Protocol Amendment I8F-MC-GPIM(b)

A Randomized, Phase 3, Double-blind Trial Comparing the Effect of the Addition of Tirzepatide versus the Addition of Placebo to Titrated Basal Insulin on Glycemic Control in Chinese Participants with Type 2 Diabetes (SURPASS-CN-INS)

NCT05691712

Approval Date: 17-Nov-2023

Title Page

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A Randomized, Phase 3, Double-blind Trial Comparing the Effect of the Addition of Tirzepatide versus the Addition of Placebo to Titrated Basal Insulin on Glycemic Control in Chinese Participants with Type 2 Diabetes (SURPASS-CN-INS)

Protocol Number: I8F-MC-GPIM

Amendment Number: b

Compound: LY3298176

Brief Title:

Comparing the Effect of the Addition of Tirzepatide or Placebo to Titrated Basal Insulin on Glycemic Control in Chinese Participants with Type 2 Diabetes

Study Phase: Phase 3

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s): NA

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

Document ID: VV-CLIN-135512

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment a	*30-Mar-2023*
Original Protocol	*12-July-2022*

Amendment [a]

Overall Rational for the Amendment:

This clinical protocol has been amended mainly to add Visit 99 for the purpose of collecting additional data at Week 40 and to remove the test for anti-glutamic acid decarboxylase (GAD) antibody. The overall changes and rationale for the changes made to this protocol are described in the following table. Please be noted that minor edits have been made throughout the protocol, which are not captured in the amendment summary table.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA) 4.1.1. Overview of Study Periods Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances	Visit 99 was added for 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.	Visit 99 will be used for collecting additional data, including HbA1c, body weight, fasting serum glucose, vital signs (2 sitting blood pressure and pulse rate), adverse events, concomitant medications, and hypoglycemic events collected in the diary and reviewed by the investigator at Week 40.
1.3. Schedule of Activities (SoA) 10.2. Appendix 2: Clinical Laboratory Tests	The test for anti-glutamic acid decarboxylase (GAD) antibody was removed.	As expected, the number of subjects being positive for anti-GAD antibody and the likelihood of future exploratory analyses are low.
1.3. Schedule of Activities (SoA)	"Dispense BG meter/supplies, as needed" was checked for Visits 19 and 99 and early termination (ET) Visit.	Blood glucose (BG) meter/supplies will be used for testing blood glucose.
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
3. Objectives, Endpoints, and Estimands		
1.1. Synopsis 3. Objectives, Endpoints, and Estimands	"Occurrence of hypoglycemic episodes" was changed to "Hypoglycemic episodes".	This revision was made for description consistency.
1.1 Synopsis 3. Objectives, Endpoints, and Estimands	"Endpoints" was changed to "Endpoints/Estimands" in the header row of the table in each section.	Both population-level summaries and endpoints are presented in the table of each section. This revision was made for accuracy.
3. Objectives, Endpoints, and Estimands	For the description of "treatment condition", "adheres to treatment without antihyperglycemic rescue medication" was removed.	This revision was made to avoid the repetition with the description of the "intercurrent event".
9.2. Analyses Sets	Per-protocol population was removed.	According to ICH E9 (R1) addendum, it may not be possible to construct a relevant estimand to which analysis of the Per Protocol Set is aligned.
9.3.2.1. Participant Disposition	In the 3rd row, "mITT" was changed to "randomized".	This is a correction.
10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event	Laboratory tests for complements C3a and C5a were removed.	The central laboratory in Beijing does not have the test setup for complements C3a and C5a.

Amendment [b]

Overall Rational for the Amendment:

This clinical protocol has been amended mainly to update the value of hemoglobin and clinical laboratories and specimen disposal unit information required for Human Genetic Resources filing. The overall changes and rationale for the changes made to this protocol are described in the following table.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion criterion 29: Hemoglobin of males should be less than 110 g/L and hemoglobin of females should be less than 100 g/L, instead of 11.0 g/L and 10.0 g/L.	The value of hemoglobin was wrong. This revision was made to correct this error.
10.2 Appendix 2	Added clinical laboratories and specimen disposal unit information for Hematology and HbA1c test.	The clinical laboratories and specimen disposal unit information are required for Human Genetic Resources filing.
10.5.2. Hepatic Monitoring Tests	Added clinical laboratories and specimen disposal unit information for Hepatic Hematology Panel test.	The clinical laboratories and specimen disposal unit information are required for Human Genetic Resources filing.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Randomized, Phase 3, Double-blind Trial Comparing the Effect of the Addition of Tirzepatide versus the Addition of Placebo to Titrated Basal Insulin on Glycemic Control in Chinese Participants with Type 2 Diabetes (SURPASS-CN-INS).

Brief Title:

Comparing the Effect of the Addition of Tirzepatide or Placebo to Titrated Basal Insulin on Glycemic Control in Chinese Participants with Type 2 Diabetes

Regulatory Agency Identifier Number(s): NA

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).

Initial pharmacological therapy for T2DM is based on stepwise addition of oral antihyperglycemic medications (OAMs) when patients become persistently hyperglycemic despite treatment with lifestyle measures (CDS 2021). With further progression of the disease, many patients eventually require injectable therapies to maintain adequate glycemic control. Basal insulin, such as insulin glargine, is a common choice when initiating injectable therapy, but there are drawbacks to treating patients with T2DM with a single injection of basal insulin. For instance, a significant proportion of patients is not able to achieve glycemic targets (Rosenstock et al. 2014), and hypoglycemia and weight gain are the main limitations of insulin therapy (ADA 2022a). In real world, limited insulin dose titration was also one of barriers to achieving better glycemic control with insulin (Ji et al. 2017). Therefore, it is important to provide additional treatment options for patients that allow for enhanced glucose control and weight loss while preserving an overall acceptable benefit/risk profile.

Tirzepatide (LY3298176) is a once weekly GIP (glucose dependent insulinotropic polypeptide) and GLP-1 (glucagon like peptide-1) receptor agonist (RA). It is a 39 amino acid synthetic peptide with agonist activity at both the GIP and 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 subcutaneously. Tirzepatide received regulatory approval in the United States on 13 May 2022, indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

The international multicenter Phase 3 Study SURPASS-5 (GPGI) compared the effect of addition of tirzepatide versus placebo in patients with T2DM inadequately controlled on insulin glargine with or without metformin. In this study, tirzepatide demonstrated superior efficacy on glycemic control and body weight loss on background of titrated basal insulin with an overall safety profile consistent to GLP-1 RAs (Dahl et al. 2022).

Study SURPASS-CN-INS (I8F-MC-GPIM [GPIM]) will compare tirzepatide (3 doses) to placebo, added to titrated once-daily basal insulin glargine in Chinese participants with T2DM previously treated with insulin glargine alone or in combination with metformin with or without SGLT-2i (sodium-glucose transport protein 2 inhibitor). There are no available published reports on the effects of the combination of basal insulin and a long-acting, once weekly (QW) GIP and GLP-1 RA on blood glucose (BG) in Chinese patients to date. The combination of insulin glargine with tirzepatide is expected to provide improved glucose control and attenuate the weight gain and hypoglycemia risk associated with the more intensive titration and higher daily doses of insulin glargine.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints/Estimands
Primary	
• To demonstrate superiority of QW tirzepatide 10 mg and/or 15 mg versus placebo when added to titrated basal insulin alone or in combination with metformin with or without SGLT-2i, with respect to glycemic control at 40 weeks for:	• Mean change in HbA1c from baseline
Key Secondary (controlled for type 1 error)	
• To demonstrate superiority of QW tirzepatide 5 mg versus placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i, with respect to glycemic control at 40 weeks for:	• Mean change in HbA1c from baseline
• To demonstrate superiority of QW tirzepatide 5 mg, 10 mg, and/or 15 mg versus placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i, at 40 weeks for:	• Mean change in body weight from baseline • Proportion of participants with HbA1c <7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol) • Mean change in fasting serum glucose (central laboratory) from baseline
• To demonstrate superiority of QW tirzepatide 10 mg and/or 15 mg versus placebo when added to titrated basal insulin glargine alone or in combination	• Proportion of participants with HbA1c <5.7% (39 mmol/mol)

with metformin with or without SGLT-2i, at 40 weeks for:	
Additional Secondary (not controlled for type 1 error)	
<u>Efficacy</u> • To compare QW tirzepatide 5 mg to placebo at 40 weeks for:	• Proportion of participants with HbA1c <5.7% (39 mmol/mol)
• To compare QW tirzepatide 5 mg, 10 mg, and 15 mg to placebo at 40 weeks for:	• Mean 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% from baseline • Percentage change from baseline in daily mean insulin glargine dose • Proportion of participants with HbA1c <7.0%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.0 mmol/L [54 mg/dL] or severe hypoglycemia) • Proportion of participants with HbA1c ≤6.5%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.0 mmol/L [54 mg/dL] or severe hypoglycemia) • Proportion of participants with HbA1c <7.0%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.9 mmol/L [70 mg/dL]) • Proportion of participants with HbA1c ≤6.5%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.9 mmol/L [70 mg/dL])
<u>Safety</u> • To compare QW tirzepatide 5 mg, 10 mg, and 15 mg to placebo to the end of safety follow up for:	• TEAEs • Early discontinuation of study drug due to AEs • Adjudicated pancreatitis • Serum calcitonin

	• Incidence of allergic and hypersensitivity reactions • Mean change in systolic and diastolic blood pressure and pulse rate from baseline • Hypoglycemic episodes • Incidence of initiation of rescue therapy for severe, persistent hyperglycemia

Abbreviations: AE = adverse events; HbA1c = hemoglobin A1c; QW = once weekly; SGLT-2i = sodium-glucose transport protein 2 inhibitor; TEAE = treatment emergent adverse events.

Overall Design

Study GPIM is a multicenter, randomized, double-blind, parallel, placebo-controlled Phase 3 study which will assess the efficacy and safety of the addition of 5 mg, 10 mg, or 15 mg tirzepatide, as compared with placebo in participants with T2DM as an add-on to titrated basal insulin alone or in combination with metformin with or without SGLT-2i over a 40-week treatment. Approximately, 256 participants with T2DM who have been treated with insulin glargine (U100) once daily alone or in combination with metformin with or without SGLT-2i ≥90 days prior to Visit 1, will be randomized.

Brief Summary:

The purpose of this study is to compare the effect of the addition of tirzepatide or placebo to titrated basal insulin on glycemic control in Chinese participants with type 2 diabetes.

The study will consist of 3 periods:

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

Study Population:

Chinese participants with type 2 diabetes previously treated with basal insulin glargine (U100), once daily alone or in combination with metformin with or without SGLT-2i.

Number of Participants:

Approximately 256 participants (64 participants per treatment group or placebo) will be randomized.

Intervention Groups and Duration:

