Protocol: I8F-MC-GPHD (c)

A Randomized, Phase 3, Open-label Trial Comparing the Effect of the Addition of Tirzepatide Once Weekly Versus Insulin Lispro (U100) Three Times Daily in Participants With Type 2 Diabetes Inadequately Controlled on Insulin Glargine (U100) With or Without Metformin (SURPASS-6)

NCT04537923

Approval Date: 29-Jan-2021

Title Page

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Protocol Number: I8F-MC-GPHD

Amendment Number: c

Compound: LY3298176

Study Phase: 3B

Short Title: Tirzepatide versus Insulin Lispro Three Times Daily in Background of Insulin Glargine (U100) with or without Metformin in Participants with Type 2 Diabetes

Acronym: SURPASS-6

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

Registry IND: ID 128801

Approval Date: Protocol Electronically Signed and Approved by Lilly on 01 April 2020.
Protocol Amendment (a) Electronically Signed and Approved by Lilly on 14 April 2020.
Protocol Amendment (b) Electronically Signed and Approved by Lilly on 13 January 2021
Protocol Amendment (c) Electronically Signed and Approved by Lilly date provided below.

Approval Date: 29-Jan-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment b	13 January 2021
Amendment a	14 April 2020
Original Protocol	01 April 2020

Amendment (c)
This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Protocol Amendment (b) Summary of Changes Table	The following text should not have been included "because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study."	Since Amendment (b) was substantial, this text should not have been included.
Section 10.9. Appendix 9: Provisions for Changes in Study Conduct during Exceptional Circumstances	Updated language for Exceptional Circumstances appendix	Updated as per Exceptional Circumstances appendix posted on 25 Jan 2021

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Phase 3, Open-label Trial Comparing the Effect of the Addition of Tirzepatide Once Weekly versus Insulin Lispro (U100) Three Times Daily in Participants with Type 2 Diabetes Inadequately Controlled on Insulin Glargine (U100) with or without Metformin (SURPASS-6)

Short Title: Tirzepatide versus Insulin Lispro Three Times Daily in Background of Insulin Glargine (U100) with or without Metformin in Participants with Type 2 Diabetes

Rationale

Type 2 diabetes mellitus is a progressive disease characterized by a gradual loss of beta cell function during its clinical course, resulting in the addition of insulin therapy in most cases as part of the continuum of care. When a person fails to attain optimal glycemic control with oral glucose lowering medications, therapy with a GLP-1 RA or 1 of the conventional insulin regimens is often initiated. Oral glucose lowering medications are typically continued with conventional insulin therapy, especially metformin.[1] Basal insulin is often the drug of choice when it is time to initiate insulin therapy. Due to its nearly 24-hour time action profile and perceived lack of a pronounced peak in concentration after injection, insulin glargine (U100) is often preferred over other basal insulins.

In a 3-year study evaluating the glycemic control of patients with T2DM and initiating basal insulin, only 29% of patients reached the glycemic goal of less than or equal to 7%.[2] Hypoglycemia risk and weight gain are the key limitations of any insulin therapy.[3] Hence, therapies which may be used in combination with insulin, or in lieu of insulin, that not only lower BG, but also reduce the risk of hypoglycemia and weight gain, may be of value in the treatment of T2DM.

In the Treat-to-Target Trial,[4] which optimized insulin glargine (U100) administration using a forced weekly dose escalation algorithm, less than 60% of patients achieved HbA1c levels less than or equal to 7%, and only 33.2% of patients obtained the target HbA1c without hypoglycemia. A significant weight gain, approximately 3 kg, was noted over the course of the 6-month study. Subsequent studies such as AT.LANTUS, LANMET, and INSIGHT using forced escalation of insulin therapy demonstrated similar results.[5-7] Therefore, a large proportion of patients treated with basal insulin regimen requires intensification of insulin therapy by addition of prandial insulin (basal/bolus).[1] Two reported studies explored the effect of intensive insulin therapy in patients with T2DM, the majority of which (approximately 80%) were previously treated with conventional insulin regimens.[8,9] In both studies, basal-bolus therapy enabled patients to achieve optimal glycemic control, but the increased risk of hypoglycemic events remained a concern (57%[9]; 37%[8]). In addition, both studies demonstrated an increase in body weight for insulin glargine (U100)-treated patients. Therefore, a diabetes therapy without these side-effects would be a valuable addition to diabetes care.

