregnancy tests will be performed at Visits 6, 9, and 11. Pregnancy tests may be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period. For sites who can't perform urine pregnancy test, a local serum pregnancy test can be performed instead.

[o] Performed as needed to confirm postmenopausal status, see Section 10.4.

[p] Screening visit assessment will serve as baseline.

[q] The CKD-EPI equation will be used by the central lab to estimate and report eGFR.

[r] Confirmation by hepatitis C virus RNA will be performed if positive for hepatitis C virus antibody.

[s] Confirmation by hepatitis B virus DNA will be performed if positive for hepatitis B core antibody.

[t] All PROs should be completed before any other study procedures if the participant is not adversely affected by the fasting condition or completed after the participant has sufficiently recovered from the preceding visit procedures.

Note: Patients will be encouraged to collect fasting BG 4 times a week. Missing a fasting BG measurement will not be considered a protocol deviation.

2. Introduction

2.1. Study Rationale

Diabetes is a global health issue that affects approximately 536.6 million adults (20 to 79 years) worldwide, with T2DM accounting for over 90% of all diabetes worldwide (IDF 2021). In China, based on IDF 2021, there are 140.9 million people (20 to 79 years) living with diabetes, which accounts for 1 in 4 of all adults living with diabetes worldwide (IDF 2021). Type 2 diabetes mellitus is associated with a higher risk for macrovascular and microvascular complications. The results of UK Prospective Diabetes Study published in 2021 suggest that intensive glucose control from the time of diagnosis is essential to maximize reduction of the long-term risk of the complications (Lind et al. 2021).

In the study GPGK (also known as SURPASS-1), tirzepatide demonstrated superior improvements as monotherapy in comparison to placebo in glycemic control and body weight reduction without increased risk of hypoglycemia. However, there is limited tirzepatide monotherapy evidence in Chinese patients with T2DM in early phase.

Study GPIU (monotherapy) is a Phase 3, multicenter, randomized, double-blind, parallel, placebo-controlled, 40-week study that investigates the efficacy and safety of 3 doses of tirzepatide compared with placebo in Chinese participants with T2DM, inadequately controlled with diet and exercise alone, and have not been treated with any antihyperglycemic medication during the 90 days preceding the start of the study. This study aims to provide evidence of the tirzepatide as monotherapy for the treatment of Chinese patients with T2DM in early phase.

2.2. Background

Tirzepatide (LY3298176) is a 39-amino acid synthetic peptide with agonist activity at both the glucose dependent insulinotropic polypeptide (GIP) and glucagon like peptide-1 (GLP-1) receptors. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety that prolongs the duration of action. It is administered as QW subcutaneous injection.

Tirzepatide: Mechanism of Action

In a 28-week clinical pharmacology study, Study GPGT, tirzepatide was shown to

- improve β-cell function adjusted for insulin sensitivity, as shown by improved clamp disposition index
- improve first and second phase, as well as overall β-cell insulin secretion
- improve insulin sensitivity
- improve metabolism, including
    - simultaneous effects to increase insulin sensitivity
    - reduction of glucagon secretion
    - improvement of β-cell function, and
- reduce body weight, fat mass, appetite, and food intake.

Phase 3 clinical studies

Clinical reductions in HbA1c and body weight

In a series of global Phase 3 SURPASS studies, tirzepatide demonstrated clinically meaningful reductions in HbA1c and body weight, which were greater than placebo, semaglutide 1 mg, titrated insulin degludec, and titrated insulin glargine (Rosenstock et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Del Prato et al. 2021; Dahl et al. 2022). These treatment effects were sustained up to 104 weeks (Del Prato et al. 2021).

Tirzepatide has been shown to normalize blood glucose (BG) levels as reflected by HbA1c <5.7%. These levels of HbA1c were achieved by up to 62% of participants treated with tirzepatide 15 mg while on treatment and without the effects of rescue (Dahl et al. 2022).

Improvements in metabolic endpoints

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

Common adverse events

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

Hypoglycemia events

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

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Study Intervention

The most commonly reported treatment-emergent adverse events (TEAEs) observed in the tirzepatide clinical studies, in healthy participants and participants with T2DM, are gastrointestinal effects, including nausea, diarrhea, and vomiting.

Most were mild to moderate in severity and tended to occur during the dose escalation period.

Potential risks associated with tirzepatide include:

- acute pancreatitis
- increases in pulse rate
- hypoglycemia
- hypersensitivity reactions
- thyroid C-cell effects (only observed in rodents), and
- developmental (pregnancy) safety.

More detailed information about the adverse events of special interest may be found in Section 8.3.4 or in the IB.

Study Procedures

For the safety consideration of the participants in the placebo group, the following procedures and measures are planned.

- Participants must have HbA1c of ≥7.0% (≥53 mmol/mol) to ≤9.5% (≤80 mmol/mol) and have not used any antihyperglycemic medication during the 90 days preceding Visit 1.
- Participants will be provided with diet and exercise guidance during the whole study.
- Participants will receive a glucometer and training on how to perform self-monitoring of blood glucose (SMBG). Also they will be provided diaries and trained as appropriate to record BG values and hypoglycemic events. Participants will also be trained on disease management (symptoms of hypoglycemia and hyperglycemia) and study procedures.
- If participants fulfill the criteria for severe persistent hyperglycemia (See Section 6.9.1.1), rescue therapy will be started.

2.3.2. Benefit Assessment

The potential benefits from participation in this study include improved glycemic control, weight loss, potential delayed deterioration of β-cell function, and continued expert medical care of T2DM for the study duration.

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

2.3.3. Overall Benefit Risk Conclusion

The safety and efficacy profile seen to date for tirzepatide, supports the overall benefit risk for participants in this study. Considering the measures taken to minimize risk to participants in this study as outline in the protocol, the potential risks identified in association with tirzepatide are justified by the anticipated benefits that may be afforded to participants living with T2DM.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To demonstrate that tirzepatide QW 5 mg, and/or 10 mg, and/or 15 mg are superior to placebo QW in HbA1c change from baseline to Week 40	• Change in HbA1c from baseline
Key Secondary (controlled for type 1 error)	
• To demonstrate superiority of tirzepatide QW 5 mg, and/or 10 mg, and/or 15 mg to placebo QW at Week 40 for:	• Proportion of participants with HbA1c target values of <7.0% (<53 mmol/mol) • Change in fasting serum glucose (central laboratory) from baseline • Proportion of participants with HbA1c target values of ≤6.5% (≤48 mmol/mol) • Change in body weight from baseline • Proportion of participants with HbA1c target values of <5.7% (<39 mmol/mol)
Additional Secondary (not controlled for type 1 error)	
• To compare tirzepatide QW 5 mg, 10 mg, and 15 mg to placebo QW at Week 40 for:	• Change in daily average 7-point self-monitored blood glucose profiles from baseline • Proportion of participants who achieved weight loss of ≥5%, ≥10%, and ≥15%
Safety	
• To compare the safety of tirzepatide QW 5 mg, 10 mg, and 15 mg to placebo QW for:	• Incidence of treatment-emergent adverse events • Incidence of early discontinuation of study intervention due to AEs • Incidence of adjudicated pancreatic AEs • Change in serum calcitonin from baseline • Incidence of allergic and hypersensitivity reactions • Change in systolic blood pressure, diastolic blood pressure and pulse rate from baseline • Occurrence of hypoglycemic episodes • Time to initiation of rescue therapy for severe persistent hyperglycemia
CCI	

Abbreviations: AE = adverse events; HbA1c = hemoglobin A1c; CCI QW = once weekly; CCI .

Primary estimand

The primary efficacy assessment is guided by the "treatment-regimen" estimand. This estimand aims at reflecting how participants with T2DM are treated in clinical practice and takes into account both tolerability and efficacy.

The treatment-regimen estimand answers the following question of interest for the primary objective: What is the treatment difference in change from baseline in HbA1c after 40 weeks of treatment in participants with T2DM regardless of treatment discontinuation for any reason and regardless of initiation of antihyperglycemic rescue?
The treatment-regimen estimand is described by the following attributes.

- *Population:* Participants with T2DM who are inadequately controlled on diet and exercise alone, and have not been treated with any antihyperglycemic medication during the 90 days preceding the start of the study.
- *Endpoint:* Change from baseline to week 40 after randomization in HbA1c.
- *Treatment condition*: The randomized treatment regardless of adherence to treatment with or without antihyperglycemic rescue medication. Further details on study treatment and rescue therapy can be found in Study Protocol Section 6.
- *Intercurrent events:* no ICEs are defined since treatment adherence and the initiation of additional antihyperglycemic medications are a part of the treatment condition.
- *Population-level summary*: Difference in mean changes between treatment conditions.

Secondary estimand(s)

This estimand focuses on the treatment effect if participants who underwent randomization continued to receive the study treatment without treatment discontinuation or rescue antihyperglycemic medication for severe, persistent hyperglycemia.

The efficacy estimand answers the following question of interest for the primary objective: What is the treatment difference in HbA1c change from baseline to week 40 after randomization in participants with T2DM assuming that participants had stayed on treatment and not taken antihyperglycemic rescue medication?

The efficacy estimand is described by the following attributes.