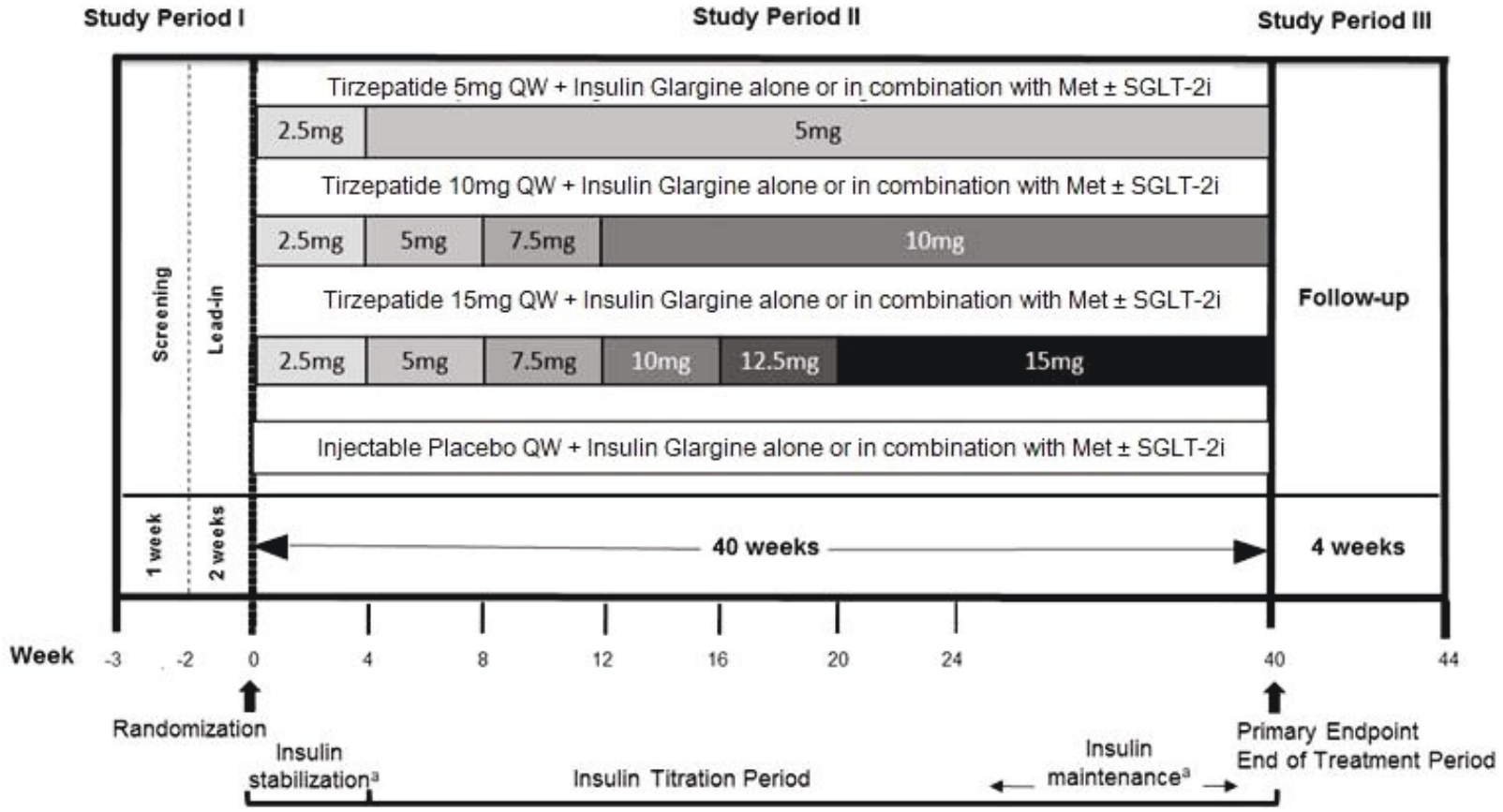
Study GPIM will consist of 3 periods: an approximately 3-week screening/lead in period, followed by a 40-week treatment period and a 4-week safety follow up period. Participants will be randomized in a 1:1:1:1 ratio (tirzepatide 5 mg, tirzepatide 10 mg, tirzepatide 15 mg, and placebo).

Ethical Considerations of Benefit/Risk:

The participants in this trial may benefit from improvement in glycemic control and weight loss, and the potential benefits outweigh the risks related to tirzepatide use, considering comprehensive analysis of all safety events in completed and ongoing clinical studies with tirzepatide.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: Met = metformin; QW = once weekly; SGLT-2i = sodium-glucose transport protein 2 inhibitor.

[a] Stabilization Period = first 4 weeks after randomization, with restricted insulin dose adjustments.
Basal insulin Titration Period = Weeks 4 to 40 (end of treatment), with unrestricted insulin dose adjustments.
Maintenance Period = Weeks 24 to 40 (end of treatment), the period when basal insulin dose is expected to be stable.

1.3. Schedule of Activities (SoA)

The Schedule of Activities (SoA) described below should be followed for all participants enrolled in Study GPIM. However, for those participants whose participation in this study is affected by any unexpected circumstances such as the novel Coronavirus Disease 2019 (COVID-19), please refer to Section 10.8 for additional instructions.

	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**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**99[b]**	**ET[c]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**32**	**40**	**40**		**44**
Allowable Deviation (days)[d]	-	**±3**	**±7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**		**±7**
Fasting Visit[e]			**X**		**X**		**X**				**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Telephone Visit						**X**		**X**		**X**		**X**		**X**								
Informed consent	X																					
Randomization			X																			
Clinical Assessments																						
Medical history[f]	X																					
Physical Examination	X																		X		X	
Height	X																					
Weight	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
Electrocardiogram			X																X		X	X
Vital signs (2 sitting BP and PR)[g]	X		X	X	X		X		X		X		X		X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundoscopic examination[h]		X																				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**99[b]**	**ET[c]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**32**	**40**	**40**		**44**
Allowable Deviation (days)[d]	-	**±3**	**±7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**		**±7**
Fasting Visit[e]			**X**		**X**		**X**				**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Telephone Visit						**X**		**X**		**X**		**X**		**X**								
Review hypoglycemic events collected in the diary			X	X	X	X	X	X	X	X	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																				
Dispense BG meter/supplies, as needed		X	X	X	X		X		X		X		X		X	X	X	X	X	X	X	
Study drug and insulin glargine injection training[j]			X																			
Hand out diary, instruct in use[j]		X	X	X	X		X		X		X		X		X	X	X	X	X		X	
Review fasting/4-point SMBG[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Remind participants about 7-point SMBG[l]		X														X		X				
Review 7-point SMBG values collected in the diary			X														X		X		X[m]	

	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**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**99[b]**	**ET[c]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**32**	**40**	**40**		**44**
Allowable Deviation (days)[d]	-	**±3**	**±7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**		**±7**
Fasting Visit[e]			**X**		**X**		**X**				**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Telephone Visit						**X**		**X**		**X**		**X**		**X**								
Dispense study drug and injection supplies			X				X				X		X		X	X	X	X				
Observe participant administer study drug[n]			X																			
Participant returns study drugs and injection supplies							X				X		X		X	X	X	X	X		X	
Assess study drug compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Review insulin dose and adjustment per TTT algorithm			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Assess compliance with insulin dose adjustment per TTT algorithm[o]				X	X		X		X		X		X		X	X	X	X	X		X	
Laboratory Tests																						
Serum pregnancy test[p]	X																					
Urine pregnancy test[q]			X										X				X		X		X	
Follicle-stimulating hormone test[r]	X																					
Chemistry panel	X[s]												X				X		X		X	X
Serum glucose			X		X		X				X		X		X	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**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**99[b]**	**ET[c]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**32**	**40**	**40**		**44**
Allowable Deviation (days)[d]	-	±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		±7
Fasting Visit[e]			X		X		X				X		X		X	X	X	X	X	X	X	X
Telephone Visit						X		X		X		X		X								
Lipid panel			X														X		X		X	X
Urinary albumin/creatinine ratio	X[s]																		X		X	X
eGFR (CKD-EPI)[t]	X[s]												X				X		X		X	X
Calcitonin	X[s]												X				X		X		X	X
Hematology	X[s]												X				X		X		X	X
HbA1c	X		X				X				X		X		X	X	X	X	X	X	X	X
Pancreatic amylase	X[s]												X				X		X		X	X
Lipase	X[s]												X				X		X		X	X
Patient Reported Outcomes-to be completed by participant at site[u]																						
APPADL			X																X		X	
IW-SP			X																X		X	
DTSQs			X																			
DTSQc																			X		X	
EQ-5D-5L			X																X		X	

Abbreviations: APPADL = Ability to Perform Physical Activities of Daily Living; BG = blood glucose; BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; DTSQc = Diabetes Treatment Satisfaction Questionnaire change; DTSQs = Diabetes Treatment Satisfaction Questionnaire status; ECG = electrocardiogram; eCRF =electronic case report form; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Qualtiy of Life- 5

dimensions-5 levels; ET = early termination; F/U = follow-up; HbA1c = hemoglobin A1c; IW-SP = Impact of Weight on Self-Perception; PR = pulse rate; PRO = patient-reported outcome;; SMBG = self-monitored blood glucose; TTT = treat to target; Tx = treatment.

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

[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 collecting data, including HbA1c, body weight, fasting serum glucose, vital signs (2 sitting blood pressure and pulse rate), adverse events, concomitant medications, and hypoglycemic events collected in the diary and reviewed by the investigator.

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

[e] On visits 3, 5, 7, 11, 13, 15, 16, 17, 18, 19, 99, ET, and at follow-up, participants should be reminded to report to the site 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 drug(s), basal insulin, metformin (if used) or SGLT-2i (if used).

[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] 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.

[h] Dilated fundoscopic exam will be performed by a qualified eye care professional (ophthalmologist or optometrist) for all participants between Visit 2 and Visit 3, unless there is a contraindication to dilate the eye (ie. closed angle glaucoma), to exclude participants with proliferative diabetic retinopathy and/or diabetic macular edema, or nonproliferative diabetic retinopathy that requires acute treatment. The results from this exam will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy. Follow up dilated fundoscopic exam should be performed when clinically indicated, and, the results recorded on the retinopathy eCRF.

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

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

[k] Participants will be encouraged to collect a daily fasting BG, as well as a 4-point SMBG (3 before each meal and one at bedtime) once weekly between Visit 2 and 3, twice weekly from Visits 3 to 7 (Weeks 0 to 4) followed by weekly for the remainder of the treatment period.

[l] Participant is required to collect two 7-point SMBGs on nonconsecutive days in the 2-week period 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 7-point SMBG is not performed, then data from the most recent nonconsecutive 4-point SMBG profiles can be used. If more than two 7-point SMBG profiles are available, the two most recent nonconsecutive profiles should be used.

[m] Review 7-point SMBG values collected in the diary, only if applicable, based on previous study visit.

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

[o] Assessment of the participant's compliance to the TTT algorithm will be collected in the eCRF at Visits 4, 5, 7, 9, 11, 13, 15, 16, 17, 18, 19, and ET for the period since the previous clinic visit.

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

[q] A urine pregnancy test must be performed at Visit 3 with the result available prior to randomization and first injection of study drug(s) for women of childbearing potential only. Additional pregnancy tests will be performed at Visits 13, 17, and 19. Pregnancy tests may be also performed at the investigator's discretion during the study.

[r] Performed as needed to confirm postmenopausal status, see Section 10.4.1.

[s] Screening visit assessment will serve as baseline.

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

[u] 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 procedure.

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 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).

Initial pharmacological therapy for T2DM is based on stepwise addition of oral antihyperglycemic medications (OAMs) when patients become persistently hyperglycemic despite treatment with lifestyle measures (CDS 2021). With further progression of the disease, many patients eventually require injectable therapies to maintain adequate glycemic control. Basal insulin, such as insulin glargine, is a common choice when initiating injectable therapy, but there are drawbacks to treating patients with T2DM with a single injection of basal insulin. For instance, a significant proportion of patients is not able to achieve glycemic targets (Rosenstock et al. 2014), and hypoglycemia and weight gain are common side effects of therapy with insulin (ADA 2022a). In real world, limited insulin dose titration was also one of barriers to achieving better glycemic control with insulin (Ji et al. 2017). Therefore, it is important to provide additional treatment options for patients that allow for enhanced glucose control and weight loss while preserving an overall acceptable benefit/risk profile.

2.2. Background

Tirzepatide (LY3298176) is a once weekly GIP (glucose dependent insulinotropic polypeptide) and GLP-1 (glucagon like peptide-1) receptor agonist (RA). It is a 39 amino acid synthetic peptide with agonist activity at both the GIP and 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 subcutaneously. Tirzepatide (MOUNJARO™) received regulatory approval in the United States on 13 May 2022, indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

Five global Phase 3 studies (SURPASS clinical program, including GPGK, GPGL, GPGH, GPGM, and GPGI) were designed to assess the efficacy and safety of tirzepatide 5, 10, and 15 mg once weekly (40- or 52-week treatment duration at the primary endpoint) versus placebo or active comparators in adults with T2DM (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022). Results from the Phase 3 studies demonstrate that tirzepatide provides better glycemic control and superior weight loss, in a safe manner, for participants across the T2DM disease continuum.

The international multicenter Phase 3 Study SURPASS-5 (GPGI) compared the effect of the addition of tirzepatide versus placebo in participants with T2DM inadequately glycemic controlled on insulin glargine with or without metformin. Tirzepatide demonstrated superior improvements in glycemic control and body weight loss on background of titrated basal insulin compared to placebo. The risk of severe or clinically significant hypoglycemia (blood glucose

<3.0 mmol/L [54 mg/dL]) was similar across the treatment groups and the safety profile was consistent to the GLP-1 (RA) class.

The international multicenter Phase 3 Study SURPASS-AP-Combo (GPHO) compared the effect of tirzepatide versus titrated insulin glargine in participants with T2DM on metformin with or without a sulfonylurea. It was the first registration trial of tirzepatide that enrolled a majority of Chinese participants with T2DM. Tirzepatide demonstrated superior improvements in glycemic control and body weight loss compared with insulin glargine and showed consistent safety profile with other global SURPASS trials.

These data support continued development of tirzepatide as a therapy for T2DM in China.

Study SURPASS-CN-INS (I8F-MC-GPIM [GPIM]) will compare tirzepatide (3 doses) to placebo, added to titrated once-daily basal insulin glargine in Chinese participants with T2DM previously treated with insulin glargine alone or in combination with metformin with or without SGLT-2i (sodium-glucose transport protein 2 inhibitor). There is no evidence available on the effects of the combination of basal insulin and a long-acting, once weekly (QW) GIP and GLP-1 RA on glycemic control in Chinese patients to date. The combination of insulin glargine with tirzepatide is expected to provide improved glucose control and attenuate the weight gain and hypoglycemia risk associated with the more intensive titration and higher daily doses of insulin glargine.