Several studies have demonstrated the superiority of combined use of basal insulin and GLP-1 RAs over a basal-bolus regimen in terms of glycemic control, weight loss, and hypoglycemia. GLP-1 RAs are effective glucose lowering medications, but more recent development of dual

GIP/GLP-1 RAs can exceed the efficacy of selective GLP-1 RAs (for example, additional effect on adipose tissue as indicated by the observation of increased energy utilization)[10] and has the potential to reach higher efficacy in target tissues that express both GIP R and GLP-1 R. Therefore, there is a scientific rationale to hypothesize that tirzepatide, a long-acting weekly GIP/GLP-1 RA, when added to basal insulin in patients with advanced T2DM who need additional glycemic control can provide better glycemic control without weight gain and lower rates of hypoglycemia compared to basal-bolus regimen.

Objectives and Endpoints

Objectives	Endpoints
Primary • To demonstrate noninferiority of tirzepatide pooled cohort of 5 mg, 10 mg, and 15 mg QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin, with respect to glycemic control at 52 weeks for:	• Mean change in HbA1c from baseline
Key Secondary (controlled for type 1 error)	
Efficacy • To demonstrate superiority of tirzepatide pooled cohort 5 mg, 10 mg, and 15 mg QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks for:	• Mean change in HbA1c from baseline • Mean change in body weight from baseline • Proportion of participants with HbA1c target values of <7.0% (53 mmol/mol)
• To demonstrate noninferiority of tirzepatide 5 mg, 10 mg, and/or 15 mg QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks for:	• Mean change in HbA1c from baseline
• To demonstrate superiority of tirzepatide 5 mg, 10 mg, and/or 15 mg QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks for:	• Mean change in HbA1c from baseline • Mean change in body weight from baseline
Additional Secondary (not controlled for type 1 error)	
Efficacy • To demonstrate that tirzepatide pooled cohort of 5 mg, 10 mg, and 15 mg QW is superior to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks for:	• Proportion of participants achieving HbA1c target ≤6.5% (48 mmol/mol) • Mean change in fasting serum glucose (central laboratory) from baseline • Mean change in daily average 7-point

	SMBG profiles from baseline • Proportion of participants who achieved HbA1c target value of <7.0% (53 mmol/mol) without hypoglycemia (confirmed glucose <54 mg/dL (3.0 mmol/L) or report of severe hypoglycemia) • Proportion of participants who achieved weight loss of ≥5% from baseline • Mean change from randomization in SF-36v2 Acute Form o Physical Component Summary score o Mental Component Summary score o Physical Functioning domain score o General Health domain score o Vitality domain score o Role-Physical domain score o Bodily Pain domain score o Social Functioning domain score o Role-Emotional domain score o Mental Health domain score
• To demonstrate superiority of tirzepatide 5 mg, 10 mg, and/or 15 mg QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks for:	• Proportion of participants with HbA1c target values of <7.0% (53 mmol/mol) • Proportion of participants achieving HbA1c target ≤6.5% (48 mmol/mol) • Mean change in fasting serum glucose (central laboratory) from baseline • Mean change in daily average 7-point SMBG profiles from baseline • Proportion of participants who achieved HbA1c target value of <7.0% (53 mmol/mol) without hypoglycemia (confirmed glucose <54 mg/dL (3.0 mmol/L) or report of severe hypoglycemia) • Proportion of participants who achieved weight loss of ≥5% from baseline • Mean change from randomization in SF-36v2 Acute Form o Physical Component Summary