- *Population*: Participants with T2DM who are inadequately controlled on diet and exercise alone, and have not been treated with any antihyperglycemic medication during the 90 days preceding the start of the study.
- *Endpoint*: Change from baseline to Week 40 after randomization in HbA1c.
- Treatment condition: The randomized treatment. Further details on study treatment and rescue therapy can be found in Study Protocol Section 6.
- *Intercurrent event*: Intercurrent events of interest: "Treatment discontinuation for any reason" and "Initiation of antihyperglycemic rescue treatment" will be addressed using the following strategies:
    - Had participants stayed on treatment (hypothetical strategy).
    - Had participants not taken antihyperglycemic rescue medication (hypothetical strategy).
- *Population-level summary*: Difference in mean changes between treatment conditions.

The efficacy estimand will be evaluated for all primary, secondary, and tertiary efficacy objectives. The treatment-regimen estimand will be evaluated for the primary and all key secondary objectives. The population, treatment condition, and intercurrent events specified above for each estimand for the primary objective will also apply to the other efficacy objectives, and the population-level summary might be adjusted according to the endpoints of the objectives.

4. Study Design

4.1. Overall Design

Study GPIU is a multicenter, randomized, double-blind, parallel, placebo-controlled, Phase 3 study which will investigate the efficacy and safety of tirzepatide monotherapy compared with placebo in Chinese participants with T2DM, inadequately controlled with diet and exercise alone, and have not been treated with any antihyperglycemic medication during the 90 days preceding the start of the study.

Approximately, 200 participants will be randomized in a CCI ratio (tirzepatide 5 mg QW, 10 mg QW, 15 mg QW, and placebo QW). Participants will be stratified based on HbA1c [≤8.5% (≤69 mmol/mol) or >8.5% (>69 mmol/mol)], and any past prior use (Yes or No) of any antihyperglycemic medication.

Study GPIU will consist of 3 periods:

- Period I: approximately CCI screening/lead-in period
- Period II: CCI treatment period, and
- Period III: CCI safety follow-up period.

Study Period I (Screening and Lead-in)

Screening (Visit 1)

The purpose of screening procedures at Visit 1 is to establish initial eligibility and to obtain blood samples for laboratory assessments needed to confirm eligibility at Visit 2. The participant will sign the informed consent form (ICF) before any study procedures are performed. Procedures at this visit will be performed as shown in the SoA (Section 1.3).

Lead-in (Visit 2 to Visit 3)

At Visit 2, the screening laboratory results will be reviewed. For those participants meeting all other eligibility requirements, a dilated fundoscopic examination, performed by an ophthalmologist or optometrist, will be completed between Visit 2 and Visit 3 to confirm eligibility unless a dilated fundoscopic examination was performed by an ophthalmologist or optometrist within 90 days of study entry (Visit 1) (section 5.2 Exclusion Criterion [10]).

Additionally, at Visit 2, participants and their caregiver(s), if applicable, will receive a glucometer and training on how to perform SMBG. Participants will be asked to monitor fasting blood glucose (FBG) 4 times a week. Participants will also be asked to monitor two 7-point SMBG profiles done on 2 nonconsecutive days in the 2-week period prior to Visit 3 (randomization), Visit 9 (Week 24), Visit 11 (Week 40).

Participants will be provided diaries and will be trained as appropriate to record BG values and hypoglycemic events. During this period, participants will also be trained on disease management (symptoms of hypoglycemia and hyperglycemia) and study procedures; this training can be repeated at subsequent visits as deemed appropriate. Participants should monitor BG any time a hypoglycemic event is suspected.

Study Period II (CCI treatment period)

Randomization (Visit 3)

At Visit 3, eligible participants will perform all required baseline study procedures (including the collection of all baseline laboratory measures and electrocardiogram [ECG]) prior to randomization and prior to administering the first dose of study intervention. Participant should arrive to the clinic in the fasting state; the fasting state should have lasted at least 8 hours (water is allowed). The questionnaires (European Quality of Life-Dimensions [EQ-5D-5L] and Impact of Weight on Quality of Life-Lite Clinical Trials Version [IWQOL-Lite-CT]) should be completed before any other study procedures if the participant is not adversely affected by the fasting condition or completed after the participant has sufficiently recovered from the preceding visit procedures.

Participants will be instructed on how to use the single-dose pen (SDP) and will inject their first dose of study intervention while in the clinic for Visit 3. The date and time of the first dose of study intervention should be recorded on the case report form (CRF).

Following randomization, participants will participate in a CCI treatment period.

Postrandomization period (end of Visit 3 to Visit 11):

The starting dose of study intervention will be 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW, for the duration of the study in the 5-mg group.

For the 10-mg group, the starting dose of study intervention will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study.

For the 15-mg group, the starting dose of study intervention will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg to 12.5 mg to 15 mg) until the 15-mg dose is reached and maintained for the duration of the study.

For the placebo group, participants will inject matched QW placebo for the duration of the study.

Visit 99

Visit 99 is only applicable to participants who discontinue the study treatment prematurely before Week 40 and decline to complete the remaining study visits but are willing to return for Visit 99 at Week 40 after randomization. This visit is critical to ensure complete data collection for the primary and key secondary endpoints.

Participants should attend this visit in the fasting state. Procedures to be completed are:

- measurement of HbA1c, FSG and weight
- listing of concomitant medications, and
- assessment of AEs.

For participants unwilling to attend this visit, their refusal to attend should be documented in the participant medical record.

Study Period III (safety follow-up period)

Safety follow-up (Visit 801) visits:

All participants who complete the treatment period (complete Visit 11 or Visit 99) are required to complete Visit 801, a safety follow-up visit approximately 4 weeks after their last treatment visit. Participants discontinuing the study early and performing an early termination (ET) visit

will also be asked to perform the safety follow-up visit, so that the safety follow-up visit will be their final visit. During the safety follow-up period, participants will not receive study intervention. Participants may be treated with another glucose-lowering intervention decided upon by the investigator (except for prohibited antihyperglycemic medications, see section 6.9.1). If any new antihyperglycemic medication is initiated during the safety follow-up period, it will not be classified as rescue therapy.

Participants are also required to return any remaining study diaries to the study site at the end of this period.

The participants who complete the treatment period (complete Visit 11 or Visit 99) and safety follow-up (Visit 801) are considered as complete the study.

4.2. Scientific Rationale for Study Design

Study GPIU is designed to assess the efficacy and safety of tirzepatide QW (5 mg, 10 mg, and 15 mg) as monotherapy versus placebo QW in Chinese patients with T2DM.

Placebo was chosen as the comparator to meet the authority requirement to compare the study intervention versus a placebo in pivotal study. The planned treatment duration of 40 weeks is considered appropriate to assess the full effects and benefit/risk of each maintenance dose of tirzepatide on both glycemic control and body weight based on the experience of the international multicenter Phase 3 Study SURPASS-1 (GPGK).

The parallel-group design for treatment comparison was chosen to avoid any interaction between treatments that may interfere with the interpretation of the trial outcome. To minimize the potential confounding effect of changes to concomitant medications, participants will be permitted to use concomitant medications that they require during the study. Medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments will not be allowed (see Section 6.9).

4.3. Justification for Dose

Tirzepatide doses of 5 mg, 10 mg, and 15 mg administered subcutaneously QW will be evaluated in this study.

Based on the findings in completed Phase 3 studies in participants with T2DM (SURPASS clinical program, including GPGK, GPGL, GPGH, GPGM, GPGI, and GPHO [the first registration trial of tirzepatide that enrolled a majority of Chinese participants with T2DM]) (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022), tirzepatide 5 mg, 10 mg, and 15 mg

- Demonstrated superior efficacy for glycemic control and body weight reduction as well as an improvement in different factors associated with an increased risk of longer-term cardiometabolic complications in participants with T2DM.
- Similar to the GLP-1 receptor agonist class, most of the tirzepatide AEs were gastrointestinal related, consisting mainly of nausea, vomiting, and diarrhea. In general, these events were mild or moderate in severity, and transient.

The starting dose of tirzepatide is 2.5 mg QW, which is to be escalated at 4-week intervals at 2.5 mg increments (2.5 to 5 to 7.5 to 10 to 12.5 to 15 mg) until the participant reaches 5, 10 or 15 mg. Such approach should permit the development of tolerance to gastrointestinal events and is expected to minimize gastrointestinal AEs consistent with the completed Phase 3 studies in the SURPASS-program.

4.4. End of Study Definition

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

5. Study Population

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

5.1. Inclusion Criteria

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

Type of Participant and Disease Characteristics

[1] Have been diagnosed with T2DM based on the World Health Organization classification (Section 10.6), and have not used any antihyperglycemic medication during the 90 days preceding Visit 1

Note: An exception is for the use of insulin for short-term use (≤14 days) for certain clinical situations such as acute illness, hospitalization, or elective surgery.

Participant Characteristics

[2] Have HbA1c ≥7.0% (≥53 mmol/mol) to ≤9.5% (≤80 mmol/mol) despite diet and exercise treatment, as determined by the central laboratory at Visit 1 (Note: HbA1c value as determined by the central lab at Visit 1)

[3] Are of stable weight (±5%) during the 90 days preceding Visit 1 and agree to not initiate a diet and/or exercise program during the study with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment

[4] Have BMI ≥23.0 kg/m^2 at Visit 1

[5] Are ≥18 years old

Males and females may participate in this trial.