2.3. Benefit/Risk Assessment

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

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

2.3.1. Risk Assessment

The most common AEs observed in the tirzepatide clinical trials in healthy participants and participants with T2DM have been GI effects. Other safety topics of interest include pancreatic safety, cardiovascular events, hypoglycemia, hypersensitivity reactions, and thyroid C-cell effects; refer to Section 8.3.4 for further details. Please refer to the IB Section 6 for more details.

2.3.2. Benefit Assessment

In global Phase 3 studies, tirzepatide demonstrated superior efficacy on glycemic control and body weight reduction as well as an improvement in different measures that are associated with increased risk of longer-term cardiometabolic complications in participants with T2DM (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022). The results indicate that clinically meaningful improvements in glucose control and body weight reductions with all tirzepatide doses could be achieved with minimal increased risk of hypoglycemia when added to titrated basal insulin.

2.3.3. Overall Benefit Risk Conclusion

The data from global Phase 3 studies (SURPASS clinical program) indicate that the safety and tolerability profile of tirzepatide is consistent with the safety profile of GLP-1 RA class (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022).

In the SURPASS program, the safety profile of tirzepatide was characterized in participants with T2DM. As expected, similar to the GLP-1 RA class, the most common AEs were GI related. For the key risk of acute pancreatitis, adjudication-confirmed cases were low in frequency in SURPASS program (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022). This risk is well understood by the healthcare community and is readily managed with risk minimization measure and monitored via routine pharmacovigilance.

Potential risks associated with tirzepatide are considered acceptable in this study. The participants in this trial may benefit from improvement in glycemic control and weight loss, and the potential benefits outweigh the risks related to tirzepatide use, considering comprehensive analysis of all safety events in completed and ongoing clinical studies with tirzepatide.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints/Estimands
Primary	
• To demonstrate superiority of QW tirzepatide 10 mg and/or 15 mg versus placebo when added to titrated basal insulin alone or in combination with metformin with or without SGLT-2i, with respect to glycemic control at 40 weeks for:	• Mean change in HbA1c from baseline
Key Secondary (controlled for type 1 error)	
• To demonstrate superiority of QW tirzepatide 5 mg versus placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i, with respect to glycemic control at 40 weeks for:	• Mean change in HbA1c from baseline
• To demonstrate superiority of QW tirzepatide 5 mg, 10 mg, and/or 15 mg versus placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i, at 40 weeks for:	• Mean change in body weight from baseline • Proportion of participants with HbA1c <7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol) • Mean change in fasting serum glucose (central laboratory) from baseline
• To demonstrate superiority of QW tirzepatide 10 mg and/or 15 mg versus placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i, at 40 weeks for:	• Proportion of participants with HbA1c <5.7% (39 mmol/mol)
Additional Secondary (not controlled for type 1 error)	
<u>Efficacy</u> • To compare QW tirzepatide 5 mg to placebo at 40 weeks for:	• Proportion of participants with HbA1c <5.7% (39 mmol/mol)

Objectives	Endpoints/Estimands
• To compare QW tirzepatide 5 mg, 10 mg, and 15 mg to placebo at 40 weeks for:	• Mean 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% from baseline • Percentage change from baseline in daily mean insulin glargine dose • Proportion of participants with HbA1c <7.0%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.0 mmol/L [54 mg/dL] or severe hypoglycemia) • Proportion of participants with HbA1c ≤6.5%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.0 mmol/L [54 mg/dL] or severe hypoglycemia) • Proportion of participants with HbA1c <7.0%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.9 mmol/L [70 mg/dL]) • Proportion of participants with HbA1c ≤6.5%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.9 mmol/L [70 mg/dL])
<u>Safety</u> • To compare QW tirzepatide 5 mg, 10 mg, and 15 mg to placebo to the end of safety follow up for:	• TEAEs • Early discontinuation of study drug due to AEs • Adjudicated pancreatitis • Serum calcitonin • Incidence of allergic and hypersensitivity reactions • Mean change in systolic and diastolic blood pressure and pulse rate from baseline • Hypoglycemic episodes

Objectives	Endpoints/Estimands
	• Incidence of initiation of rescue therapy for severe, persistent hyperglycemia
Tertiary	
• To compare QW tirzepatide 5 mg, 10 mg, and 15 mg to placebo at 40 weeks for:	• Mean change in lipids (total cholesterol, HDL, LDL, VLDL, non-HDL and TG) • Mean change in UACR • Mean change in waist circumference • Changes from baseline in mean body mass index • Patient reported outcomes ○ Ability to Perform Physical Activities of Daily Living ○ Impact of Weight on Self-Perception ○ Diabetes Treatment Satisfaction Questionnaire status/Diabetes Treatment Satisfaction Questionnaire change ○ European Quality of Life 5 Dimensions 5 level

Abbreviations: AE = adverse events; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; QW = once weekly; SGLT-2i = sodium-glucose transport protein 2 inhibitor; TEAE = treatment emergent adverse events; TG = triglycerides; UACR = urine albumin/creatinine ratio; VLDL = very low-density lipoprotein.

Primary estimand

The primary efficacy assessment, guided by the "efficacy" estimand. This estimand focuses on the treatment effect if participants who underwent randomization continued to receive the study treatment without 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 hemoglobin A1c (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 inadequately controlled on insulin glargine alone or in combination with metformin with or without SGLT-2i.
- *Endpoint*: HbA1c change from baseline to Week 40 after randomization.
- *Treatment condition:* The randomized treatment. Further details on study treatment and rescue therapy can be found in Section 6.

- *Intercurrent event:* Intercurrent events of interest: "Treatment discontinuation for any reason" and "Initiation of antihyperglycemic rescue treatment" will be addressed using the following strategies:
  - Had participants stayed on treatment (hypothetical strategy).
  - Had participants not taken antihyperglycemic rescue medication (hypothetical strategy).
- *Population-level summary:* Difference in mean changes between treatment conditions.

Secondary estimand

A robustness of the primary efficacy assessment, guided by the "treatment-regimen" estimand, will be conducted. 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 inadequately controlled on insulin glargine alone or in combination with metformin with or without SGLT-2i.
- *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 Section 6.
- *Intercurrent events:* Intercurrent events of interest: "treatment discontinuation for any reason" and "initiation of rescue antihyperglycemic treatment" are addressed by the treatment condition.
- *Population-level summary*: Difference in mean changes between treatment conditions.

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

4. Study Design

4.1. Overall Design

Study GPIM is a multicenter, randomized, double-blind, parallel, placebo-controlled Phase 3 study which will assess the efficacy and safety of the addition of 5 mg, 10 mg, or 15 mg tirzepatide, as compared with placebo in participants with T2DM as an add-on to titrated basal insulin alone or in combination with metformin with or without SGLT-2i over a 40-week treatment period.

Study GPIM will consist of 3 periods:

- Period I: approximately 3-week screening/lead in period,
- Period II: 40-week treatment period, and
- Period III: 4-week safety follow up period.

Approximately, 256 participants with T2DM who have been treated with insulin glargine (U100) once daily alone or in combination with metformin with or without SGLT-2i ≥90 days prior to Visit 1, will be randomized at a 1:1:1:1 ratio to 5 mg, 10 mg, or 15 mg tirzepatide or placebo, and will be stratified based on HbA1c (≤8.0% or >8.0% [≤64, >64 mmol/mol]), and SGLT-2i use (Yes or No).

4.1.1. Overview of Study Periods

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 Study SoA (Section 1.3).
- Participants who meet all applicable inclusion criteria and none of the applicable exclusion criteria (Section 5) at Visit 1 will continue their pre-study therapy doses between Visits 1 and 2.

Lead-in (Visit 2 to Visit 3)

At Visit 2:

- Screening laboratory results will be reviewed. For those participants meeting all other eligibility requirements, a dilated fundoscopic examination performed by an ophthalmologist or optometrist, must be completed between Visit 2 and Visit 3 to ensure that participants with proliferative diabetic retinopathy, diabetic macular edema, or nonproliferative diabetic retinopathy who require acute treatment, are identified and not enrolled, unless there is a contraindication to dilate the eye (ie. closed angle glaucoma).
- Participants and their caregiver(s), if applicable, will receive a glucometer and training on how to perform self-monitoring of blood glucose (SMBG).

- Participants will be provided diaries and will be trained as appropriate to record the following data:
  - SMBG,
  - hypoglycemic events,
  - insulin glargine doses, and
  - insulin glargine dose adjustments, etc.
- Participants will be trained on disease management and study procedures; this training can be repeated at subsequent visits as deemed appropriate.

After Visit 2:

- Participants will be encouraged to perform 4-point SMBG (3 before each meal and one at bedtime) profiles at least once weekly through the end of the treatment period (Visit 19 [Week 40]), starting at Visit 2.
- Participants will need to perform two 7-point SMBG profiles done on 2 nonconsecutive days in the 2-week period prior to Visit 3 (randomization), Visit 17 (Week 24) and Visit 19 (Week 40).
- During the lead-in period, participants should continue their prestudy therapy and should not change the dose for both metformin and SGLT-2i. In addition, the formulation should not be changed for metformin (for example, from short-acting to long-acting), and participants should be on the same SGLT-2i for entire study duration, in order to allow reliable assessment of HbA1c at baseline (Visit 3).
- Participants will start insulin dose assessments once weekly for the remainder of the lead in period (the use of the algorithm is restricted during the lead in and stabilization periods, as described below).
  Insulin doses should be adjusted only in the case of significant safety risks related to insulin dose:
  - occurrence of hypoglycemia, defined as:
    - If ≥2 episodes of nonsevere hypoglycemia (<3.9 mmol/L [<70 mg/dL]) were recorded during the assessment period at any time during the day; and/or
    - If ≥1 episode that met the criteria for severe hypoglycemia (events requiring assistance of a third person to administer therapy) or was associated with SMBG value <3.0 mmol/L (<54 mg/dL) was recorded during the assessment period.
  - severe hyperglycemia, defined as
    - mean daily BG from 4-point SMBG profile >15 mmol/L (>270 mg/dL).

  In these situations, the participant should contact the site in order to adjust the dose per the treat to target (TTT) algorithm (see Section 6.1.3).
- Participants who are taking concomitant metformin with or without SGLT-2i and develop any condition that is a contraindication for its use will be considered ineligible and will be discontinued from the trial before randomization.

Study Period II (40-Week 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 ECG) prior to randomization and prior to taking the first dose of study drug.
- Participants should arrive to the clinic in the fasting state; the fasting state should have lasted at least 8 hours without having taken any doses of study drug, insulin glargine and metformin (if used) and SGLT-2i (if used).
- Responsible study-site personnel will review the diary and assess the need to adjust the insulin glargine dose per the TTT algorithm criteria (Table GPIM.1). Only participants who require further insulin glargine dose increase at Visit 3 per the TTT algorithm based on the SMBG data: ≥50% FBG values >5.6 mmol/L collected during the week prior to Visit 3, will be eligible for further participation in the study.
- The questionnaires (EQ-5D-5L, Ability to Perform Physical Activities of Daily Living [APPADL], Impact of Weight on Self-Perception [IW-SP], and Diabetes Treatment Satisfaction Questionnaire status [DTSQs]) 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 drugs under the supervision of the medical personnel while still at the study site. Participants will also be trained on how to use the prefilled injection pen and will administer insulin glargine once daily ideally at bedtime. The date and time of the first dosing of study drug should be recorded on the electronic case report form (eCRF).

Treatment period: General Considerations

The treatment period will last 40 weeks, starting with a 4-week stabilization period immediately after randomization and followed by a 36-week insulin glargine titration period. The maintenance period is defined as a part of the titration period when insulin glargine dose is expected to be stable and optimized (Weeks 24 to 40 [Visits 17 to 19]).

Participants will:

- perform daily BG measurements per their weekly SMBG plan as outlined in this section and in Section 1.3.
- perform insulin glargine dose assessments once or twice per week, depending on the study period, as described in the sections below.
- discuss other relevant clinical information, for example, AEs and concomitant medications at each visit. Participants who are taking concomitant metformin with or without SGLT-2i during the lead-in period will be required to continue using the same dose of metformin or SGLT-2i throughout the treatment period. Discontinuation of metformin or SGLT-2i, or changes in its dose will not be permitted, except in the cases of development of contraindications (per country specific label) for its use or in the case

of increased risk of hypoglycemia (see Section 6.5.2 for details) or severe, persistent hyperglycemia (see Section 8.3.4.2 for details).