	score o Mental Component Summary score o Physical Functioning domain score o General Health domain score o Vitality domain score o Role-Physical domain score o Bodily Pain domain score o Social Functioning domain score o Role-Emotional domain score o Mental Health domain score
Safety • To evaluate the safety of tirzepatide pooled cohort of 5 mg, 10 mg, and 15 mg QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks, and at the end of the safety follow-up period, with respect to the following outcomes:	• TEAEs • SAEs • Early discontinuation of study intervention, tirzepatide or insulin lispro (U100), due to AEs • Adjudicated pancreatitis • Serum calcitonin • Incidence of treatment-emergent ADAs and systemic hypersensitivity reactions • Mean change in systolic and diastolic blood pressure and heart rate from baseline • Incidence of initiation of rescue therapy for severe, persistent hyperglycemia • Occurrence of hypoglycemic episodes

Abbreviations: ADA = anti-drug antibody; AE = adverse event; HbA1c = hemoglobin A1c; QW = once weekly; SAE = serious adverse event; SF-36v2 = Short-Form-36 Health Survey version 2 acute form; SMBG = self-monitored blood glucose; TEAE = treatment-emergent adverse event; TID = three times a day.

Overall Design

Study I8F-MC-GPHD (SURPASS-6) is a Phase 3b, open-label, multicenter, parallel-arm, randomized study to compare the efficacy and safety of tirzepatide QW (pooled cohort of 5 mg, 10 mg, and 15 mg) to insulin lispro (U100) TID in adult study participants with T2DM inadequately controlled on basal insulin glargine (U100) with or without metformin. Participants will be randomized to receive 5 mg tirzepatide, 10 mg tirzepatide, 15 mg tirzepatide, or insulin lispro (U100). The study duration is approximately 68 weeks over 3 required study periods:

- Study period 1: an approximately 12-week screening/insulin optimization period for participants who need insulin glargine (U100) optimization / an approximately 5-week screening period for participants who do not need insulin glargine (U100) optimization
- Study period 2: study intervention period for 52 weeks beginning at randomization to last treatment visit, and
- Study period 3: post-treatment 4-week safety follow-up period.

Disclosure Statement

This is a parallel treatment study with 4 arms and no masking.