Female participants must not be pregnant, intending to be pregnant, breastfeeding, or intending to breastfeed.

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see section 10.4 Appendix 4.

[6] In the investigator's opinion, are well motivated, capable, and willing to

(a) perform finger-stick BG monitoring, including scheduled BG profiles with up to 7 measurements in 1 day

(b) learn how to self-inject study interventions, as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study intervention; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study intervention)

(c) are willing and able to inject study interventions

(d) maintain study diaries, as required for this protocol

(e) have a sufficient understanding of the provided language that they will be able to complete the participant questionnaires

Informed Consent

[7] Capable of giving signed informed consent as described in section 10.1 Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

[8] Have T1DM

[9] Have a history of chronic or acute pancreatitis any time prior to study entry (Visit 1)

[10] Are currently requiring or receiving treatment for diabetic retinopathy and/or macular edema (e.g., laser photocoagulation or intravitreal injections of anti–vascular endothelial growth factor inhibitors). Must be verified by dilated fundoscopic examination performed by an ophthalmologist or optometrist if applicable within 90 days prior to Visit 1 or between Visit 2 and Visit 3.

Note: For participants with a contraindication to pharmacological pupil dilation (for example, closed angle glaucoma), a non-dilated fundoscopic examination performed by an ophthalmologist or optometrist is allowed.

[11] Have a history of ketoacidosis or hyperosmolar state/coma

[12] Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction), have undergone or plan to have during the course of the study: gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or chronically take drugs that directly affect gastrointestinal motility

[13] Have any of the following cardiovascular conditions within 60 days prior to Visit 1: acute myocardial infarction, cerebrovascular accident (stroke), or hospitalization due to congestive heart failure (CHF)

[14] Have a history of New York Heart Association Functional Classification IV CHF

[15] Have acute or chronic hepatitis including a history of autoimmune hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the central laboratory at Visit 1:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥3.0 times the upper limit of normal (ULN) for the reference range
- Alkaline phosphatase (ALP) level ≥1.5× ULN for the reference range, or

- Total bilirubin (TBL) level ≥1.5× ULN for the reference range (except for cases of known Gilbert's Syndrome)
- Hepatitis B infection, defined as:
  - Positive hepatitis B core antibody and positive for hepatitis B virus DNA or
  - Positive hepatitis B surface antigen
- Positive hepatitis C antibody and positive hepatitis C virus RNA

Note: Participants with nonalcoholic fatty liver disease are eligible to participate in this trial if their ALT level is <3.0× ULN for the reference range

[16] Have an estimated glomerular filtration rate <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory at Visit 1

[17] Have evidence of a significant, uncontrolled endocrine abnormality (for example, thyrotoxicosis or adrenal crises), in the opinion of the investigator

[18] Have family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2)

[19] Have a serum calcitonin level of ≥35 ng/L, as determined by central laboratory at Visit 1

[20] Known or suspected hypersensitivity to trial product(s) or related products

[21] Have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 12 months

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

[23] Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy for less than 5 years. Exceptions for this criterion are:
- basal or squamous cell skin cancer
- *in situ* carcinomas of the cervix, and
- *in situ* or grade 1 (for example, Gleason 6 or lower) prostate cancer

[24] Have a history of any other condition (such as known drug, alcohol abuse, or psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol

[25] Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle cell disease)

Prior/Concomitant Therapy

[26] Use of insulin 1 year preceding Visit 1 and between Visit 1 and Visit 3; use of any antihyperglycemic medication 90 days preceding Visit 1 and between Visit 1 and Visit 3.

Note: An exception is for the use of insulin for gestational diabetes or short-term use (≤14 days) for certain clinical situations such as acute illness, hospitalization, or elective surgery.

[27] Have been treated with prescription drugs that promote weight loss (for example, Saxenda [liraglutide 3.0 mg], Wegovy [semaglutide 2.4mg], Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Adipex® [phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], Contrave® [naltrexone/bupropion], or similar other body weight loss medications including OTC medications [for example, alli®]) within 90 days prior to Visit 1 and/or between study entry (Visit 1) and randomization (Visit 3)

[28] Are receiving chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, or inhaled preparations) or have received such therapy within 30 days of Visit 1 or between Visits 1 and Visit 3

Prior/Concurrent Clinical Study Experience

[29] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[30] Have participated, within the last 30 days in a clinical study involving an investigational product. If the previous investigational product has 5 half-lives or 30 days (whichever is longer), should have passed prior to screening

[31] Were previously enrolled and assigned to study intervention in this study, **received tirzepatide in any other study investigating tirzepatide**, or are currently taking or have used tirzepatide for any other reason outside of a clinical study

Other Exclusions

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

[33] Are Lilly employees

[34] Are unwilling or unable to comply with the use of a paper diary to directly record data from the participant.

5.3. Lifestyle Considerations

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

Participants should continue their usual exercise habits and generally follow a healthy meal plan (with consistent meal size and time of day) throughout the course of the study. Dietary counseling may be reviewed throughout the study, as needed. Per Inclusion Criterion [3]

(Section 5.1), participants should not initiate an organized diet and/or exercise (weight reduction) program during the study other than the lifestyle and dietary measures for diabetes treatment.

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

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

Assignment to study intervention (tirzepatide 3 doses or placebo) will occur at randomization. Beginning at randomization, all participants will receive study intervention according to the randomized treatment group for the duration of the CCI treatment period. Following randomization, the participant will inject the first dose of study intervention at the study site. The date and time of study intervention should be recorded on the paper diary and transcribed to the CRF.

6.1.1. Study intervention

This table lists the interventions used in this clinical study.

Intervention Name	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
Dosage Level(s)	2.5 mg QW 5 mg QW	2.5 mg QW 5 mg QW 7.5 mg 10 mg QW	2.5 mg QW 5 mg QW 7.5 mg 10 mg QW 12.5 mg QW 15 mg QW	NA
Route of Administration	SC			
Use	Investigational compound			Comparator
Drug formulation	SDP			

Abbreviations: NA=not applicable; QW=once weekly; SDP= single-dose pen; SC=subcutaneous.

Tirzepatide dosing

The starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW, for the duration of the study for the 5-mg group.

For the 10-mg group, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study.

For the 15-mg group, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg to 12.5 mg to 15 mg) until the 15-mg dose is reached and maintained for the duration of the study.

Placebo dosing

Participants randomized to the placebo group will inject matched placebo QW for the entire treatment period.

Timing of doses of study intervention

There are no restrictions on the time of day each weekly dose of study intervention is given, but it is advisable to administer the subcutaneous injections on the same day and same time each week, with or without meals. The actual date and time of all dose administrations will be recorded by the participant. If a dose of study intervention is missed, the participant should take it as soon as possible unless it is within 72 hours of the next dose, in which case, that dose should be skipped and the next dose should be taken at the appropriate time. The day of weekly administration can be changed if necessary, as long as the last dose was administered 72 or more hours before.

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

Study intervention returning

Participants should return all study interventions to the site according to the SoA (Section 1.3). Participants should be instructed to discard all used SDPs in a closeable, puncture-resistant container according to local regulations.

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

Packaging and labeling

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

The sponsor will provide tirzepatide and placebo in SDP which will be packaged in cartons to be dispensed. Clinical study materials will be labeled according to the country's regulatory requirements.

6.1.2. Medical Devices

The combination products used in the study are tirzepatide investigational SDP and placebo SDP.

6.2. Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

- The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3. Assignment to Study Intervention

Participants who meet all criteria for enrollment will be randomized to 1 of the study treatment groups at Visit 3. Assignment to treatment groups will be determined by a computer generated random sequence using an Interactive Web Response System (IWRS). Participants will be randomized in a CCI ratio to receive tirzepatide 5 mg, 10 mg, 15 mg, or placebo.

6.4. Blinding

This study is designed as a randomized, double-blind study to minimized bias. Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS. Investigators, site staff, clinical monitors, and participants will remain blinded to the treatment assignments until the study is complete.

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

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

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician (CRP) for the participant to continue in the study.

6.5. Study Intervention Compliance

Study intervention compliance will be determined by the following:

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

In the 3 tirzepatide treatment groups, as well as the placebo group, treatment compliance for each visit interval is defined as taking at least CCI of the required doses of study intervention.

Similarly, a participant will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

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

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

6.6. Dose Modification

6.6.1. Tirzepatide

Please refer to Section 6.1.1 for tirzepatide administration. Study intervention dose modification is not permitted except for management of intolerable gastrointestinal symptoms.

Management of Participants with Gastrointestinal Symptoms

In participants who experience intolerable gastrointestinal symptoms (for example, nausea, vomiting, or diarrhea) at any time during the study, the following measures are recommended:

1. counseling on dietary behaviors that may help mitigate nausea and vomiting, (for example, eating smaller meals, splitting 3 daily meals into 4 or more smaller ones, and stopping eating when they feel full).
2. if symptoms persist despite #1, prescribing symptomatic medication (for example, antiemetic or antidiarrheal medication), at the investigator's discretion.
3. if symptoms persist despite #1 and #2, temporarily interrupting study intervention (omit 1 dose, the participant will take 3 of 4 doses at that dose level). Study intervention should be resumed at the assigned dose immediately, either alone or in combination with symptomatic medication, which can also be utilized to manage symptoms.