Post randomization period (end of Visit 3 to Visit 19):

Stabilization Period (End of Visit 3 through Visit 7 [Weeks 0 through 4])

The main purposes of this period are to introduce randomized study drugs (QW tirzepatide or QW placebo) in a safe manner, to assure regular and correct use of the self-monitoring and insulin dose adjustment procedures, and to assure study diaries are completed correctly. Participants will be encouraged to perform 4-point SMBG profiles twice weekly (generally 3 days apart) during this period. Participants will be required to perform insulin dose assessment per the TTT algorithm twice weekly during this period. In an effort to allow appropriate time for tirzepatide to reach steady state, insulin glargine dose adjustments during the 4-week stabilization period should be restricted to those needed in the case of significant safety risks related to insulin dose:

- occurrence of hypoglycemia, defined as:
  - If ≥2 episodes of nonsevere hypoglycemia <3.9 mmol/L (<70 mg/dL） were recorded during the assessment period at any time during the day; and/or
  - If ≥1 episode that met the criteria for severe hypoglycemia (events requiring assistance of a third person to administer therapy) or was associated with SMBG value <3.0 mmol/L (<54 mg/dL) was recorded during the assessment period.
- severe hyperglycemia, defined as
  - mean daily BG from 4point SMBG profile >15 mmol/L (>270 mg/dL).

In above case, insulin dose will be adjusted per the TTT algorithm (Table GPIM.1).

Participants should be instructed to contact the sites if any of the above situations occurred, in order to adjust the insulin glargine dose per the TTT algorithm. In addition, for participants with baseline HbA1c ≤8.0%, the insulin glargine dose will be decreased by 20% immediately after randomization, not later than 7 days after the first dose of study drug, and will then remain unchanged during the stabilization period to decrease the risk of hypoglycemia. The insulin glargine dose will remain unchanged if baseline HbA1c is >8.0%. If the baseline HbA1c value for a participant is not available within the first 7 days after randomization, the insulin dose adjustment could be based on the HbA1c value at Visit 1.

In addition to the clinic visits, 1 telephone visit will be scheduled during this period (Visit 6, Week 3). At this visit, procedures will include

- assessments of SMBG,
- adjustment of insulin dose for safety reasons (hypoglycemia and/or severe hyperglycemia),
- study drug compliance (will be re-assessed at the office visit),
- hypoglycemic events,
- concomitant medications, and
- AEs.

The data obtained at these telephone visits will be entered into the case report forms (CRFs) at the next office visit.

Titration Period (End of Visit 7 through Visit 19 [Weeks 5 through 40])

Throughout the treatment period, participants will collect the following data in the participant diary to be reviewed at the next office visit:

- SMBG,
- hypoglycemic events，
- insulin glargine doses,
- insulin glargine dose adjustments, and
- study drug injection, etc.

For that purpose, at each visit, study diaries for the period after the previous office visit, will be collected, and instructions will be reviewed at each visit. Study drug and injection supplies will be returned per the SoA (Section 1.3) and according to local requirements. New supplies will be dispensed as needed.

In addition to the clinic visits, 4 telephone visits will be scheduled during this period. At each of these visits, procedures will include

- assessments of SMBG,
- compliance with insulin titration algorithm,
- insulin dose,
- study drug compliance (will be re-assessed at the office visit),
- hypoglycemic events,
- concomitant medications, and
- AEs.

The data obtained at these telephone visits will be entered into the CRFs at the next office visit.

At the beginning of the titration period, the participant will be instructed to start using the TTT algorithm without restrictions in order to reach the optimal dose of insulin glargine as soon as possible. The participant will be requested to perform insulin dose assessment once weekly during this period. Results of SMBG and hypoglycemic events will be used by the participant to assess insulin glargine doses per the titration algorithm. Additional assessments may be requested by the investigator based on his or her clinical judgment. Outcome of the assessment will be recorded in participant diaries.

Compliance with study drug administration schedule and compliance with the insulin glargine titration algorithm will be assessed at every office visit and collected in the eCRF at prespecified visits (Section 1.3). Based on the outcome of these reviews, the site personnel should discuss additional insulin glargine dose adjustments while the participant is still at the site and provide retraining, if needed.

Participants should be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties administering their study drugs or with the titration algorithm at any time during the study. Participants should also be advised about the appropriate

course of action in the event that study drug is not taken as instructed (for example: missing doses).

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, serum glucose, and weight
- assessment of AEs and vital signs (2 sitting blood pressure and pulse rate)
- listing of concomitant medications, and
- review of hypoglycemic events collected in the diary

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 (Visit 19 or Visit 99) are required to complete Visit 801, a safety follow-up visit, approximately 4 weeks after their last 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 drug.

Participants will be treated with another glucose-lowering intervention decided upon by the investigator according to the requirements in Section 6.8. Initiation of new antihyperglycemic therapy for the safety follow-up period 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.

4.2. Scientific Rationale for Study Design

Study GPIM is designed to determine the comparative benefits and risks of QW tirzepatide (5 mg, 10 mg, or 15 mg) versus placebo in participants with T2DM who have inadequate glycemic control on stable doses of insulin glargine alone or in combination with metformin with or without SGLT-2i.

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-5 (GPGI). Moreover, the duration of the study is considered sufficient and appropriate for participants to optimize dosing of insulin glargine in the placebo group for comparison with the tirzepatide treatment groups with respect to change in HbA1c.

The parallel-group design for treatment comparison was chosen to avoid any interaction between treatments that may interfere with the interpretation of the study outcome. 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 6.8).

4.3. Justification for Dose

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

The dose selection of tirzepatide and associated escalation schemes in this study are based on the findings in 5 completed global Phase 3 studies (SURPASS clinical program, including GPGK, GPGL, GPGH, GPGM, and GPGI) in participants with T2DM (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022) , as well as 1 completed Phase 3 study (SURPASS-AP-Combo [GPHO]) which is the first registration trial of tirzepatide that enrolled a majority of Chinese participants with T2DM. 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 GI events and is expected to minimize GI AEs consistent with the completed 6 Phase 3 T2DM studies.

Tirzepatide 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. (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022). Similar to the GLP-1 RA class, most of the tirzepatide AEs were dose dependent and GI related, consisting mainly of nausea, vomiting, and diarrhea. In general, these events were mild or moderate in severity, with few severe episodes, and transient (Del Prato et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Rosenstock et al. 2021; Dahl et al. 2022).

Tirzepatide doses were selected based principally on the following criteria:

- each dose provides clinically meaningful weight loss relative to placebo, and
- safety and tolerability were supported by Phase 3 T2DM results.

4.4. End of Study Definition

End of the study is 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 they meet all of the following criteria at screening:

Type of Participant and Disease Characteristics

[1] Have been diagnosed with T2DM based on the World Health Organization classification (Section 10.6)

Participant Characteristics

[2] Have HbA1c ≥7.0% (53 mmol/mol) to ≤11% (97 mmol/mol), as determined by the central laboratory at Visit 1

[3] Have been treated with insulin glargine (U100) once daily alone, or in combination with metformin with or without SGLT-2i ≥90 days prior to Visit 1

[4] Doses of once daily insulin glargine and OAMs (if used) must be stable during the 90-day period prior to Visit 1

- All insulin glargine doses must be ≥0.2 U/kg/day or ≥15 U/day during the 90-day period prior to Visit 1. Insulin glargine dose is considered stable when all doses during this period are within the range defined by ±20% of the most commonly used insulin dose during this same period.
- Doses of metformin (if used) are considered stable when dose and formulation are unchanged during the same period, and the doses must be ≥1000 mg/day and no more than the maximum approved dose per country specific label.
- Doses of SGLT-2i (if used) are considered stable when participants are on the same SGLT-2i and the dose is unchanged during the same period, and the doses must be at least the recommended starting dose and no more than the maximum approved dose per country specific label.

[5] Require further insulin glargine dose increase at Visit 3 per the TTT algorithm based on the SMBG data: ≥50% FBG values >5.6 mmol/L collected during the week prior to Visit 3.

[6] Are of stable weight (±5%) during the 90-day period prior to 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.

[7] Have body mass index (BMI) ≥23 kg/m^2 at Visit 1

[8] Are ≥18 years old or of an acceptable age to provide informed consent according to local regulations, whichever is older

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 definitions and the contraception requirements of this protocol, see Appendix 4 (Section 10.4).

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

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

(b) learn how to self-inject study drugs 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 drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug)

(c) are willing and able to inject study drugs

(d) maintain a study diary, as required for this protocol

(e) have a sufficient understanding of one of the provided languages of the country such that they will be able to complete the participant questionnaires

Informed Consent

[10] Have given written informed consent to participate in this study in accordance with local regulations and the ethical review board (ERB) governing the study site

5.2. Exclusion Criteria

Participants will be excluded from the study if they meet any of the following criteria at Visit 1 (screening), or when indicated below for specific criteria, at Visit 3 (baseline) or at any time during the screening and lead-in periods (Visits 1-3):

Medical Conditions

[11] Have type 1 diabetes mellitus (T1DM)

[12] Have a history of chronic or acute pancreatitis prior to Visit 1 or between Visit 1 and Visit 3

[13] Have history of:

- proliferative diabetic retinopathy

or

- diabetic macular edema

or

- nonproliferative diabetic retinopathy that requires acute treatment

(a dilated fundoscopic examination performed by an ophthalmologist or optometrist between Visit 2 and Visit 3 is required to confirm eligibility)

[14] Have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1

[15] Have a history of diabetic ketoacidosis or hyperosmolar state/coma within the 6 months prior to Visit 1

[16] 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: a gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or chronically take drugs that directly affect GI motility

[17] Have any of the following cardiovascular (CV) conditions within 2 months prior to Visit 1 or between Visit 1 and Visit 3: acute myocardial infarction, or cerebrovascular accident (stroke) or hospitalization due to congestive heart failure (CHF)

[18] Have New York Heart Association Functional Classification III and IV CHF within 2 months prior to Visit 1 or between Visit 1 and Visit 3

[19] Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or alanine aminotransferase (ALT) level >3.0 times the upper limit of normal (ULN), as determined by the central laboratory at Visit 1; participants with NAFLD are eligible for participation in this trial only if their ALT level is ≤3.0 times ULN

[20] Have an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology (CKD-EPI) as determined by central laboratory at Visit 1; for participants on metformin, eGFR (CKD-EPI) <45 mL/min/1.73 m^2 as determined by the central laboratory at Visit 1; for participants on metformin and SGLT-2i, eGFR (CKD-EPI) either <45 mL/min/1.73 m^2 or lower than the threshold defined in SGLT-2i label, as determined by central laboratory at Visit 1.

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

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

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

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

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

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

[27] Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy for less than 5 years. Exceptions 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

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

[29] Males with hemoglobin <~~11.0~~ 110 g/L and females with hemoglobin <~~10.0~~100 g/L; or any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias and sickle cell disease)

Prior/Concomitant Therapy

[30] Treatment with any glucose-lowering agent(s) other than stated in the inclusion criteria [3] in a period of 90 days prior to Visit 1 and between Visit 1 and Visit 3

Note: Short-term treatment with a nonstudy insulin for up to 14 days is allowed for certain clinical situations.

Examples: Elective surgery, during hospitalization or hyperosmolar states

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

[32] Are receiving chronic (>14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular or inhaled preparations) or have received such therapy within 1 month of Visit 1 or between Visits 1 and 3

Prior/Concurrent Clinical Trial Experience

[33] 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

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

[35] Have previously completed or withdrawn from this study or any other study investigating tirzepatide

Other Exclusions

[36] 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

[37] Are Lilly employees

[38] Are unwilling or unable to comply with the use of a paper diary to directly record data from the subject

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), qualified medical personnel 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 [6] (Section 5.1), participants should not initiate during the study an organized diet and/or exercise weight reduction program 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 randomly assigned to study drug. 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 serious adverse event (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 the study drug (tirzepatide 3 doses or placebo) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Assignment to tirzepatide (3 doses) or placebo will occur at randomization. Beginning at randomization, all participants will receive study drug according to the randomized treatment group for the duration of the 40-week treatment period. Following randomization, the participant will inject the first dose of study drug/placebo at the study site. The date and time of all doses of study drug should be recorded on the eCRF.

This table lists the interventions used in this clinical study.

Group Name	**Tirzepatide 5 mg**	**Tirzepatide 10 mg**	**Tirzepatide 15 mg**	**Placebo**	**Concomitant background insulin for all treatment arms**
Intervention Name	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo	Insulin Glargine U100
Dosage Level(s)	5 mg QW	10 mg QW	15 mg QW	NA	Titrated
Route of Administration	SC				
Frequency of Administration	QW				QD
Use	Experimental intervention			comparator	Concomitant background insulin
Sourcing	Provided centrally by the Sponsor and dispensed via IWRS				
Packaging and Labeling	Will be provided in autoinjectors (single-dose pens) and packaged in cartons to be dispensed. Clinical study materials will be labeled according to country regulatory requirements.				Will be provided in single-participant-use prefilled injection pens in a carton.