Number of Participants

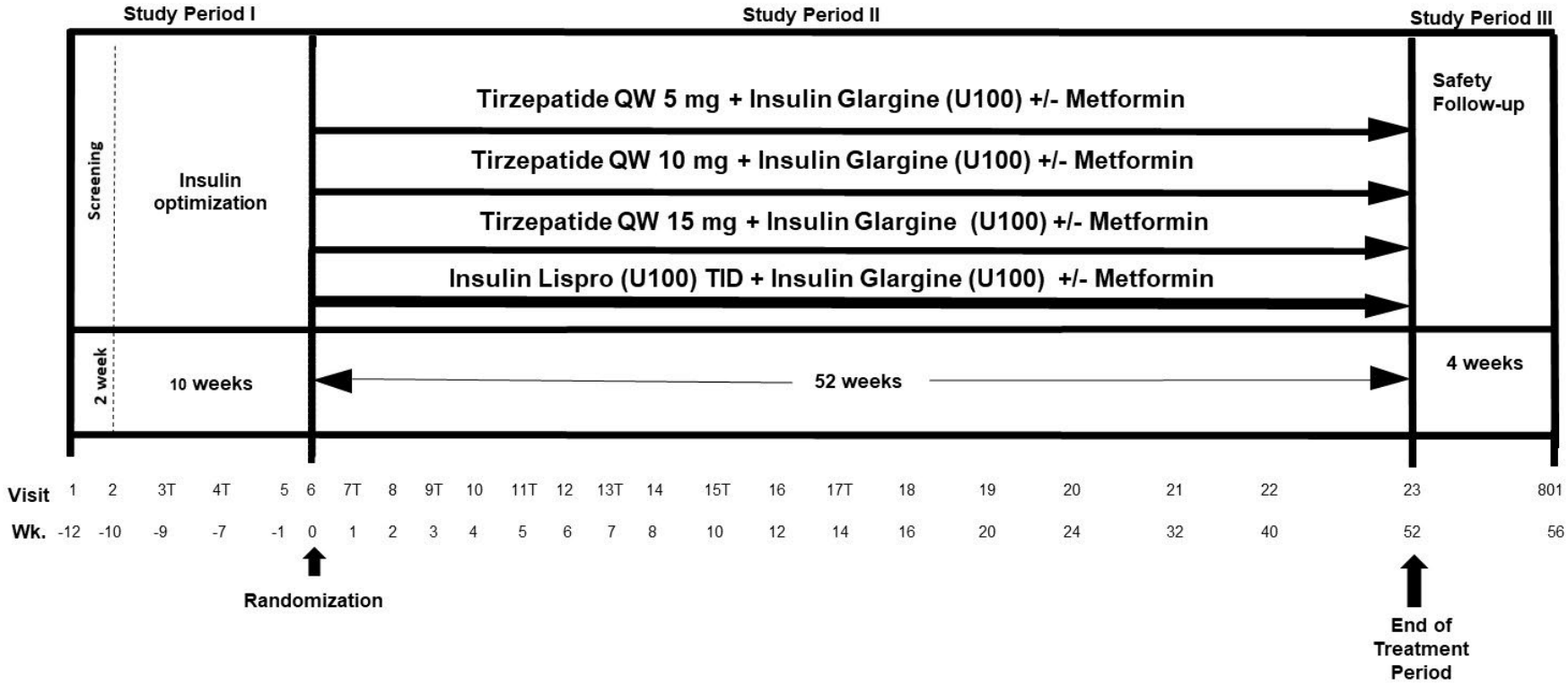
Approximately 1182 participants will be randomized in a 1:1:1:3 ratio to 5 mg tirzepatide (197 participants), 10 mg tirzepatide (197 participants), 15 mg tirzepatide (197 participants) or insulin lispro (U100) (591 participants). See Section 9.2.

Intervention Groups and Duration

Study GPHD will consist of 3 periods: an approximately 12-week screening/insulin optimization period for participants who need insulin glargine (U100) optimization / an approximately 5-week screening period for participants who do not need insulin glargine (U100) optimization, followed by a 52-week treatment period and a 4-week safety follow-up period. Participants will be randomized to either tirzepatide 5 mg, tirzepatide 10 mg, tirzepatide 15 mg, or insulin lispro (U100).

1.2. Schema

Figure 1. Illustration of Study GPHD Design



Abbreviations: QW= once weekly, T= telephone, TID = three times a day; Wk = week.

1.3. Schedule of Activities (SoA)

The Schedule of Activities described below should be followed for all participants enrolled in Study GPHD. However, for those participants whose participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Section 10.9. Appendix 9 for additional guidance.

Table 1. Study Period I-Screening/Insulin Optimization

Activity	**Screening/Insulin Optimization**					**Comments**
Visit Number	1	2	3	4	5	
Weeks from Randomization	-12	-10	-9	-7	-1	Will differ for Group 1A participants. See Section 4.1.1.1 for definition of Group 1A participants
Study Day						
Visit interval tolerance (days)	--	±3	±3	±3	±3	The visit date during screening/insulin optimization is determined in relation to the date of Visit 1 (± the allowed visit window)
Fasting Visit						
Telephone Visit			X	X		
Informed Consent	X					
Inclusion and exclusion criteria review	X	X	X	X	X	
Demographics	X					
Preexisting conditions and medical history, including relevant surgical history	X					Medical history includes assessment of preexisting conditions (including history of gallbladder disease, cardiovascular disease, diabetic retinopathy, and medullary thyroid carcinoma).
Concomitant medications	X	X	X	X	X	
Adverse events	X	X	X	X	X	
Physical Evaluation OR Clinical Assessments						