If intolerable gastrointestinal symptoms (for example, nausea, vomiting, or diarrhea) persist despite the above measures before or at Visit 5 (the scheduled visit in Week 8), the participant should discontinue the study intervention.

If intolerable gastrointestinal symptoms (for example, nausea, vomiting, or diarrhea) persist despite the above measures after Visit 5 (the scheduled visit in Week 8) the investigator should contact Lilly to consider continuing treatment at a lower maintenance dose of study intervention in a blinded fashion, for example:

- Participants at 5 mg will decrease the dose to placebo.
- Participants at 7.5 mg or 10 mg will decrease the dose to 5 mg.
- Participants at 12.5 mg or 15 mg will decrease the dose to 10mg.

If de-escalation of the tirzepatide dose is necessary, the investigator will use the IWRS to receive the appropriate tirzepatide dispensing information. If de-escalation is needed between scheduled visits, the IWRS will have unscheduled visits dedicated to providing dispensing information for

participants whose dose has been de-escalated. Those participants who have their dose de-escalated, will not be escalated again. The dose can be de-escalated only once and should before Week 24 (after Week 24, dose decreases will not be allowed). After that, the participants will have to discontinue study intervention if intolerable gastrointestinal AE persists and stay in the study.

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

Study completion will occur after all participants complete the follow up visit. Investigators will continue to follow SoA (Section 1.3) for all participants until notified by Lilly that study completion has occurred.

Tirzepatide will not be made available after conclusion of the study to participants.

6.8. Treatment of Overdose

Overdose was defined as administration of more than a total of 15 mg of tirzepatide in less than a 72-hour period (Note: to preserve blinding of the study intervention, administration of study intervention more than 1 injection in less than 72 hours will be reported as an AE for further evaluation).

In the event of overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted, and reinitiate when the investigator believes it is safe to do so (see section 7.1.2 for reinitiation based on number of doses missed).
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate until, for example, study intervention no longer has a clinical effect or can no longer be detected systemically (at least 30 days).
- Appropriate supportive treatment should be initiated according to the participant's clinical signs and symptoms.

6.9. Concomitant Therapy

Participants will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments, such as GLP-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, pramlintide, drugs with approved weight loss indication and systemic glucocorticoid therapy >14 days.

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

Any nonstudy medications that the participant is receiving at the time of enrollment or receives during the study must be recorded on the CRF along with:

- Reason for use

- Dates of administration including start and end dates
- Dosage information including dose and frequency for concomitant therapy of special interest.

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

6.9.1. Initiation of New Antihyperglycemic Medication

The introduction of new antihyperglycemic medication is expected during the study only in the following situations:

- As an antihyperglycemic intervention for severe, persistent hyperglycemia ("rescue therapy"), as defined in Section 6.9.1.1
- In those participants who require permanent discontinuation of study intervention, but remain in the study (Section 7.1)
- During the safety follow-up period (between Visit 11 [Week 40] or ET and Visit 801).
- Short-term insulin use for up to 14 days is allowed for certain clinical situations (for example, acute illness, hospitalization, or elective surgery). This insulin use must be differentiated from insulin use as rescue therapy when reported in the CRF.

The choice of new antihyperglycemic medication will be at the discretion of the investigator and follow clinical guidelines. Glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and pramlintide are not allowed at any time during the study.

6.9.1.1. Rescue Therapy

If a participant develops severe, persistent hyperglycemia after randomization, a new antihyperglycemic medication ("rescue therapy") may be medically indicated after investigator assessment.

Investigators will be trained on the application of criteria for deciding when and how to intervene with participants who do not reach glycemic targets. If met the following prespecified severe, persistent hyperglycemia criteria and no intercurrent cause of the hyperglycemia could be identified (investigators should first confirm that the participant is fully compliant with the assigned therapeutic regimen and that he or she does not have an acute condition causing severe hyperglycemia), rescue medication will be prescribed as an add-on to randomized treatment. Participants will continue in the trial until they complete all study visits.

Severe, Persistent Hyperglycemia

- If any of the FBG values within 1 week for 2 consecutive weeks,
  - >270 mg/dL (>15.0 mmol/L) from baseline to end of Week 5, or
  - >240 mg/dL (>13.3 mmol/L) from Week 6 to end of Week 11, or
  - >200 mg/dL (>11.1 mmol/L) from Week 12 to end of trial, or
  - HbA1c ≥8.5% (≥69 mmol/mol) by and after Week 24

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention, could receive another glucose-lowering intervention and will remain in the study and follow procedures for all remaining study visits, as shown in the SoA. The new glucose-lowering intervention will be recorded on the CRF specified for collecting antihyperglycemic medications.

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study (will also be withdrawn from the study)
- the participant is diagnosed with T1DM (will also be withdrawn from the study)
- the participant discontinues due to a hepatic event or liver test abnormality (see section 7.1.1)
- the participant requests to discontinue study intervention.
- the participant is diagnosed with an acute or chronic pancreatitis
- the participant is diagnosed with MTC after randomization, or has post randomization calcitonin value ≥35 ng/L that has increased at least 50% over baseline
- the participant is diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
- the participant has any significant study intervention related hypersensitivity reaction
- the participant has any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation due to a hepatic event or liver test abnormality

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

The study intervention should be **interrupted** and close hepatic monitoring initiated (Section 10.5) if one or more of these conditions occur:

Elevation	Exception
ALT or AST >8× ULN	
ALT or AST >5× ULN for more than 2 weeks	
ALT or AST >3× ULN and either TBL >2× ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2× ULN.

ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3× ULN, when the source of increased ALP is the liver	
ALP >2.5× ULN and TBL >2× ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2× ULN.
ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications	

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

Resuming study intervention after elevated liver tests

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

7.1.2. Temporary Discontinuation

In certain situations after randomization, the investigator may need to temporarily interrupt study intervention. Every effort should be made by the investigator to maintain participants on study intervention and to restart after any temporary interruption, as soon as it is safe to do so. The investigator will use the IWRS to receive the appropriate study intervention dispensing information to preserve blinding of the study intervention.

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

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

Abbreviations: IWRS = interactive web response service.

If the study intervention interruption is due to AE, the event is to be documented and followed according to the procedures in Section 8.3 of this protocol.

If the study intervention interruption is due to intolerable persistent gastrointestinal AE, such as nausea, vomiting, or diarrhea, the participant should be treated as suggested in Section 6.6.1.

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

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request for any reason or without providing any reason
- 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 investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

A participant will be withdrawn from the study:

- if a female participant becomes pregnant
- if a participant is diagnosed with T1DM
- if inadvertently enrolled (Section 7.2.1).

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit (ET visit) and safety follow-up 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.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant must be discontinued from the study unless exceptional circumstances that provide sufficient evidence that discontinuation of the study participant from the trial is not medically justified. If discontinuation of the study participant from the trial is not medically justified, approval must be obtained from the Sponsor Chief Medical Officer. Safety follow up is as outlined in Section 1.3 (SoA), Section 8.3 (AEs), and Section 8.2 (Safety) of this protocol.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are

expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

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

8.1. Efficacy Assessments

Primary efficacy assessments

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

Other efficacy assessments

Other efficacy assessments include change in HbA1c, FSG, body weight, 7-point SMBG, C-peptide, insulin level, waist circumference, BMI, lipids, urinary albumin to creatinine ratio, and patient-reported outcomes (PROs).

8.1.1. Self-Monitoring of Blood Glucose (SMBG)

Participants must use only the study-provided monitors during the study.

Glucometer for participant use during the study

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

Glucometer training

Site personnel will train the participant on correct use of the glucometer for SMBG and reporting of hypoglycemia data.

When to measure FBG during the study

Participants will be asked to monitor FBG 4 times a week. The FBG should be measured upon waking in the morning, prior to food or caloric beverage intake.

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

8.1.2. Patient-Reported Outcomes

8.1.2.1. European Quality of Life-Dimensions

Generic health-related quality of life will be assessed using the EQ-5D-5L (EuroQol Research Foundation 2019). The EQ-5D-5L is a standardized 5-item instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems), for a total of 3125 possible health states. In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). In addition, the EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analog scale. In conjunction with the health state data, it provides a composite picture of the respondent's health status.

The EQ-5D-5L is used worldwide and is available in more than 130 different languages. Details on the instrument, and scoring, organizing, and presenting the data collected can be found in the EQ-5D-5L User Guide (EuroQol Research Foundation 2019).

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

The IWQOL-Lite-CT is a 20-item PRO instrument developed in accordance with FDA's guidance on PROs to assess the impact of weight on quality of life in clinical trials (Kolotkin et al. 2019). The IWQOL-Lite-CT includes 2 primary domains: physical (7 items) and psychosocial (13 items), and a 5-item subset of the physical domain – the physical function composite. Items in the physical function composite describe physical impacts related to general and specific physical activities. All items are rated on either a 5-point frequency ("never" to "always") scale or a 5-point truth ("not at all true" to "completely true") scale (Kolotkin et al. 2017; Kolotkin et al. 2018). The IWQOL-Lite-CT yields a total score and three composite scores for the Physical domain, Physical Function, and Psychosocial domain. Higher scores indicate higher levels of functioning.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular system, respiratory system, gastrointestinal system, neurological system, thyroid examination, and foot examination, including evaluation for diabetic neuropathy. Height, weight, and waist circumference will also be measured and recorded (Section 10.7).