Abbreviations: IWRS= interactive web-response system, QD= once daily, QW=once weekly, SC=subcutaneous.

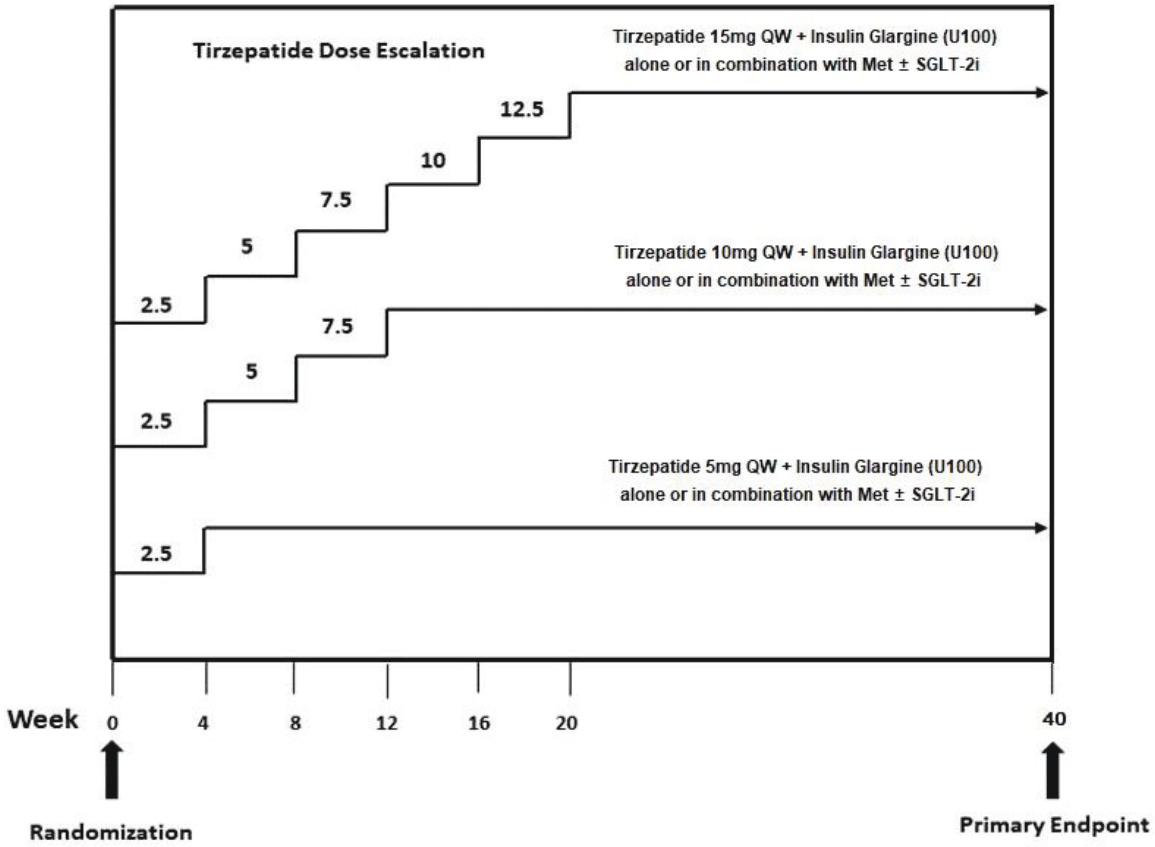
6.1.1. Tirzepatide Dosing

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 in 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 to 5 to 7.5 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 to 5 to 7.5 to 10 to 12.5 to 15 mg) until the 15-mg dose is reached and maintained for the duration of the study.

Figure GPIM.1 illustrates the tirzepatide dose escalation regimen.



Abbreviations: Met = metformin; QW = once weekly; SGLT-2i = sodium-glucose transport protein 2 inhibitor.

Figure GPIM.1. Tirzepatide Dose Escalation

There are no restrictions on the time of day each weekly dose of study drug is given, but it is advisable to administer the subcutaneous (SC) injections on the same day and same time each week. The actual date and time of all dose administrations will be recorded by the participant. If a dose of study drug is missed, the participant should take it as soon as possible unless it is within 72 hours of the next scheduled 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 drug subcutaneously in the abdomen or thigh using the SDP; a caregiver may administer the injection in the participant's upper arm. A new SDP will be used for each injection. If study drug is to always be injected in the same body region, participants should be advised to use a different injection site each week.

6.1.2. Placebo Dosing

Participants randomized to the placebo group will inject matched placebo subcutaneously QW for the entire treatment period. This is a double-blind study, and therefore it will not be possible for investigators and participants to know which treatment they are receiving.

6.1.3. Insulin Glargine Dosing

Insulin glargine will be injected once daily, as a single SC injection, always at the same time of day, ideally at bedtime. Participants will be instructed to adjust insulin glargine doses to a target FBG of ≤5.6 mmol/L (100 mg/dL) according to the schedule below (Table GPIM.1). For this purpose, participants will be encouraged to measure their FBG each morning and to collect 4-point SMBG profiles at least once a week through the end of the treatment period (Visit 19 [Week 40]). The 4-point SMBG profile will consist of fasting, pre-midday meal, pre-evening meal, and bedtime measures. Participants will collect the 4-point SMBG profiles once weekly between Visit 2 and Visit 3, twice weekly from Visits 3-7 (Weeks 0-4) followed by once weekly for the remainder of the treatment period.

The decision to adjust insulin glargine doses will be based upon the median of the last 3 daily FBG (SMBG) values collected after the previous dose assessment. If only 2 values are available for assessment, then the average value will be calculated and used to adjust the dose. If only one value is available, the participant should contact the investigator site for instructions on adjusting insulin dose. In case of recorded hypoglycemic episodes any time during the period included in the assessment, the criteria provided as footnotes to Table GPIM.1 should be followed.

Table GPIM.1. Treat-to-Target Algorithm

Median Fasting Blood Glucose[a]		Adjustment of Insulin Glargine Dose
mg/dL	mmol/L	
<79	<4.4	−2 units[b,c]
79 to 99	4.4 to 5.5	No adjustment
100 to 119	5.6 to 6.6	+(0-2) units (at the discretion of investigator)
120 to 139	6.7 to 7.7	+2 units
140 to 179	7.8 to 9.9	+4 units
≥180	≥10.0	+6 units

Abbreviations: SMBG = self-monitored blood glucose.

[a] Based on the last 3 fasting glucose values (SMBG).

[b] Dose should also be decreased by 2 units in the following situations:

- If ≥2 episodes of nonsevere hypoglycemia <3.9 mmol/L (<70 mg/dL) were recorded during the assessment period at any time during the day; and/or
- If ≥1 episode that met the criteria for severe hypoglycemia (events requiring assistance of a third person to administer therapy) or was associated with SMBG value <3.0 mmol/L (<54 mg/dL) was recorded during the assessment period.

[c] If only 1 hypoglycemic episode with SMBG value ≥3.0 mmol/L (≥54 mg/dL) and <3.9 mmol/L (<70 mg/dL) was recorded, insulin dose should not be changed.

Source: Davies et al. 2005; Ran et al. 2020; Ji et al. 2018.

The site personnel will instruct the participant, with the participant insulin dose adjustment from the participant diary and study-specific training materials provided to the study sites, when and how to assess whether an insulin dose adjustment is needed using the algorithm. The investigator or his or her designee is responsible to ensure that the insulin dose titration regimen used by study participants follows the same requirements defined in the TTT plan throughout the study. The participant is responsible for completing the insulin dose assessments and making the required dose adjustments (self-adjustment). Assessment of insulin doses per the TTT algorithm and administered insulin doses will be recorded by the participant in study period-specific diaries. Participants should be instructed to contact the study site if they are unable to decide on the appropriate dose adjustment at any time during the trial. Site personnel will verify at each office or telephone visit that the assessment(s) has been made and that the insulin adjustment was appropriate. If needed, they will propose further adjustments based upon their review of data collected since the previous visit. If assessments were not made or the algorithm was not correctly followed, participants will receive additional training and instructions.

During the lead-in period (Visits 2 and 3 [randomization]), insulin doses should be adjusted only when needed to protect the safety of participants (occurrence of hypoglycemia or severe hyperglycemia). If these events occur, the insulin dose should be adjusted according to the TTT algorithm (Table GPIM.1). See Section 4.1.1 for more details. Insulin dose assessments during this period will occur once per week.

During the treatment period, office visits will occur weekly or every other week during the first 16 weeks, and thereafter every 4 to 8 weeks to enable the site to properly monitor participants' usage of the TTT algorithm. After randomization, during the 4-week stabilization period, the insulin glargine dose will remain unchanged if the participant's HbA1c at randomization (baseline, Visit 3) is >8.0%. For participants with baseline HbA1c ≤8.0%, the insulin glargine dose will be decreased by 20% immediately (within 7 days) after randomization and will then remain unchanged during the stabilization period. Insulin doses should be adjusted per TTT algorithm only when needed to protect the safety of participants (occurrence of hypoglycemia or severe hyperglycemia). If these events occur, the insulin dose should be adjusted according to the TTT algorithm (Table GPIM.1). See Section 4.1.1 for more details.

Participants will be requested to perform insulin dose assessments twice per week during the stabilization period for safety purposes. Following stabilization, participants will be treated for an additional 36 weeks, and they will be required to assess their insulin glargine dose once weekly, using the FBG values for that week. During this period, the insulin dose will be adjusted per the TTT algorithm as described in Section 4.1.1 with no restriction.

6.1.4. Medical Devices

The combination products used in the study are tirzepatide investigational SDP and a marketed insulin glargine prefilled injection pen.

6.2. Preparation, Handling, Storage, and Accountability

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

2. Only participants enrolled in the study may receive study drug(s). Only authorized study personnel may supply, prepare, or administer study drug(s). All study drug(s) 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.
3. The investigator or authorized study personnel are responsible for study drug(s) accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study drug(s) are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This study is designed as a randomized, double-blind study to minimized bias.

Participants who meet all criteria for enrollment will be randomized to one 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 1:1:1:1 ratio to receive tirzepatide 5 mg, 10 mg, 15 mg, or matched placebo.

The randomization will be stratified based on HbA1c (≤8.0% or >8.0% [≤64, >64 mmol/mol]), and SGLT-2i use (Yes or No).

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency codes, generated by a computer drug labeling system, will be available to the investigator. These codes, which reveal the participant's treatment group when opened, may be opened during the study ONLY if the participant's well-being requires knowledge of the participant's treatment assignment.

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 calls resulting in an unblinding event are recorded and reported by the IWRS.

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 Lilly clinical research physician (CRP) for the participant to continue in the study.

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 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.

6.4. Study Intervention Compliance

Study drug compliance will be determined by the following:

- Study drug 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 drug 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 is defined as taking at least 75% of the required doses of study drug. Similarly, a participant will be considered 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 drug 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 not to be compliant with their medication and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol.

6.5. Dose Modification

6.5.1. Tirzeptide

Please refer to Section 6.1.1 for tirzeptide administration. Study drug dose modification is not permitted except for management of intolerable GI symptoms (see Section 6.5.1.1).

6.5.1.1. 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, interrupting study drug for 1 dose, provided the participant has taken the last 3 weekly doses. Study treatment should be resumed at the assigned dose immediately, either alone or in combination with symptomatic medication, which can also be utilized to manage symptoms (Section 6.8). Management of study drug after interruptions >1 dose is discussed in Section 7.1.2.

If intolerable GI symptoms (for example, nausea, vomiting, or diarrhea) persist despite the above measures after Visit 11 (after the scheduled visit in Week 8) the investigator should contact Lilly to consider continuing treatment at a lower maintenance dose of study drug 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 interactive web-response system (IWRS) to receive the appropriate tirzepatide dispensing information. If de-escalation is needed between scheduled visits, the IWRS will have unscheduled visits (for example, Visit 13a) dedicated to provide 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. After that, the participants will have to discontinue study drug if intolerable GI AE persists and stay in the study.

If intolerable persistent GI symptoms occur, the investigator should take the above measures to keep the participant on study treatment. However, after the escalation period (Week 24), dose decreases will not be allowed.