Activity	Screening/Insulin Optimization					Comments
Visit Number	1	2	3	4	5	
Weeks from Randomization	-12	-10	-9	-7	-1	Will differ for Group 1A participants. See Section 4.1.1.1 for definition of Group 1A participants
Study Day						
Visit interval tolerance (days)	--	±3	±3	±3	±3	The visit date during screening/insulin optimization is determined in relation to the date of Visit 1 (± the allowed visit window)
Fasting Visit						
Telephone Visit			X	X		
Height	X					Measurements must be in centimeter. For instructions see Section 10.8 Appendix 8
Weight	X				X	Measurements must be in kilogram. For instructions see Section 10.8 Appendix 8
Vital Signs (Systolic and diastolic blood pressure, pulse rate)	X				X	Vital sign measurements should be taken 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. BP must be taken with an automated blood pressure machine.
Physical examination	X					
Dilated Fundoscopic examination		X				Dilated fundoscopic examination will be performed by an eye care professional (ophthalmologist or optometrist) for all participants within 3 weeks after Visit 2 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.
Participant Education						
Diabetes education		X				Includes counseling on diet and exercise, symptoms and management of hypoglycemia, etc.; should be repeated as needed.
BG meter, SMBG training		X				Should be repeated as needed

Activity	Screening/Insulin Optimization					Comments
Visit Number	1	2	3	4	5	
Weeks from Randomization	-12	-10	-9	-7	-1	Will differ for Group 1A participants. See Section 4.1.1.1 for definition of Group 1A participants
Study Day						
Visit interval tolerance (days)	--	±3	±3	±3	±3	The visit date during screening/insulin optimization is determined in relation to the date of Visit 1 (± the allowed visit window)
Fasting Visit						
Telephone Visit			X	X		
Dispense BG meter/supplies (as needed)		X			X	
Study intervention training		X				Appropriate training on the insulin pen [explanation of instruction for use with demo device (if available)] for injection of insulin glargine (U100) will be provided. Training should be repeated as needed
Participant Diary (Paper)						
Dispense diary; instruct in use		X				Should be repeated as needed
Remind participants about 7-point SMBG			X		X	See Section 4.1.1.1 for definitions of Group 1 and 2 participants: 1. Group 1A - remind at Visit 3 2. Group 1B and Group 2 participants- remind at Visit 5 Participant is required to collect two 7-point SMBGs on nonconsecutive days during the week prior to randomization. A 7-point SMBG consists of measurements before and 2 hours after each of 3 main meals within the same day and at bedtime (Pre-first meal BG can be same as fasting BG). If more than two (2) 7-point SMBG profiles are available, the 2 most recent profiles on nonconsecutive days should be used.
Review hypoglycemic events collected in the diary			X	X	X	

Activity	Screening/Insulin Optimization					Comments
Visit Number	1	2	3	4	5	
Weeks from Randomization	-12	-10	-9	-7	-1	Will differ for Group 1A participants. See Section 4.1.1.1 for definition of Group 1A participants
Study Day						
Visit interval tolerance (days)	--	±3	±3	±3	±3	The visit date during screening/insulin optimization is determined in relation to the date of Visit 1 (± the allowed visit window)
Fasting Visit						
Telephone Visit			X	X		
Diary compliance check			X	X	X	
Laboratory Tests and Sample Collections						
Hematology	X					
HbA1c	X				X	HbA1c lab test at Visit 5 is only for group 1B and group 2. Must be from central laboratory.
Clinical Chemistry	X					
Serum Pregnancy	X				X	Only for women of childbearing potential.
Follicle Stimulating Hormone (FSH)	X					Performed at Visit 1 to confirm post-menopausal status for women 40 to less than 55 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause. (**Note:** FSH >40 mIU/mL confirms post-menopausal status)
Calcitonin	X					
Pancreatic amylase	X					
Lipase	X					