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

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

8.2.2. Vital Signs

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

Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required. The participant should sit quietly for 5 minutes before vital sign measurements are taken. For each parameter, 2 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart. Blood pressure must be taken with an automated blood pressure machine.

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

8.2.3. Electrocardiograms

For each participant, 12-lead ECGs should be collected locally according to the SoA (Section 1.3). Electrocardiograms should be performed after vital signs are collected and prior to the collection of blood samples for laboratory testing if the participant is not adversely affected by the fasting condition. Participant should be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection. Electrocardiograms should be recorded according to the study-specific recommendations.

Electrocardiograms must be interpreted by the investigator or qualified designee at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, for immediate participant management, if needed. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via the CRF.

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

8.2.4. Dilated Fundoscopic Examination

A dilated fundoscopic examination will be performed by an ophthalmologist or optometrist for all participants between Visit 2 and Visit 3 to confirm eligibility. A previous examination ≤90 days meeting study requirements from Visit 1 is acceptable to confirm eligibility. Additional dilated fundoscopic examinations should be performed when clinically indicated by any AE suspected of worsening retinopathy.

8.2.5. Clinical Safety Laboratory Tests

- See Section 10.2 Appendix 2 for the list of clinical laboratory tests to be performed and the SoA 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 or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2 Appendix 2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor if a central vendor is used for the clinical trial.
- Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the participant receives the first dose of investigational product should be reported to Lilly or its designee as an AE via CRF.

8.2.6. Pregnancy Testing

Serum pregnancy test will be performed by central laboratory at Visit 1 for women of childbearing potential. A local urine pregnancy test must be performed at Visit 3 with the result available prior to randomization and first injection of study intervention for women of childbearing potential only. Additional pregnancy tests will be performed at Visits 6, 9, and 11. Pregnancy tests may be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period. For sites who can't perform urine pregnancy test, a local serum pregnancy test can be performed instead.

8.2.7. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. The study team will review safety reports in a blinded fashion according to the schedule provided in the Trial-Level Safety Review plan. Lilly will also review SAEs within time frames mandated by company procedures. The Lilly CRP will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist.

8.2.7.1. Hepatic Safety Monitoring

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

Laboratory tests, including ALT, AST, ALP, TBL, direct bilirubin (D. Bil), gamma-glutamyltransferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

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

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

What to do if the abnormal condition persists or worsens

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

Frequency of monitoring

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

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

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

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

A comprehensive evaluation (Section 10.5 Appendix 5) should be performed to search for possible causes of liver injury if one or more of these conditions occur:

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

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

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

What a comprehensive evaluation should include

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

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

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

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

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

5. Discontinuation of study intervention due to a hepatic event

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

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

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

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in section 10.3 Appendix 3.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
AE					
AE	Signing of the ICF	The safety follow-up visit or participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
SAE					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE CRF and AE CRF	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE and SAE updates – after start of study intervention	start of intervention	The safety follow-up visit or participation in study has ended	Within 24 hours of awareness	SAE CRF and AE CRF	SAE paper form
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	At least 30 days after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

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

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After learning of a pregnancy in the female partner of a study participant, the investigator will
  - obtain a consent to release information from the pregnant female partner directly, and

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

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed in Section 10.3.2.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE

reporting requirements and timelines (see Section 8.3.1) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the CRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in participants once they have discontinued and/or completed the study (the participant disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he or she considers that the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

8.3.3.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

8.3.4. Adverse Events of Special Interest

8.3.4.1. Hypoglycemia

Participants will collect information on episodes of hypoglycemia starting from Visit 2 until the last study visit (Follow-up Visit or ET Visit). For that purpose, participants will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia in the study according to the SoA (Section 1.3). Site personnel will enter this information into the CRF at each visit.

Investigators should use the following classification of hypoglycemia (ADA 2023b):

Level 1 hypoglycemia:

Glucose <3.9 mmol/L (<70 mg/dL) and ≥3.0 mmol/L (≥54 mg/dL): 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 <3.0 mmol/L (<54 mg/dL): Level 2 hypoglycemia is also referred to as documented or BG confirmed hypoglycemia with glucose <3.0 mmol/L (<54 mg/dL). 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.

To avoid duplicate reporting, all consecutive BG values <3.9 mmol/L occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013; ADA 2023b).

8.3.4.2. Severe, Persistent Hyperglycemia

Severe, persistent hyperglycemia (Section 6.9.1.1) will be collected during the trial to assess the risk of extreme imbalance in glycemic control.

Investigators will be trained on the application of criteria for deciding when and how to intervene with participants who do not reach glycemic targets. An additional therapeutic intervention should be considered in participants who develop severe, persistent hyperglycemia after randomization. Rescue medication will be prescribed as add-on to randomized treatment, and participants will continue to follow the protocol-specified visit schedule as described in Section 6.9.1.1.

8.3.4.3. Pancreatitis

Diagnosis of acute pancreatitis

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

- abdominal pain, characteristic of acute pancreatitis, that is, epigastric pain radiating to the back, often associated with nausea and vomiting
- serum amylase (total, pancreatic, or both) and/or lipase ≥3× ULN, or
- characteristic findings of acute pancreatitis on CT scan or magnetic resonance imaging (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
- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone/gall bladder disease, hypertriglyceridemia, and concomitant medications.

Discontinuation for acute pancreatitis

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

Case adjudication and data entry

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

In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from participants with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed CRF page by study site or Lilly personnel. The adjudication committee representative will enter the results of adjudication in a corresponding CRF page.

Asymptomatic elevation of serum amylase and/or lipase

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

Reporting AEs and SAEs of acute pancreatitis

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

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

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

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

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

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

Individuals with personal or family history of MTC and/or MEN2 will be excluded from the study. The assessment of thyroid safety during the study will include reporting of any case of thyroid malignancy including MTC and papillary carcinoma and measurements of calcitonin. This data will be captured in specific CRFs. The purpose of calcitonin measurements is to assess the potential of tirzepatide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Study intervention should be discontinued (after first confirming the value) if post randomization calcitonin value is ≥35 ng/L and has increased at least 50% over baseline. A consultation with a thyroid specialist (if not available, an endocrinologist) should be obtained.

If the increased calcitonin value (≥35 ng/L AND increases by ≥50% compared with baseline) is observed in a participant who has been administered a medication that is known to increase serum calcitonin, this medication should be stopped and calcitonin levels should be measured after an appropriate washout period. If the confirmed calcitonin value is <35 ng/L, study intervention should be restarted when it is safe to do so.

8.3.4.5. Major Adverse Cardiovascular Event

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

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

8.3.4.6. Arrythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders will be further evaluated. Participants who develop any event from this group of disorders should undergo an ECG. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 10.3.2 must be reported as SAEs.

8.3.4.7. Hypersensitivity Reactions

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

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

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2.1 Appendix 2. Laboratory results are provided to the sponsor via the central laboratory.

Study intervention should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study intervention. Study intervention may be restarted when/if it is safe to do so, in the opinion of the investigator. If study intervention is permanently discontinued, the participant will receive another glucose-lowering treatment, judged by the investigator to be appropriate based on the participant's clinical status, and will continue in the trial to collect all planned efficacy and safety measurements.

8.3.4.8. Injection Site Reactions

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

If an ISR is reported by a participant or study personnel, the ISR CRF will be used to capture additional information about this reaction, for example, injection site pain, degree and area of erythema, induration, pruritis, and edema.

8.3.4.9. Diabetic Retinopathy Complications

Dilated retinal fundoscopic examination for all participants will be performed by a qualified eye care professional (ophthalmologist or optometrist) between Visit 2 and Visit 3 or at a previous examination ≤90 days of screening meeting study requirements. The results from this examination will be recorded on a specific retinopathy CRF as a baseline measure of retinopathy.

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

8.3.4.10. Hepatobiliary Disorders

All events of treatment emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.2.7.1 and Section 10.5 Appendix 5.

8.3.4.11. Severe Gastrointestinal Adverse Events

Tirzepatide may cause severe gastrointestinal AEs, such as nausea, vomiting, and diarrhea. Information about severe gastrointestinal AEs as well as antiemetic/antidiarrheal use will be collected in the CRF/AE form. For detailed information concerning the management of gastrointestinal AEs, please refer to Section 6.6.1.

8.3.4.12. Acute Renal Events

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

8.3.4.13. Metabolic Acidosis, Including Diabetic Ketoacidosis

Ketoacidosis, a serious lifethreatening condition requiring urgent hospitalization, has been reported rarely in participants with T2DM. Participants who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting BG levels, as ketoacidosis may be present even if BG levels are less than 13.9 mmol/L (250 mg/dL). If ketoacidosis is suspected, participant should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

8.3.4.14. Amputation/Peripheral Revascularization

All cases of amputation and peripheral revascularization should be reported as an AE.