6.5.2. Background Antihyperglycemic Medications

1. If increased risk of hypoglycemia during the period between 2 insulin dose assessments is judged to be related to the treatment regimen, the following changes should be made:
    - Decrease the insulin glargine dose by 2 U, per the TTT algorithm, in the following cases:
        - If ≥2 episodes of nonsevere hypoglycemia (<3.9 mmol/L [<70 mg/dL]) were recorded at any time during the day for the assessment period; and/or
        - If ≥1 episode that met the criteria for severe hypoglycemia (events requiring assistance to administer therapy) or was associated with SMBG value <3.0 mmol/L (<54 mg/dL) was recorded during the assessment period; and/or
        - If the median FPG value for the assessment period is <4.4 mmol/L (<79 mg/dL).
    - In the case of repeated hypoglycemic events, even with a very low glargine dose and despite glargine dose decreases per the TTT algorithm, administration of insulin glargine may be temporarily or permanently discontinued.
    - If increased risk of hypoglycemia persists despite discontinuation of insulin glargine, then dose reduction or discontinuation of OAMs (for participants who are taking) should be considered.
2. In certain situations, short-term discontinuation will be allowed in line with the product(s) labeling (for example, for metformin: severe dehydration, elective surgery, or need for radiologic examination involving intravenous injection of iodinated contrast dye; for SGLT-2i: ketoacidosis or clinical condition known to predispose to ketoacidosis [eg, prolonged fasting due to acute illness or surgery]). Once the situation that led to temporary discontinuation of the drug resolved, treatment should be restarted at investigator discretion.

3. If a participant develops contraindications to metformin or SGLT-2i (if used), such that the use of the drug is contraindicated according to the country specific label (eg, eGFR [CKD-EPI] lower than the threshold defined in country specific label), the drug should be discontinued; in this case, the insulin glargine dose may need to be further adjusted.

A participant will be considered noncompliant with the protocol (protocol deviation) if he or she changes the dose, or discontinues metformin or SGLT-2i (if used) for reasons other than those described here. Doses of background OAMs could be increased as rescue therapy for severe, persistent hyperglycemia, at the discretion of investigators (see Section 8.3.4.2 for details).

6.6. 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.

6.7. Treatment of Overdose

Study drug overdose (more than the specified number of injections) will be reported as an AE.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study drug should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study drug no longer has a clinical effect or can no longer be detected systemically (at least 30 days).

6.8. 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 (Table GPIM.2).

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

- for participants who require permanent discontinuation of tirzepatide but remain in the study.
- for rescue therapy after randomization due to severe, persistent hyperglycemia
- during the safety follow-up period.

GLP-1 RAs, DPP 4 inhibitors, pramlintide, and other basal insulins are prohibited medications and are not allowed during the study. Short-term treatment with a nonstudy insulin for up to 14 days is allowed for certain clinical situations, for example, elective surgery, during hospitalization, or hyperosmolar states (this will not be considered as rescue therapy).

Investigative site personnel will inform participants that they must consult with the investigator or a designated site personnel 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 personnel member as soon as possible. Any additional medication initiated during the course of the study (including over the counter [OTC] drugs, such as paracetamol or aspirin) must be documented, and the name of the drug and the date(s) of administration must be recorded on the "Concomitant Medications" section of the eCRF.

All nonstudy medications will be recorded on source documents at all visits.

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.

Table GPIM.2. Use of Concomitant Medications that May Interfere with Efficacy and Safety Assessments

Drug Class	Use During Screening/Lead-In	Conditions for Use after Randomization		
		Acute therapy[a]	Rescue therapy	During Safety Follow-Up Period
Drugs with approved weight loss indication[b]	Excluded	N	N/A	N
Systemic glucocorticoid therapy[c]	Excluded except for acute therapy[a]	Y	N/A	N (except for acute therapy[a])
Antihyperglycemia medications				
GLP-1 RAs and related fixed-dose combination	Excluded	N	N	N
DPP-4 inhibitors and related fixed-dose combination	Excluded	N	N	N
Pramlintide	Excluded	N	N	N
Metformin[d]	Allowed	N/A	Y[f]	Y
SGLT-2i[e]	Allowed	N/A	Y[f]	Y
Insulins[g]	Excluded	Y	Y	Y
Meglitinides	Excluded	N	Y	Y
Alpha-glucosidase inhibitors	Excluded	N	Y	Y
Sulphonylureas	Excluded	N	Y	Y
Thiazolidinediones	Excluded	N	Y	Y

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; N = no; N/A = not applicable; SGLT-2i = sodium-glucose transporter 2 inhibitor; Y = yes.

a Acute therapy = treatment for up to 14 days.

b Wegovy® [semaglutide 2.4 mg], Saxenda [liraglutide 3.0 mg], Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Apidex® [phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], Contrave® [naltrexone/bupropion], or similar other body weight loss medications including over the counter (OTC) medications [for example, allī®]) within 3 months prior to Visit 1 or any time during the trial.

c Chronic systemic glucocorticoid therapy (>14 days) should be excluded within 1 months prior to Visit 1, between Visits 1 and 3, and is not allowed during treatment period or safety follow-up period; does not apply to topical, intraocular, intranasal, intra-articular, or inhaled preparations.

d Switching metformin manufacturers is allowed as long as the dose is the same, but changing to a metformin formulation with a different action profile (for example, from short-acting to long-acting metformin) is not permitted.

e Switching SGLT-2i manufacturers is allowed as long as the dose is the same.

f For rescue therapy, metformin and/or SGLT-2i dose can be increased if the dose is below maximum approved dose per country-specific label and is well tolerated.

g Use of insulin glargine U100 is allowed during screening/lead-in period. For rescue therapy and therapy during safety follow-up period, use of other basal insulin except for insulin glargine U100 will not be allowed. Short-term treatment with a nonstudy insulin for up to 14 days is allowed for certain clinical situations, for example, elective surgery, during hospitalization, or hyperosmolar states (this will not be considered as rescue therapy).

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study drug. If so, the participant will remain in the study and complete all visits and procedures as shown in the SoA (Section 1.3). If the participant discontinues from study, the participant should complete an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA (Section 1.3).

7.1.1. Permanent Discontinuation from Study Intervention

Possible reasons leading to permanent discontinuation of investigational product:

- **Participant Decision**
  - the participant requests to discontinue investigational product.
- **Discontinuation due to a hepatic event or liver test abnormality.**
  - The study drug should be **interrupted** and close hepatic monitoring initiated (see Section 10.5.1) 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%)	

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

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications

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

- Otherwise, the study drug should be discontinued if a self-limited nondrug etiology cannot be identified.

In addition, participants will be discontinued from the investigational product in the following circumstances:

- If a participant is inadvertently enrolled and it is determined that continued treatment with study drug would not be medically appropriate
- Acute or chronic pancreatitis
- If a participant is diagnosed with MTC after randomization, or has post randomization calcitonin value ≥35 ng/L that has increased at least 50% over baseline
- If a 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
- Any significant study drug -related hypersensitivity reaction
- Any other Treatment emergent adverse event (TEAE), SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
- If female participant becomes pregnant
- If a participant is diagnosed with T1DM

Participants who stop the study drug permanently will receive another glucose-lowering intervention (Section 6.8) and will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements.

Participants discontinuing from the investigational product prematurely for any reason should complete adverse event and other follow-up procedures per Section 1.3 (SoA), Section 8.3 (Adverse Events), and Section 8.2 (Safety) of this protocol.

7.1.2. Temporary Interruption of Study Intervention

In certain situations after randomization, the investigator may need to temporarily interrupt study drug. Every effort should be made by the investigator to maintain participants on study drug and to restart study drug after any temporary interruption, as soon as it is safe to do so.

If study drug interruption is…	then…
≤2 consecutive doses	the treatment can be restarted at the same dose if the drug was well tolerated prior to discontinuation.
≥3 consecutive doses	the IWRS will dispense 5 mg/matched placebo and escalated as required by protocol.
due to AE	the event is to be documented and followed according to the procedures in Section 8.3 of this protocol.

due to intolerable persistent GI AE (eg: nausea, vomiting, or diarrhea)	the participants should be treated as suggested in Section 6.5.1.1.

Abbreviations: AE = adverse event; GI = gastrointestinal; IWRS = interactive web response service.

Investigators should inform Lilly that study drug has been temporarily interrupted.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an 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.

Participants who agree to provide information relevant to any study endpoint at the end of the study are not considered to have discontinued from the study.

A participant who withdraws consent and clearly indicates that there will be no further contact of any kind with the site will be considered to have discontinued from the study.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA (Section 1.3). If the participant has not already discontinued the study drug, the participant will be permanently discontinued from the study drug 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 (CMO). Safety follow up is as outlined in Section 1.3 (SoA), Section 8.3 (Adverse Events), 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 drug.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessments

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

8.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be assessed at 40 weeks based on data collected at the times shown in the Study Schedule (see Section 1.3).

- Mean change in body weight
- Proportion of participants with HbA1c <7% (53 mmol/mol), ≤6.5% (48 mmol/mol), or <5.7% (39 mmol/mol)
- Mean change in fasting serum glucose values measured in the central laboratory
- Mean change in daily average 7-point SMBG profiles
- Proportion of participants who achieved weight loss ≥5%, ≥10%, and ≥15%
- Proportion of participants with HbA1c <7.0%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.0 mmol/L [54 mg/dL] or severe hypoglycemia)
- Proportion of participants with HbA1c ≤6.5%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.0 mmol/L [54 mg/dL] or severe hypoglycemia)
- Proportion of participants with HbA1c <7.0%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.9 mmol/L [70 mg/dL])
- Proportion of participants with HbA1c ≤6.5%, without weight gain (<0.1 kg) and without hypoglycemia (blood glucose <3.9 mmol/L [70 mg/dL])

- Percentage change in daily mean insulin glargine dose

8.1.3. Tertiary Assessments and Procedures

The following secondary efficacy measures will be assessed based on data collected at the times shown in the Study Schedule (see Section 1.3).

- Mean change in waist circumference
- Changes from baseline in mean BMI
- Mean change in lipids (total cholesterol, high-density lipoprotein, low-density lipoprotein, non-high-density lipoprotein, very low-density lipoprotein, and triglycerides)
- Mean change in urine albumin/creatinine ratio
- APPADL scores
- IW-SP scores
- DTSQs/DTSQc
- EQ-5D-5L scores

8.1.4. Appropriateness of Assessments

Efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to the efficacy and safety assessments in individuals and populations with T2DM.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

- Skin
- Cardiovascular system
- Respiratory system
- Gastrointestinal system
- Neurological system
- Thyroid examination
- Foot examination, including evaluation for diabetic neuropathy.

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

Height, weight, and waist circumference will also be measured and recorded (Section 10.7). 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).

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

8.2.3. Electrocardiograms

For each participant, electrocardiograms (ECGs) should be collected according to the SoA (Section 1.3). Electrocardiograms should be recorded according to the study-specific recommendations included in Manual of Operations for the study.

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

All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be overread by a cardiologist at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements. The machine-read ECG intervals and heart rate may be used for data analysis and report-writing purposes, unless a cardiologist overreading of the ECGs is conducted prior to completion of the final study report (in which case, the overread data would be used).

8.2.4. Clinical Safety Laboratory Tests

For each patient, laboratory tests detailed in Section 10.2 should be conducted according to the SoA (Section 1.3).

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 patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via CRF.

8.2.5. 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.

Hepatic Safety Monitoring

In cases of elevated liver laboratory tests, hepatic monitoring should be initiated as outlined in Section 10.5.1.

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

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

- AEs
- SAEs
- Product complaints (PCs)

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

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

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE and SAE updates – prior to start of study drug **and** deemed reasonably possibly related to study procedures	signing of the ICF	start of drug	Within 24 hours of awareness	AE eCRF and SAE eCRF	SAE paper form
SAE and SAE updates – after start of study drug	start of intervention	participation in study has ended	Within 24 hours of awareness	AE eCRF and SAE eCRF	SAE paper form
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	AE eCRF and SAE eCRF	SAE paper form
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study drug	at least 30 days after the last dose	Within 24 hours (see Section 8.3.3)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study drug	End of study drug	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study drug	End of study drug	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

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

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the 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.

All AEs occurring after signing the ICF are recorded in the eCRF 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 adverse event should have additional data collected using the eCRF.

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 case report form [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.

8.3.2.1. 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 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.

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

8.3.4. 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 Early Termination 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 eCRF at each visit.

Investigators should use the following classification of hypoglycemia (ADA 2022c):

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 blood glucose 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 2022c).

8.3.4.2. Severe, Persistent Hyperglycemia

Severe, persistent hyperglycemia 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 at the discretion of investigator in accordance with American Diabetes Association/European Association for the Study of Diabetes guidance (Inzucchi et al. 2015). Rescue medication will be prescribed as add-on to randomized treatment, and participants will continue to follow the protocol-specified visit schedule.

Because insulin glargine dose adjustments without restrictions will be initiated at the end of the stabilization period (see Section 4.1), decision on the presence of severe, persistent hyperglycemia can be first considered 12 weeks after the initiation of this period (approximately 16 weeks after randomization).

Add-on glycemic rescue therapy will be allowed for participants who met any one of the following prespecified criteria for severe, persistent hyperglycemia 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 the participant does not have an acute condition causing severe hyperglycemia):

a) Average daily BG from the once weekly 4-point SMBG profile >13.3 mmol/L (>240 mg/dL) over a consecutive 2-week period at any time 16 to 24 weeks post randomization.