Activity	Screening/Insulin Optimization					Comments
Visit Number	1	2	3	4	5	
Weeks from Randomization	-12	-10	-9	-7	-1	Will differ for Group 1A participants. See Section 4.1.1.1 for definition of Group 1A participants
Study Day						
Visit interval tolerance (days)	--	±3	±3	±3	±3	The visit date during screening/insulin optimization is determined in relation to the date of Visit 1 (± the allowed visit window)
Fasting Visit						
Telephone Visit			X	X		
eGFR (CKD-EPI)	X					The CKD-EPI equation will be used by the central lab to estimate and report eGFR.
Dosing						
Review insulin glargine (U100) dosing and assess the need for dose adjustment			X	X	X	See Section 6.1.2 for more details
Dispense insulin glargine (U100)		X			X	

Table 2. Study Period II-Treatment Period

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Inclusion and exclusion criteria review	X																			
Concomitant medications	X	X	X	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	
Physical Evaluation OR Clinical Assessments																				
Weight	X				X				X		X		X	X	X	X	X	X	X	Measurements must be in kilogram. For instructions see Section 10.8 Appendix 8
Waist Circumference	X				X				X		X		X	X	X	X	X	X	X	Measurement must be in centimeter. For instructions see Section 10.8 Appendix 8

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Vital Signs (Systolic and diastolic blood pressure, pulse rate)	X		X		X		X		X		X		X	X	X	X	X	X	X	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 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 BP machine.

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Physical examination																	X	X	X	
12-lead ECG (local)	X																X	X	X	
Participant Education																				
Diabetes education	X																			Includes counseling on diet and exercise, symptoms and management of hypoglycemia, etc.; should be repeated as needed.
BG meter, SMBG training	X																			Should be repeated as needed
Dispense BG meter/supplies (as needed)	X		X		X		X		X		X		X	X	X	X	X	X	X	

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Study intervention training	X																			<u>Participants randomized to tirzepatide QW:</u> Site-personnel will provide appropriate training on tirzepatide autoinjector [explanation of instruction for use with demo device (if available)] <u>Participants randomized to insulin lispro (U100) TID:</u> Site personnel will provide appropriate training on the insulin pen [explanation of instruction for use with demo device (if available)] Training should be repeated as needed

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Participant Diary (paper)																				
Dispense diary; instruct in use	X				X				X		X		X	X	X	X	X	X	X	

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Remind participants about 7-point SMBG														X		X	X			Participant is required to collect two 7-point SMBGs on nonconsecutive days within a week prior to the next visit. A 7-point SMBG consists of measurements before and 2 hours after each of 3 largest meals within the same day and at bedtime (Pre-first meal BG can be same as fasting BG). If more than two (2) 7-point SMBG profiles are available, the 2 most recent profiles on nonconsecutive days should be used.

Activity	**Treatment Period**																			**Comments**
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Review 7-point SMBG values collected	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	
Diary collection and/or return	X		X		X		X		X		X		X	X	X	X	X	X	X	

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Patient Reported Outcomes (paper)																				PRO 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.
IW-SP	X																	X	X	
APPADL	X																	X	X	
EQ-5D-5L	X																	X	X	
SF-36v2 acute	X																	X	X	
Laboratory Tests and Sample Collections																				
Hematology	X										X				X		X	X	X	

Activity	**Treatment Period**																			**Comments**
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
HbA1c	X				X				X		X		X	X	X		X	X	X	Must be from central laboratory
Clinical Chemistry	X										X				X		X	X	X	
Glucose (central laboratory)	X		X		X				X		X		X	X	X		X	X	X	
Lipid Panel	X																X	X	X	