8.3.4.15. Major Depressive Disorder/Suicidal Ideation

The prevalence of depressive symptoms and disorders is increased in participants with T1DM or T2DM (ADA 2023a). Any AE of major depressive disorder or suicidal ideation should be reported.

8.3.5. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

8.4. Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity parameters are not evaluated in this study.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan (SAP) 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

The alternative hypotheses for the primary and key secondary objective are as follows,

- $H_{5,1}$, $H_{10,1}$, and $H_{15,1}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in HbA1c change from baseline at Week 40 respectively.
- $H_{5,2}$, $H_{10,2}$, and $H_{15,2}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in proportion of participants achieve HbA1c <7% at Week 40 respectively.
- $H_{5,3}$, $H_{10,3}$, and $H_{15,3}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in FSG change from baseline at Week 40 respectively.
- $H_{5,4}$, $H_{10,4}$, and $H_{15,4}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in proportion of participants achieve HbA1c ≤6.5% at Week 40 respectively.
- $H_{5,5}$, $H_{10,5}$, and $H_{15,5}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in body weight change from baseline at Week 40 respectively.
- $H_{5,6}$, $H_{10,6}$, and $H_{15,6}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in proportion of participants achieve HbA1c <5.7% at Week 40 respectively.

9.1.1. Multiplicity Adjustment

The primary and the key secondary objectives will be evaluated align to both the treatment-regimen estimand and the efficacy estimand. No multiplicity adjustment will be made for conducting analysis aligned to the two estimands.

A prespecified graphical scheme (Bretz et al. 2009; Bretz et al. 2011) will be implemented to control the family-wise error rate at a 2-sided alpha level of 0.05. This graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all endpoints (Bretz et al. 2009; Bretz et al. 2011; Alosh et al. 2014).

The testing scheme will be fully detailed in the SAP. The testing scheme will be finalized before database lock.

9.2. Analyses Sets

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

Population/Analysis Set	Description
Screened population	All participants who signed informed consent
Randomized population	All participants who are randomly assigned to a treatment group.
Modified intention-to-treat (mITT) population	All randomly assigned participants who are exposed to at least 1 dose of study intervention.
Efficacy analysis set (EAS): This analysis set will be used to estimate the efficacy estimand for all efficacy objectives	Data obtained during Study Period II from the mITT population, excluding data after initiating rescue antihyperglycemic medication or stopping study intervention.

Full analysis set: This analysis set will be used to estimate the treatment-regimen estimand for the primary and key secondary objectives	Data obtained during Study Period II from the mITT population, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.
Safety analysis set (SS): This analysis set will be used to assess the safety of study treatment	Data obtained during Study Periods II or III from the mITT population, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.

9.3. Statistical Analyses

9.3.1. General Considerations

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol (section 9.3) and in the SAP, where appropriate. Adjustments to the planned analyses will be described in the final clinical study report (CSR).

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

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

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval will be calculated at 95%, 2-sided. In statistical summaries and analyses, all data will be analyzed by randomized treatment assignment. Participants will be analyzed according to the treatment they were randomly assigned to, regardless of the treatment actually received.

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

Efficacy analyses will use the full analysis set (FAS) to evaluate the treatment-regimen estimand and the efficacy analysis set to evaluate the efficacy estimand. Safety will be assessed using safety analysis set (SS). Selected safety analyses may be conducted after excluding data on rescue therapy or data after starting another antihyperglycemic medication.

Summary statistics for continuous measures will include sample size, mean, standard deviation (SD), median, minimum, and maximum. The analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time will be a mixed model for repeated measures (MMRM) with terms:

- treatment,
- visit,
- treatment-by-visit interaction,
- any past prior use (yes or no) of any antihyperglycemic medication,
- baseline HbA1c category [≤8.5% (≤69 mmol/mol) or >8.5% (>69 mmol/mol)],
- and baseline measurement as a covariate.

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

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

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

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

9.3.2. Treatment Group Comparability

9.3.2.1. Participant Disposition

Frequency counts and percentages of all participants screened, randomized, and receiving at least 1 dose of study intervention will be presented by treatment groups. A listing of randomized participants not receiving study intervention will be provided. Of the participants in the randomized population, frequency, counts and percentages of participants completing the study, prematurely discontinuing the study, including the reason for premature discontinuation; and prematurely discontinuing study intervention including the reason for premature discontinuation of study intervention will be presented by treatment group. A Kaplan-Meier analysis of time from randomization to premature discontinuation from study by treatment group will be provided.

9.3.2.2. Participant Characteristics

Demographics will be summarized by treatment group using the randomized population. Medical history and concomitant illness will be summarized using the mITT population.

9.3.2.3. Concomitant Therapy

Concomitant medications will be summarized by anatomical therapeutic chemical classification and treatment group using the mITT population. In particular, the time of initiation of rescue therapy for severe, persistent hyperglycemia will be analyzed and summarized.

9.3.2.4. Treatment Compliance

A Kaplan-Meier analysis of time from randomization to premature study intervention discontinuation by treatment group will be provided.

Treatment compliance is defined as taking at least 75% of required injections of study intervention. Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment arm using the mITT population.

9.3.3. Primary Endpoint(s) Analysis

The primary endpoint for this study is HbA1c change from baseline at Week 40. This endpoint will be used to evaluate the primary objective of the study for both the treatment-regimen and efficacy estimands (Section 3).

The alternative hypothesis corresponding to the primary objective is as follows: tirzepatide 5 mg, and/or 10 mg, and/or 15 mg is superior to placebo with respect to HbA1c change from baseline at Week 40 (Section 9.1).

The primary efficacy analysis will be guided by the "treatment-regimen" estimand defined in Section 3. This assessment will analyze change from baseline in HbA1c to Week 40 using an analysis of covariance (ANCOVA) with terms: treatment, any past prior use (yes or no) of any antihyperglycemic medication, and baseline HbA1c as a covariate. The ANCOVA analysis will be conducted using FAS (section 9.2). Missing HbA1c values at Week 40 will be imputed using multiple imputation. Details regarding missing data will be included in the SAP. Statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

To explore the treatment efficacy without the influence of rescue therapy, the primary endpoint will be conducted on the "efficacy" estimand. This assessment will be conducted using efficacy analysis set (EAS) dataset (section 9.2). The primary analysis model for HbA1c measurements over time will be a MMRM. The response variable of MMRM will be change in HbA1c values from baseline obtained at each scheduled postbaseline visit. The independent variables of the MMRM model are treatment, visit, and treatment-by-visit interaction, any past prior use (yes or no) of any antihyperglycemic medication, baseline HbA1c and baseline HbA1c-by-visit interaction. Missing data will be addressed by the MMRM model under missing at random assumption. No explicit imputation methods for missing data will be employed.

An unstructured covariance structure will model the relationship of within-patient errors. If the analysis fails to converge, the following variance-covariance matrix will be used (in order) until convergence is achieved: heterogeneous compound symmetry, compound symmetry, and first-order autoregressive. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

9.3.4. Secondary Endpoints Analysis

The secondary study objectives subject to type 1 error rate control are as follows:

- Superiority of tirzepatide dose(s) to placebo relative to proportion of participants achieving the target value of HbA1c <7.0% (<53 mmol/mol) at Week 40
- Superiority of tirzepatide dose(s) to placebo relative to change in FSG (central laboratory) at Week 40
- Superiority of tirzepatide dose(s) to placebo relative to proportion of participants achieving the target value of HbA1c ≤6.5% (≤48 mmol/mol) at Week 40
- Superiority of tirzepatide dose(s) to placebo relative to change in body weight from baseline to Week 40
- Superiority of tirzepatide dose(s) to placebo relative to proportion of participants achieving the target value of HbA1c <5.7% (<39 mmol/mol) at Week 40

The type 1 error-controlled strategy for the primary and secondary endpoints will be described in the SAP. Key secondary objectives will be evaluated based on the treatment-regiment and efficacy estimands (Section 3), similar to the primary objective.

Analysis of change from baseline in body weight and FSG at Week 40 will be conducted in a manner similar to the primary efficacy analyses (Section 9.3.1). Baseline HbA1c category [≤8.5% (≤69 mmol/mol) or >8.5% (>69 mmol/mol)] and baseline of the corresponding variable will be added in the model for body weight and FSG.

Comparisons among treatments relative to the proportion of participants achieving the HbA1c target value of <7.0% (<53 mmol/mol), ≤6.5% (≤48 mmol/mol), and <5.7% (<39 mmol/mol) at Week 40 will be conducted using a logistic regression analysis with terms: treatment, any past prior use (yes or no) of any antihyperglycemic medication and baseline HbA1c as a covariate.

9.3.6. Safety Analyses

Safety assessments will be done using SS dataset (See section 9.2) irrespective of adherence to study intervention or initiation of rescue therapy. Selected safety analyses may be conducted after excluding data after the introduction of another antihyperglycemic therapy.

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized MedDRA Queries.