OR

b) Average daily BG from the once weekly 4-point SMBG profile >11.1 mmol/L (>200 mg/dL) over a consecutive 2-week period at any time beyond the first 24 weeks post randomization.

OR

c) HbA1c ≥8.5% at 24 weeks, AND with inadequate response to the existing regimen defined as improvement in HbA1c over the last 3 months (Week 12 to Week 24) that is, <0.3%

Rescue therapy option:

The criteria described above for severe, persistent hyperglycemia will only be applicable after Week 16. The first choice before initiating any rescue therapy for those participants during the initial 16 weeks will be to follow the TTT algorithm to increase the dose of insulin glargine.

For rescue therapy, metformin or SGLT-2i dose (if used) can be increased if the dose is no more than maximum approved dose per country specific label and is well tolerated.

Rescue treatment with pramlintide, DPP-4 inhibitors, or GLP-1 RAs will not be allowed. Additionally, use of other basal insulins will not be allowed. See details in Section 6.8.

Investigators must use clinical judgment in the interest of safety of the participant at all times. In any situation that, in the investigator's opinion, may require an intervention that is not consistent with the requirements provided in this section, he or she should also consult the Lilly physician before such intervention is implemented, except when an immediate adjustment of the treatment regimen is medically required.

8.3.4.3. Pancreatitis

Acute pancreatitis is defined as an AE of interest in all trials with tirzepatide including this trial. Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks and Freeman 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half the cases [Banks and Freeman 2006; Koizumi et al. 2006]; the pain is often associated with nausea and vomiting);
- serum pancreatic amylase and/or lipase ≥3× ULN
- characteristic findings of acute pancreatitis on computed tomography (CT) scan or magnetic resonance imaging (MRI).

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed).

Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the participant must discontinue therapy with study drug(s), and will continue in the study on another glucose-lowering regimen (see Section 6.8 for details on the introduction of new antihyperglycemic interventions). The most appropriate diabetes therapeutic regimen will be decided by the investigator, based on the participant's clinical status. A review of the participant's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Each case of AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or pancreatic amylase) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug(s).

Each participant will have measurements of pancreatic amylase and lipase (assessed at the central laboratory) as shown on the SoA (Section 1.3) to assess the effects of the investigational doses of tirzepatide on pancreatic enzyme levels. Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic participants (Nauck et al. 2017; Steinberg et al. 2017a; Steinberg et al. 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic 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. Only cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis will be submitted for adjudication.

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent clinical endpoint committee (CEC). 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 eCRF page by study site or Lilly personnel. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

8.3.4.4. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or multiple endocrine neoplasia type 2 (MEN-2) will be excluded from the study. The assessment of thyroid safety during the study will include reporting of any case of thyroid malignancy including MTC and papillary carcinoma and measurements of calcitonin. This data will be captured in specific eCRFs. 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. Tirzepatide 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, tirzepatide should be restarted when it is safe to do so.

8.3.4.5. Major Adverse Cardiovascular Event

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

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

8.3.4.6. 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 which should be submitted to the central reading center. 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 8.3 must be reported as SAEs.

8.3.4.7. Hypersensitivity Events

All allergic or hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Additional data, such as type of reaction and treatment received, will be collected on any AEs or SAEs that the investigator deems related to study drug(s) via a CRF created for this purpose. Additional samples should also be collected as outlined in Section 10.2.1. Study drug(s) should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug(s). Study drug(s) may be restarted when/if it is safe to do so, in the opinion of the investigator. If study drug(s) 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 will be performed by a qualified eye care professional (ophthalmologist or optometrist) for all participants between Visit 2 and Visit 3 to exclude participants with proliferative retinopathy and/or diabetic macular edema, unless there is a contraindication to dilate the eye (ie. closed angle glaucoma). The results from this examination will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy.

A follow-up dilated fundoscopic examination should be performed when clinically indicated by any AE suspected of worsening retinopathy, and the findings should be recorded on the retinopathy eCRF.

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 8.2.5 and 10.5.

8.3.4.11. Severe Gastrointestinal Adverse Events

Tirzepatide may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the eCRF/AE form. For detailed information concerning the management of GI AEs, please refer to Section 6.5.1.1.

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 RAs (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 life-threatening 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.

Lactic acidosis has been reported rarely in participants with T2DM associated with use of metformin, excessive alcohol intake and decrease renal function. If lactic acidosis is suspected, metformin should be temporarily discontinued until the resolution of the event.

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 2022b). 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

The following questionnaires will be completed by the participants at specific clinic visits according to the SoA (Section 1.3). At these visits, the questionnaires should be completed before the participant has discussed their medical condition or progress in the study with the investigator and/or site personnel and before any other study procedures if the participant is not adversely affected by their fasting condition.

8.9.1. Ability to Perform Physical Activities of Daily Living

The APPADL questionnaire contains 7 items that assess how difficult it is for participants to engage in certain activities considered to be integral to normal daily life, such as walking, standing, and climbing stairs (Hayes et al. 2011; 2012). Items are scored on a 5-point numeric rating scale, where 5 = “not at all difficult” and 1 = “unable to do.” A raw overall score is

calculated by simply summing the scores of the 7 items, and a transformed overall score is obtained by linearly transforming the raw overall score to a 0 to 100 scale. A higher raw overall score and a higher transformed overall score are indicative of better ability to perform activities of daily living.

8.9.2. Impact of Weight on Self--Perception Questionnaire

The IW-SP questionnaire contains 3 items that assess how often the participant's body weight affects how happy they are with their appearance and how often they feel self--conscious when out in public (Hayes and DeLozier 2015). Each item is rated on a 5-point scale ranging from "always" to "never." Total scores for the IW-SP are derived by summing the item scores and dividing by the number of items. The score can also be transformed to a range from 0 to 100. Higher IW-SP scores correspond to better self--perception (Hayes and DeLozier 2015).

8.9.3. Diabetes Treatment Satisfaction Questionnaire

The status (s) and change (c) versions of the DTSQ will be used during the study to assess the participant's satisfaction with their diabetes treatment and the perceived frequency of hyperglycemia and hypoglycemia. The questionnaire contains 8 items (Bradley 1994). Each item is rated on a 7-point Likert scale. Six items (1 and 4 through 8) are summed to produce a measure of treatment satisfaction ranging from 0 "very dissatisfied" to 6 "very satisfied." The remaining 2 items (2 and 3) are treated individually. Item 2 measures the perceived frequency of hyperglycemia on a scale ranging from 0 "none of the time" to 6 "most of the time," and Item 3 measures the perceived frequency of hypoglycemia on the same scale. The change version has the same 8 items as the status version with a small alteration of the wording of Item 7. The DTSQ change response options differ from those of the DTSQ status to produce measures of relative change rather than absolute satisfaction (3 "much more satisfied now" to -3 "much less satisfied now").

8.9.4. EQ-5D-5L

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).

9. Statistical Considerations

9.1. Statistical Hypotheses

The alternative hypotheses for the primary objective are the following:

- $H_{15,1}$: QW tirzepatide 15 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for mean change in HbA1c from baseline at 40 weeks.

and/or

- $H_{10,1}$: QW tirzepatide 10 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for mean change in HbA1c from baseline at 40 weeks.

The above two hypotheses will be tested in parallel, each at a 2-sided significance level of 0.025.

The alternative hypotheses for the key secondary objective controlling for type 1 error rate are the following:

- $H_{5,1}$: QW tirzepatide 5 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for mean change in HbA1c from baseline at 40 weeks.
- $H_{15,2}$: QW tirzepatide 15 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for mean change in body weight from baseline at 40 weeks.
- $H_{10,2}$: QW tirzepatide 10 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for mean change in body weight from baseline at 40 weeks.
- $H_{5,2}$: QW tirzepatide 5 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for mean change in body weight from baseline at 40 weeks.
- $H_{15,3}$: QW tirzepatide 15 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for the proportion of participants with HbA1c <7% (53 mmol/mol) at 40 weeks.
- $H_{10,3}$: QW tirzepatide 10 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for the proportion of participants with HbA1c <7% (53 mmol/mol) at 40 weeks.
- $H_{5,3}$: QW tirzepatide 5 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for the proportion of participants with HbA1c <7% (53 mmol/mol) at 40 weeks.
- $H_{15,4}$: QW tirzepatide 15 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for the proportion of participants with HbA1c ≤6.5% (48 mmol/mol) at 40 weeks.

- $H_{10,4}$: QW tirzepatide 10 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for the proportion of participants with HbA1c ≤6.5% (48 mmol/mol) at 40 weeks.
- $H_{5,4}$: QW tirzepatide 5 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for the proportion of participants with HbA1c ≤6.5% (48 mmol/mol) at 40 weeks.
- $H_{15,5}$: QW tirzepatide 15 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for mean change in fasting serum glucose (FSG) from baseline at 40 weeks.
- $H_{10,5}$: QW tirzepatide 10 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for mean change in FSG from baseline at 40 weeks.
- $H_{5,5}$: QW tirzepatide 5 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for mean change in FSG from baseline at 40 weeks.
- $H_{15,6}$: QW tirzepatide 15 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for the proportion of participants with HbA1c <5.7% (39 mmol/mol) at 40 weeks.
- $H_{10,6}$: QW tirzepatide 10 mg is superior to placebo when added to titrated basal insulin glargine alone or in combination with metformin with or without SGLT-2i for the proportion of participants with HbA1c <5.7% (39 mmol/mol) at 40 weeks.

9.1.1. Multiplicity Adjustment

The primary and the key secondary objectives will be evaluated align to both the efficacy estimand and the treatment-regimen estimand. No multiplicity adjustment will be conducted in different estimands.

A prespecified graphical scheme (Bretz et al. 2009, 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, 2011; Alosh et al. 2014).

The testing scheme will be fully detailed in the statistical analysis plan. Unless otherwise specified, there will be no adjustment for multiple comparisons for any other analyses outside the primary and key secondary endpoints. The testing scheme will be finalized before database lock.

9.2. Analyses Sets

For purposes of analysis, the following populations are defined as follows:

Population/Analysis Set	Description
Screened participants	All participants who sign informed consent
Randomized participants	All participants who are randomly assigned a treatment group.
modified intention-to-treat (mITT) population	All randomly assigned participants who are exposed to at least 1 dose of study drug. In the event of a treatment error, participants will be analyzed according to the treatment they were randomized.

Efficacy analysis set (EAS)	Data obtained during Study Period II from the mITT population, excluding participants discontinuing study drug due to inadvertent enrollment and data after initiating rescue antihyperglycemic medication or stopping study drug.
Full analysis set	Data obtained during Study Period II from the mITT population, excluding participants discontinuing study drug due to inadvertent enrollment, regardless of adherence to study drug or initiation of rescue antihyperglycemic medication.
Safety analysis set (SS)	Data obtained during Study Periods II or III from the mITT population, regardless of adherence to study drug 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 and in the statistical analysis plan (SAP), where appropriate. Adjustments to the planned analyses are described in the final 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 clinical study report (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 (CI) 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.

Efficacy and safety will be assessed using the modified intention-to-treat (mITT) population, which consists of all randomly assigned participants who are exposed to at least 1 dose of study drug.

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

Summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The analysis model to make comparisons among treatment groups for primary efficacy analysis of HbA1c will be a mixed model for repeated measures (MMRM), with terms: treatment, visit, and treatment-by-visit interaction, SGLT-2i use (Yes or No), and baseline measurement as a covariate. An unstructured covariance matrix will model the relationship of within-patient errors. Analysis of other continuous measurements assessed over time will be conducted in a manner similar to the primary efficacy analyses with baseline HbA1c category added as a fixed effect.

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

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

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

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 drug will be presented by treatment groups. A listing of randomized participants not receiving study drug 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, 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, medical history, and concomitant illness will be summarized by treatment group using the mITT population.

9.3.2.3. Concomitant Therapy

Concomitant medications, including previous therapy for diabetes, will be summarized by anatomical therapeutic chemical classification and treatment group using the mITT population. In particular, the incidence of rescue therapy for severe, persistent hyperglycemia will be analyzed as an exploratory safety endpoint. Dose modifications of oral antihyperglycemic therapy will also be compared between treatment groups.

9.3.2.4. Treatment Compliance

Of the participants in the mITT population, frequency counts and percentages of participants prematurely discontinuing study drug, including the reason for premature discontinuation, will be presented by treatment group. A Kaplan-Meier analysis of time from randomization to premature study drug discontinuation by treatment group will be provided.

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

9.3.3. Primary Endpoint(s)/Estimand(s) Analysis

The primary efficacy measure is mean HbA1c change from baseline at 40 weeks, and the primary comparison is to compare tirzepatide 10 and/or 15 mg versus placebo. Type 1 error rate control strategy will be guided by a graphical testing procedure, with details provided in SAP.