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Urine Pregnancy (local)	X										X				X		X	X		Must be performed at Visit 6 with the result available prior to randomization and first injection of study intervention(s) for women of childbearing potential only. Additional tests will be performed at Visits 16,20,22, and 23. May also be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, testing can also occur at other times during the study treatment period.
Calcitonin	X										X				X		X	X	X	

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Pancreatic amylase	X										X				X		X	X	X	
Lipase	X										X				X		X	X	X	
eGFR (CKD-EPI)	X										X				X		X	X	X	
Urinary albumin/creatinine ratio (UACR)	X										X				X		X	X	X	
Stored Samples																				
Exploratory stored samples	X										X				X		X	X	X	Should be preferable taken before dose of study intervention when applicable.
Randomization and Dosing																				
Randomization	X																			
Dispense study intervention(s)	X		X		X		X		X		X		X	X	X	X	X	X	X	

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Observe participant administer study intervention	X																			<u>Participants randomized to Tirzepatide QW:</u> Site personnel will observe the study participant inject the first dose of tirzepatide. <u>Participants randomized to insulin lispro (U100) TID:</u> Site personnel will, if feasible, observe the study participant inject the first dose of insulin lispro (U100) prior to a main meal.

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Review and assess insulin dose adjustment [insulin glargine (U100) and insulin lispro (U100) TID, if applicable] per TTT algorithm	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess compliance with insulin dose adjustment [insulin glargine (U100) and insulin lispro (U100) TID, if applicable] TTT algorithm			X		X		X		X		X		X	X	X	X	X	X	X	Assessment of the participant's compliance to the TTT algorithm will be collected in the eCRF at Visits marked X for the period since the previous in-clinic visit.
Participant returns study intervention(s) and injection supplies	X		X		X		X		X		X		X	X	X	X	X	X	X	

Activity	Treatment Period																			Comments
Visit Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ET	
Weeks from randomization	0	1	2	3	4	5	6	7	8	10	12	14	16	20	24	32	40	52		
Study day	1	8	15	22	29	36	43	50	57	71	85	99	113	141	169	225	281	365		
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7		The visit date from visit 7 onwards is determined in relation to the actual date of Visit 6 (± the allowed visit window)
Fasting Visit	X		X		X				X		X		X	X	X		X	X	X	
Telephone Visit		X		X		X		X		X		X								
Assess study intervention(s) compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 3. Study Period III-Safety Follow-Up Period

Activity	Follow-Up Period	Comment
Visit Number	801	
Weeks from randomization	4 weeks post end of Tx	
Visit interval tolerance (days)	±7	
Fasting Visit	X	
Concomitant medications	X	
Adverse events	X	
Physical Evaluation OR Clinical Assessments		
Weight	X	Measurements must be in kilogram. For instructions see Section 10.8 Appendix 8
Waist Circumference	X	Measurements must be in centimeter. For instructions see Section 10.8 Appendix 8
Vital Signs (Systolic and diastolic blood pressure, pulse rate)	X	Vital sign measurements should be taken 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. BP must be taken with an automated blood pressure machine.
12-Lead ECG (local)	X	
Participant Diary		
Review hypoglycemic events collected in the diary	X	
Diary return	X	
Laboratory Tests and Sample Collection		
Hematology	X	
HbA1c	X	

Activity	Follow-Up Period	Comment
Visit Number	801	
Weeks from randomization	4 weeks post end of Tx	
Visit interval tolerance (days)	±7	
Fasting Visit	X	
Clinical Chemistry	X	
Glucose (central laboratory)	X	
Lipid Panel	X	
Urine Pregnancy (local)	X	
Calcitonin	X	
Pancreatic Amylase	X	
Lipase	X	
Urinary albumin/creatinine ratio (UACR)	X	
Stored Samples		
Exploratory stored samples	X	