Summary statistics will be provided for incidence of TEAEs, SAEs, study discontinuation due to AEs, study intervention discontinuation due to AEs, deaths, and other cardiovascular endpoints. Counts and proportions of participants experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

9.3.6.1. Hypoglycemic Events

Incidence of documented hypoglycemia events and severe hypoglycemia will be compared between tirzepatide doses and placebo. Rate of hypoglycemic episodes will be analyzed using a generalized linear mixed-effects model assuming negative binomial distribution for hypoglycemic episodes if data warrant. Selected safety analyses may be conducted after excluding data after the introduction of another antihyperglycemic therapy.

9.3.6.2. Gastrointestinal Events

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

9.3.6.3. Adjudicated Cardiovascular Events

Listings of deaths, myocardial infarctions, strokes, and hospitalization for unstable angina confirmed by an independent clinical endpoint committee will be provided. The dates of

randomization, event, first dose and last dose of study intervention, and time from randomization to the event will be listed.

9.3.6.4. Central Laboratory Measures and Vital sign

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

The analysis model to make comparisons among treatment groups, relative to continuous change from baseline values assessed over time will be an MMRM, with terms: treatment, visit, and treatment-by-visit interaction, any past prior use (yes or no) of any antihyperglycemic medication, baseline HbA1c category [≤8.5% (≤69 mmol/mol) or >8.5% (>69 mmol/mol)] and baseline measurement as a covariate. An unstructured covariance structure will model the relationship of within-patient errors.

The percentages of participants with treatment-emergent abnormal, high, or low laboratory measures at any time will be summarized and compared between treatment groups by using Fisher's exact test. A treatment-emergent abnormal value is defined as a change from normal value at baseline to an abnormal value at any time during Periods II and III.

9.3.7. Other Analyses

9.3.7.1. Subgroup Analyses

Subgroup analyses of change in HbA1c from baseline to Week 40 will be provided by age, gender, duration of diabetes, and baseline HbA1c (≤8.5% [≤69 mmol/mol] and >8.5% [>69 mmol/mol]).

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.

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

9.5. Sample Size Determination

Participants will be randomized in a CCI ratio to tirzepatide 5 mg, 10 mg, 15 mg, or placebo.

The trial is powered to assess superiority of tirzepatide 5 mg, 10 mg, or 15 mg versus placebo in parallel relative to change from baseline in HbA1c at Week 40 under the following assumptions:

- use of 2-sample t-test to compare treatment means utilizing HbA1c data collected before initiation of any rescue medication and premature treatment discontinuation;
- up to CCI participants in tirzepatide arms and up to CCI participants in placebo arm initiating any rescue medication or premature treatment discontinuation;
- at least CCI (placebo adjusted) mean reduction in HbA1c for the tirzepatide doses; and
- a common SD of CCI

On the basis of these assumptions, randomizing 200 participants using a CCI randomization ratio to tirzepatide 5 mg (50 participants), tirzepatide 10 mg (50 participants), tirzepatide 15 mg

(50 participants), and placebo (50 participants) will provide at least CCI power to establish superiority for a tirzepatide dose compared to placebo at a 2-sided significance level of CCI. Furthermore, this sample size will ensure at least CCI power for the HbA1c superiority evaluation utilizing all available HbA1c data at Week 40 with missing data imputed with a conservative multiple imputation method, provided that the mean reduction in HbA1c for the tirzepatide doses is at least CCI (placebo adjusted) and SD increases to no more than CCI due to the inclusion of data on rescue medications, inclusion of data after premature treatment discontinuation, and missing data imputation.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

10.1.3. Informed Consent Process

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

10.1.4. Data Protection

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

10.1.5. Committees Structure

Adjudication of major adverse cardiovascular events, death, and pancreatic AEs will be performed for this study. Section 8.3.4 outlines additional information on adjudication committee.

10.1.6. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set

would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data.

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

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

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

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

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records 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 (EDC) 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 EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data (participant-focused outcome instrument) and other data EQ-5D-5L, IWQOL-Lite-CT will be collected by the participant, via a paper source document and will be transcribed by the authorized study personnel into the EDC system.

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

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

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

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in 10.1.7.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.10. Publication Policy

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

10.1.11. Investigator Information

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

10.2. 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 and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Clinical Laboratory Tests	Laboratory Name	Comments
Hematology[a]	Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd.	
Hemoglobin		
Hematocrit		
Erythrocyte count (RBCs)		
Mean cell volume		
Mean cell hemoglobin		
Mean cell hemoglobin concentration		
Leukocytes (WBCs)		
Differential		
Absolutes Count of:		
Neutrophils,		
Lymphocytes		
Monocytes		
Eosinophils		
Basophils		
Platelets		
Cell morphology (RBCs and WBCs), if indicated		
Clinical Chemistry		Assayed by Lilly-designated laboratory
Sodium		
Potassium		

Clinical Laboratory Tests	Laboratory Name	Comments
Chloride		
Bicarbonate		
Total bilirubin		
Direct bilirubin		
ALP		
ALT		
AST		
BUN		
Creatinine		
CK		
Uric acid		
Albumin		
Calcium		
Glucose		
Lipid Panel		Assayed by Lilly designated laboratory.
Cholesterol		
Triglycerides		
HDL-C		
LDL-C		Generated by Lilly-designated laboratory. If Triglycerides are >400, direct LDL will be measured.
VLDL-C		Generated by Lilly-designated laboratory.
Hepatitis serology		Assayed by Lilly-designated laboratory.
HCV testing		
HCV antibody		
HCV RNA		Performed only for participants who test positive for HCV antibody.
HBV testing		
HBV DNA		Performed only for participants who test positive for Hepatitis B core antibody.
Hepatitis B core antibody		
Hepatitis B surface antigen		
Hormones (female)		
Serum Pregnancy		Assayed by Lilly-designated laboratory.
Urine Pregnancy[b]		Assayed and evaluated locally
FSH		Assayed by Lilly-designated laboratory.
Urine Chemistry		Assayed by Lilly-designated laboratory.

Clinical Laboratory Tests	Laboratory Name	Comments
Albumin		
Creatinine		
Calculations		Generated by Lilly-designated laboratory.
eGFR (CKD-EPI)		
UACR		
Additional Testing		
HbA1c[a]	Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd.	
Calcitonin		Assayed by Lilly-designated laboratory.
Insulin		Assayed by Lilly-designated laboratory.
C-peptide		Assayed by Lilly-designated laboratory.
Pancreatic Amylase		Assayed by Lilly-designated laboratory.
Lipase		Assayed by Lilly-designated laboratory.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatinine kinase, CKD-EPI = Chronic Kidney Disease-Epidemiology; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; HDL-C = high-density lipoprotein cholesterol; hsCRP = C-Reactive Protein, high-sensitivity; IWRS = interactive web-response system; LDL-C = low-density lipoprotein cholesterol; RBC = red blood cells; UACR = urine albumin/creatinine ratio; VLDL-C = very-low-density lipoprotein cholesterol; WBC = white blood cells.

[a] Hematology (including blood smear) and HbA1c samples were destroyed by Shanghai Solid Waste Disposal Co., Ltd.

[b] For sites who can't perform urine pregnancy test, a local serum pregnancy test can be performed instead.

10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

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

When to collect samples after a systemic hypersensitivity event occurs

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

Obtain follow-up 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	Laboratory Test [a]
Collect from 30 minutes to 4 hours after the start of the event. ● Note: The optimal collection time is from 1 to 2 hours after the start of event.	total tryptase
	complements (C3, C3a, and C5a)
	cytokine panel (IL-6, IL-1β, IL-10 or any cytokine panel that includes these 3 cytokines)
Collect up to 12 hours after the start of the event.	Tirzepatide ADA
	Tirzepatide concentration

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

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

Events <u>NOT</u> Meeting the AE Definition

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

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

10.3.2. Definition of SAE

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

- Results in death
- Is life-threatening
  - The term life-threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
  - Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Other situations:
  - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical

intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product Complaint

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

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.
  Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the

participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in 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 and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

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

SAE Reporting via Paper Form

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

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

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

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

will review and then file it along with the IB or other relevant documents and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

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

Abbreviations: SERM = selective estrogen receptor modulators; WNOCBP = women not of childbearing potential. WOCBP = woman of child-bearing potential.

10.4.2. Contraception Guidance

10.4.2.1. Females

Women of childbearing potential and women not of childbearing potential may participate in this trial. See Section 10.4.1 for definitions and additional requirements related to contraception.

Women of childbearing potential who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

Women of childbearing potential who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to treatment exposure. See the protocol SoA for subsequent pregnancy testing requirements.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective. These forms of contraception must be used during the study and after the study for at least 30 days (1 month) after the last dose of the study intervention.

Examples of different forms of contraception:

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

10.4.2.2. Male

The table below describes contraception guidance for all men.

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for 5 half-lives of study intervention, plus 90 days, corresponding 120 days (4 months) after the last dose of the study intervention.
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study, and • for 120 days (4 months) after the last dose of the study intervention.
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

Examples of highly effective, effective and unacceptable methods of contraception can be found in Section 10.4.2.1.

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

Hepatic Evaluation Testing

See Section 8.2.7.1 for guidance on appropriate test selection.

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

In circumstances where required in accordance with local regulations, local laboratory testing may be performed in lieu of Lilly-designated central laboratory testing (in the table below).