The primary efficacy assessment, guided by the "efficacy" estimand, will use the EAS. The analysis model for change from baseline in HbA1c assessed over time up to the 40-week visit will be an MMRM, with terms: treatment, visit, and treatment-by-visit interaction, SGLT 2i use (Yes or No), and baseline HbA1c as a covariate. 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.

A robustness of the primary efficacy assessment, guided by the "treatment-regimen" estimand, will be conducted. This assessment will analyze change from baseline in HbA1c to the 40-week visit using an analysis of covariance (ANCOVA) with terms: treatment, SGLT 2i use (Yes or No), and baseline HbA1c as a covariate. The ANCOVA analysis will be conducted using the Full Analysis Set (FAS) at the 40-week visit, which consists of all available changes from baseline in HbA1c data at the 40-week visit, irrespective of whether they were obtained while the participants had discontinued the study treatment or whether the participant had been given rescue medication. Additionally, data for participants with missing values will be imputed using multiple imputation. Statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

9.3.4. Secondary Endpoint(s)/Estimand(s) Analysis

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

- superiority of tirzepatide 5 mg dose to placebo relative to mean change in HbA1c from baseline to the 40-week visit
- superiority of each tirzepatide dose to placebo relative to mean change in body weight from baseline to the 40-week visit
- superiority of each tirzepatide dose to placebo relative to the proportion of participants with HbA1c <7% (53 mmol/mol) at the 40-week visit
- superiority of each tirzepatide dose to placebo relative to the proportion of participants with HbA1c ≤6.5% (48 mmol/mol) at the 40-week visit
- superiority of each tirzepatide dose to placebo relative to mean change in FSG from baseline to the 40-week visit
- superiority of tirzepatide 10 mg and/or 15 mg dose to placebo relative to the proportion of participants with HbA1c <5.7% (39 mmol/mol) at the 40-week visit

The type I error-controlled strategy for the primary and secondary endpoints will be described in the SAP. All type I error-controlled secondary efficacy analyses will be conducted relative to, the "efficacy" estimand and the "treatment-regimen" estimand, each with a family-wise type I error rate of 0.05.

Analysis of change from baseline in HbA1c for the 5 mg tirzepatide dose at the 40-week visit will be conducted in a manner similar to the primary efficacy analyses as discussed in Section 9.3.3.

Analysis of change from baseline in body weight as well as FSG assessed at the 40-week visit will be an MMRM, with terms: treatment, visit, and treatment-by-visit interaction, SGLT 2i use (Yes or No), baseline Hba1c category and baseline body weight or baseline FSG as a covariate.

Comparisons among treatments relative to the proportion of participants with HbA1c <7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol) or <5.7% (39 mmol/mol) at the 40-week visit will be conducted using a logistic regression analysis with terms of treatment, SGLT-2i use (Yes or No), and baseline HbA1c as a covariate.

9.3.5. Tertiary Endpoint(s) Analysis

All tertiary efficacy analyses will be guided by the "efficacy" estimand without imputation of missing data and will be conducted using the EAS. Details will be provided in the SAP.

9.3.6. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses with placebo irrespective of adherence to study drug or initiation of rescue therapy. Thus, safety analyses will be conducted using the SS. Selected safety analyses may be conducted excluding data after the introduction of another antihyperglycemic therapy.

AEs 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 drug discontinuation due to AEs, deaths, and other CV 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 symptomatic hypoglycemia events and severe hypoglycemia in each category (either total or nocturnal) will be compared between tirzepatide doses and placebo using negative binomial regression analysis. Selected safety analyses may be conducted excluding data after introduction of another antihyperglycemic therapy (for example, rescue 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 CEC will be provided. The dates of randomization, event, first dose and last dose of study drug, and time from randomization to the event will be listed.

9.3.6.4. Central Laboratory Measures, Vital Signs, and Electrocardiograms

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

The percentages of participants with TE abnormal, high, or low laboratory measures at any time will be summarized and compared between treatment groups by using Fisher's exact test. A TE abnormal value is defined as a change from normal value at baseline to a value greater than the high limit at any time during Periods II and III. A TE low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time during Periods II and III. High and low laboratory limits will be determined by the central laboratory reference ranges.

9.3.7. Other Analyses

9.3.7.1. Health Economics

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

9.3.7.2. Subgroup Analyses

Subgroup analyses of mean change in HbA1c from baseline to the 40-week visit will be provided by age, gender, duration of diabetes, baseline HbA1c (≤8.0% or >8.0% [≤64, >64 mmol/mol], and baseline SGLT-2i use (Yes or No).

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 1:1:1:1 ratio to tirzepatide 5 mg, 10 mg, 15 mg, or placebo.

The trial is powered to assess superiority of tirzepatide 10 mg and 15 mg, each tested in parallel, against placebo at a 2-sided significance level of 0.025, relative to the primary endpoint (mean change in HbA1c from baseline to 40 weeks), under the following assumptions: use of a 2-sample t-test utilizing HbA1c data collected before initiation of any rescue medication or premature treatment discontinuation with no more than 25% of participants initiating rescue medication or prematurely discontinuing treatment in each treatment group; 0.95% greater mean reduction in HbA1c from baseline for 10 and 15 mg tirzepatide compared with placebo; 1:1:1:1 randomization; and a common standard deviation (SD) of 1.3%. On the basis of these

assumptions, a sample size of 256 participants is required to ensure at least 90% power to demonstrate that tirzepatide 10 mg and/or 15 mg are superior to placebo relative to the primary endpoint.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of ICH guidelines, the IRB/IEC, 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 participant or the participant's legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- 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.

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 permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records 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 (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

Additionally, clinical outcome assessment (COA) data (participant-focused outcome instrument) will be collected by the participant study personnel, 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 or by the local laboratory as specified in the table below.
- 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. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in source document.
- 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.

Hematology and HbA1c tests will be performed on whole blood samples at a Lilly-designated central laboratory. The whole blood samples will be analyzed by Q Squared Solutions (Beijing) Co., Ltd. and then disposed by Beijing Ruentex Environment Technology Corp and Beijing Solid Waste Logistics Co., Ltd.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs)	
Differential	
Percent and/or Absolutes Count of:	
Neutrophils, segmented	
Bands	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	

Clinical Laboratory Tests	Comments
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
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.
Hormones (female)	
Serum Pregnancy	Assayed by Lilly-designated laboratory.
Urine Pregnancy	Assayed and Evaluated locally
FSH	Assayed by Lilly-designated laboratory.
Urine Chemistry	Assayed by Lilly-designated laboratory.
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI)	
UACR	
Additional Testing	Assayed by Lilly-designated laboratory.
HbA1c	
Calcitonin	
Pancreatic Amylase	
Lipase	

Abbreviations: ADA = antidrug antibody; 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; 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; TSH = thyroid-stimulating hormone; UACR = urine albumin/creatinine ratio; VLDL-C = very-low-density lipoprotein cholesterol; WBC = white blood cells.

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	Sample Type	Laboratory Test [a]
Collect from 30 minutes to 4 hours after the start of the event. • Note: The optimal collection time is from 1 to 2 hours after the start of event.	Serum	total tryptase
	Serum	complement C3
	Serum	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.	Serum	Tirzepatide ADA
	Plasma	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 6.1.4 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 IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

f. Other situations:

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

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

10.3.3. Definition of Product Complaints

Product Complaint

- A 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 adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with 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 Investigator's Brochure (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 post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the SAE paper form (see next section) 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 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 or the 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, Institutional Review Boards (IRB)/Independent Ethics Committees (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 [Investigator's Brochure or state other 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	Adult females are considered women of childbearing potential unless they are women not of childbearing potential.
Women not of childbearing potential	Females are considered women not of childbearing potential if • they have a congenital anomaly, such as Müllerian agenesis • they are infertile due to surgical sterilization, or • they are postmenopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state should be defined as • A woman at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with an FSH >40 mIU/mL. or • A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy. Women should not be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

Abbreviations: SERM = selective estrogen receptor modulators; WOCBP = woman of child-bearing potential.

10.4.2. Contraception Guidance

10.4.2.1. Females

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

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…
agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods o calendar o ovulation o symptothermal, or o post-ovulation • declare abstinence just for the duration of a trial, or • use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle 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 Schedule of Activities for subsequent pregnancy testing requirements.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective. These forms of contraception must be used during the study and after the study for at least 60 days (2 months) 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 (that is, condom with spermicide, diaphragm with spermicide, or female condom with spermicide) to be considered effective.

Methods	Examples
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. Males

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 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 are listed in Section 10.4.2.1.

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

10.5.1. Hepatic Safety Monitoring

Close hepatic monitoring

Laboratory tests (Section 10.5.2), including ALT, AST, ALP, TBL, D. Bil, GGT, and 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
ALT or AST ≥1.5× ULN	ALT or AST ≥2× baseline
ALP <1.5× ULN	ALP ≥2× ULN
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL <1.5× ULN	TBL ≥2× ULN (except for patients with Gilbert's syndrome)
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 level; ULN = upper limit of normal.

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

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

Comprehensive hepatic evaluation

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

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5× ULN	ALT or AST ≥3× ULN with hepatic signs/symptoms[a], or ALT or AST ≥5× ULN
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 ≥3× ULN

ALP ≥1.5× ULN	ALP ≥2× baseline
TBL <1.5× ULN	TBL ≥2× ULN (except for patients with Gilbert's syndrome)
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%.

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

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. 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 (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), 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 case report forms (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 serious adverse event (SAE)
5. Discontinuation of study drug due to a hepatic event

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

10.5.2. Hepatic Monitoring Tests

See Section 10.5.1 Appendix 5 for guidance on appropriate test selection.

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

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

Hepatic Hematology Panel tests will be performed on whole blood samples at a Lilly-designated central laboratory. The whole blood samples will be analyzed by Q Squared Solutions (Beijing) Co., Ltd. and then disposed by Beijing Ruentex Environment Technology Corp and Beijing Solid Waste Logistics Co., Ltd.

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

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

[a] Not required if anti-actin antibody is tested.
[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.
[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

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

Type 1 Diabetes: Type 1 diabetes 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: Type 2 diabetes, 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 type 2 diabetes, 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 participants with type 2 diabetes later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998).

10.7. Appendix 7: Protocol GPIM 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 insulin dose and adjustment per TTT algorithm, assessing compliance with insulin dose adjustment TTT algorithm, 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 adverse events (AEs), serious adverse events (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 personnel.

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 19. 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 personnel 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.

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 V1 are valid for a maximum of 90 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 90 days from V1 to V3 the participant will proceed to the next study visit per the usual Schedule of Activities, provided that V3 must be conducted within 90 days from V1.
    - 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 90 days from V1 to V3: 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 Schedule of Activities. 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	Within 30 days before Visit 3.
Visit 3 (Randomization)	Within 90 days after Visit 1.
Visit 3 through 16	Within 7 days before or after the intended date.
Visit 17 through 18	Within 14 days before or after the intended date.
Visit 19 or Visit 99	Within 14 days before the intended date, or up to 28 days after the intended date.
Visit 801	Up to 28 days after the intended date.

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

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, 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: Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APPADL	Ability to Perform Physical Activities of Daily Living
AST	aspartate aminotransferase
BG	Blood glucose
blinding/masking	A double-blind study is one in which neither the participant/subject nor any of the investigator or sponsor personnel who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
BMI	body mass index
CEC	clinical endpoint committee
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease-Epidemiology
CMO	Chief Medical Officer
CMV	cytomegalovirus
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.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials

COVID-19	Coronavirus Disease 2019
CRF	case report form
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
CTA	Clinical Trial Agreement
CV	cardiovascular
DPP-4	dipeptidyl peptidase-4
DTSQs	Diabetes Treatment Satisfaction Questionnaire status
EAS	efficacy analysis set
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture system
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.
EQ-5D-5L	European Quality of Life-Dimensions
ERB	ethical review board
ERCP	endoscopic retrograde cholangiopancreatography
ET	early termination
FAS	Full Analysis Set
FBG	fasting blood glucose
FSG	fasting serum glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1

HDV	hepatitis D virus
HbA1c	hemoglobin A1c
IB	Investigator's Brochure
ICF	informed consent form
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
ICH	International Council for Harmonisation
ISR	injection site reactions
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.
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participants allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
IW-SP	Impact of Weight on Self-Perception
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NAFLD	nonalcoholic fatty liver disease
OAM	antihyperglycemic medication
OTC	over the counter

PCs	Product complaints
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QW	once weekly
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SDP	single-dose pen
SGLT-2i	sodium-glucose transport protein 2 inhibitor
SMBG	self-monitoring of blood glucose
SoA	Schedule of Activities
SS	safety analysis set
SUSARs	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TTT	treat to target
ULN	upper limit of normal

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