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

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

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

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

Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA [b]
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology**
Ethyl glucuronide (EtG)	**Culture:**
Epstein-Barr virus (EBV) testing:	Blood
EBV DNA [b]	Urine

[a] Hepatic hematology samples were assayed by Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd. and were destroyed by Shanghai Solid Waste Disposal Co., Ltd.
[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.
[c] Not required if anti-actin antibody is tested.
[d] Not required if anti-smooth muscle antibody (ASMA) is tested.

10.6. Appendix 6: World Health Organization Classification of Diabetes and Diagnostic Criteria

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

Type 2 Diabetes Mellitus: Type 2 diabetes mellitus, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in T2DM, but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) due to an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with T2DM later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998).

10.7. Appendix 7: Protocol GPIU Standardized Protocols for the Measurement of Height, Weight and Waist Circumference

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEP wise approach to Surveillance (STEPS) (WHO 2017) (Available at: https://www.who.int/ncds/surveillance/steps/Section%204%20Step%202%20Physical%20Measurements.pdf) Accessed January 17, 2019.

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 centimeters (cm).

Measuring Weight

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

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

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

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

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

Measuring Waist Circumference

- Waist circumference should be measured at midpoint, between lower margin of least palpable rib and top of iliac crest (approximately 1 inch (2.54 cm) above the navel).
- Participants should be lightly clothed.

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.

10.8. Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Informed consent

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

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

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, medical history, AEs and product complaints, concomitant medications, diabetes education, reminding 7-point SMBG, reviewing diary.

Other alternative locations: Laboratory testing in local hospital is permitted based on the discretion of investigator with the approval of sponsor.

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: HbA1c and FSG at Visit 3 and Visit 11. The local laboratory must be qualified in accordance with applicable local regulations. Clinically significant laboratory findings could be recorded as an AE in the AE CRF at the discretion of investigator.

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.

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

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at Visit 1 are valid for a maximum of 60 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 60 days from Visit 1 to Visit 3: the participant will proceed to the next study visit per the usual SoA, provided that Visit 3 must be conducted within 60 days from Visit 1.
    - 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 60 days from Visit 1: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF.

Adjustments to visit windows

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

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 1 (Screening)	No change.
Visit 2	At least 4 days before Visit 3.
Visit 3 (Randomization)	Within 60 days after Visit 1.
Visit 3 through 8	Within 7 days before or after the intended date.
Visit 9 through 10	Within 14 days before or after the intended date.
Visit 11 or Visit 99	Within 14 days before the intended date, or up to 28 days after the intended date.
Visit 801	No change.

For participants whose visits have extended windows at Visit 11, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.9. Appendix 9: Abbreviations and Definitions

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
blinding/masking	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
CFR	Code of Federal Regulations
CHF	congestive heart failure
CK	creatine kinase
COA	clinical outcome assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form: a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer
CSR	clinical study report
CT	computed tomography
D. Bil	direct bilirubin
EAS	efficacy analysis set
ECG	electrocardiogram

EDC	electronic data capture
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.
EQ-5D-5L	European Quality of Life-Dimensions
ET	early termination
FAS	full analysis set
FBG	fasting blood glucose
FSG	fasting serum glucose
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GIP	glucose dependent insulinotropic polypeptide
GLP-1	glucagon like peptide-1
GPIU	I8F-MC-GPIU
HbA1c	hemoglobin A1c
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDF	International Diabetes Federation
IEC	Independent Ethics Committees
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB	Institutional Review Boards
ISR	injection site reaction
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
IWRS	Interactive Web Response System

MedDRA	Medical Dictionary for Regulatory Activities
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MEN2	multiple endocrine neoplasia syndrome type 2
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
mITT	modified intention to treat
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
OTC	over-the-counter
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
PRO	patient-reported outcome
QTL	quality tolerance limit
QW	once weekly
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation

SDP	single-dose pen
SMBG	self-monitoring of blood glucose
SoA	Schedule of Activities
SS	safety analysis set
SUSAR	Suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

11. References

[ADA] American Diabetes Association Professional Practice Committee; 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2023. *Diabetes Care.* 2023a; 46(Supple 1):S68–S96. https://doi.org/10.2337/dc23-S005.

[ADA] American Diabetes Association Professional Practice Committee; 6. Glycemic Targets: Standards of Medical Care in Diabetes-2023. *Diabetes Care.* 2023b;46(Supple 1):S97–S110. https://doi.org/10.2337/dc23-S006.

Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539-553.

Aroda VR, Ratner R. The safety and tolerability of GLP-1 receptor agonists in the treatment of type 2 diabetes: a review. *Diabetes Metab Res Rev* 2011;27(6):528-542.

Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med.* 2014;33(4):693-713.

Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol.* 2006;101(10):2379-2400.

Battelino T, Bergenstal R, Rodriguez A. et al. Effect of tirzepatide versus insulin degludec on glycaemic control captured with continuous glucose monitoring in patients with type 2 diabetes (SURPASS-3 CGM). In *Diabetologia* (Vol. 64, No. Suppl 1, pp. 244-244); 2022. New York, NY, United States: Springer.

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. *Stat Med*. 2009;28(4):586-604. https://doi.org/10.1002/sim.3495

Bretz F, Posch M, Glimm E, et al. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J*. 2011;53(6):894-913. https://doi.org/10.1002/bimj.201000239

Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: The SURPASS-5 randomized clinical trial. *JAMA*. 2022;327(6):534–545. https://doi.org/10.1001/jama.2022.0078

Danne T, Philotheou A, Goldman D, et al. A randomized trial comparing the rate of hypoglycemia – assessed using continuous glucose monitoring – in 125 preschool children with type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study). *Pediatr Diabetes*. 2013;14(8):593-601. https://doi.org/10.1111/pedi.12051

Del Prato S, Kahn SE, Pavo I, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet*. 2021;398(10313):1811-1824. https://doi.org/10.1016/S0140-6736(21)02188-7

EuroQol Research Foundation. EQ-5D-5L user guide, version 3.0. Updated September 2019. https://euroqol.org/publications/user-guide

[FDA's guidance on PROs] Food and Drug Administration. [WWW document]. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. URL http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM193282.pdf (accessed in December 2022)

Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;385(6):503-515. https://doi.org/10.1056/NEJMoa2107519

Gastaldelli A, Cusi K, Lando LF, et al. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in patients with type 2 diabetes (SURPASS-3 MRI). In *Diabetologia* (Vol. 64, No. Suppl 1, pp. 219-220); 2022. New York, NY, United States: Springer.

[IDF] International Diabetes Federation. IDF Diabetes Atlas. 10th ed. 2021. Accessed Jan 8, 2023. https://diabetesatlas.org/atlas/tenth-edition/

Koizumi M, Takada T, Kawarada Y, et al. JPN guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2006;13(1):25-32. https://doi.org/10.1007/s00534-005-1048-2

Kolotkin RL, Ervin CM, Meincke HH, et al. Development of a clinical trials version of the impact of weight on quality of life-lite questionnaire (IWQOL-Lite clinical trials version): results from two qualitative studies. *Clin Obes.* 2017;7(5):290-299. https://doi.org/10.1111/cob.12197

Kolotkin RL, WilliamsV, Ervin, CM, Meincke HH, Qin S, Smith LvH, Fehnel SE. Validation of a new measure of quality of life in obesity trials: IWQOL –Lite Clinical Trials Version. Poster presented at: *ObesityWeek* 2018

Kolotkin RL, Williams VSL, Ervin CM, et al. Validation of a new measure of quality of life in obesity trials: impact of weight on quality of life-lite clinical trials version. *Clin Obes.* 2019;9(3):e12310. https://doi.org/10.1111/cob.12310

Lind M, Imberg H, Coleman RL, Nerman O, Holman RR. Historical HbA1c Values May Explain the Type 2 Diabetes Legacy Effect: UKPDS 88. *Diabetes Care*. 2021; 44 (10): 2231–2237. https://doi.org/10.2337/dc20-2439

Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet*. 2021;398(10300):583-598. https://doi.org/10.1016/S0140-6736(21)01443-4

Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab*. 2016;18(3):203-216.

Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet*. 2021;398(10295):143-155. https://doi.org/10.1016/S0140-6736(21)01324-6. Erratum in: *Lancet*. 2021;398(10296):212. https://doi.org/10.1016/S0140-6736(21)01556-7

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons Inc.;1987.

Steinberg WM, Buse JB, Ghorbani MLM, Ørsted DD, Nauck MA, LEADER Steering Committee; LEADER Trial Investigators. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: Results from the LEADER randomized trial. *Diabetes Care*. 2017a;40(7):966-972. [Erratum in: Diabetes Care. 2018 Jul;41(7):1538.]

Steinberg WM, Rosenstock J, Wadden TA, Donsmark M, Jensen CB, DeVries JH. Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: Secondary analyses of pooled data from the SCALE clinical development program. *Diabetes Care*. 2017b;40(7):830-848.

Weinberg ME, Bacchetti P, Rushakoff RJ. Frequently repeated glucose measurements overestimate the incidence of inpatient hypoglycemia and severe hyperglycemia. *J Diabetes Sci Technol*. 2010;4(3):577-582. https://doi.org/10.1177/193229681000400311

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