Abbreviations: AE = adverse events; APPADL = Ability to Perform Physical Activities of Daily Living; BG = blood glucose; BP = blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; eGFR (CKD-EPI) = estimated glomerular filtration rate (chronic kidney disease-epidemiology); ET = early termination; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; IW-SP = Impact of Weight on Self-Perception; QW = once weekly; SF-36v2 = Short-Form-36 Health Survey version 2 acute form; SMBG = self-monitored blood glucose; TID = three times daily; TTT = treat-to-target; Tx = treatment; UACR = Urinary albumin/creating ratio

2. Introduction

Tirzepatide (LY3298176) is a once-weekly dual GIP and GLP-1 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. It is administered subcutaneously.

2.1. Study Rationale

Type 2 diabetes mellitus is a progressive disease characterized by a gradual loss of beta cell function during its clinical course, resulting in the addition of insulin therapy in most cases as part of the continuum of care. When a person fails to attain optimal glycemic control with oral glucose lowering medications, therapy with a GLP-1 RA or one of the conventional insulin regimens is often initiated. Oral glucose lowering medications are typically continued with conventional insulin therapy, especially metformin.[1] Basal insulin is often the drug of choice when it is time to initiate insulin therapy. Due to its nearly 24-hour time action profile and perceived lack of a pronounced peak in concentration after injection, insulin glargine (U100) is often preferred over other basal insulins.

In a 3-year study evaluating the glycemic control of patients with T2DM and initiating basal insulin, only 29% of patients reached the glycemic goal of less than or equal to 7%.[2] Hypoglycemia risk and weight gain are the key limitations of any insulin therapy.[3] Hence, therapies which may be used in combination with insulin, or in lieu of insulin, that not only lower BG, but also reduce the risk of hypoglycemia and weight gain may be of value in the treatment of T2DM.

In the Treat-to-Target Trial,[4] which optimized insulin glargine (U100) administration using a forced weekly dose escalation algorithm, less than 60% of patients achieved HbA1c levels less than or equal to 7%, and only 33.2% of patients obtained the target HbA1c without hypoglycemia. A significant weight gain, approximately 3 kg, was noted over the course of the 6-month study. Subsequent studies such as AT.LANTUS, LANMET, and INSIGHT using forced escalation of insulin therapy demonstrated similar results.[5-7] Therefore, a large proportion of patients treated with basal insulin regimen require intensification of insulin therapy by addition of prandial insulin (basal/bolus).[1] Two reported studies explored the effect of intensive insulin therapy in patients with T2DM, the majority of which (approximately 80%) were previously treated with conventional insulin regimens.[8,9] In both studies, basal-bolus therapy enabled participants to achieve optimal glycemic control, but the increased risk of hypoglycemic events remained a concern (57%[9]; 37%[8]). In addition, both studies demonstrated an increase in body weight for insulin glargine (U100)-treated patients. Therefore, a diabetes therapy without these side-effects would be a valuable addition to diabetes care.

Several studies have demonstrated the superiority of combined use of basal insulin and GLP-1 RAs over a basal-bolus regimen in terms of glycemic control, weight loss and hypoglycemia. GLP-1 RAs are effective glucose lowering medications, but more recent development of dual GIP/GLP-1 RAs can exceed the efficacy of selective GLP-1 RAs (for example, additional effect on adipose tissue as indicated by the observation of increased energy utilization)[10] and has the potential to reach higher efficacy in target tissues that express both GIP R and GLP-1 R. Therefore, there is a scientific rationale to hypothesize that tirzepatide, a long acting weekly

GIP/GLP-1 RA, when added to basal insulin in patients with advanced T2DM who need additional glycemic control, can provide better glycemic control without weight gain and lower rates of hypoglycemia compared to basal-bolus regimen.

2.2. Background

Two global Phase 2 studies, Studies I8F-MC-GPGB (GPGB) and I8F-MC-GPGF (GPGF), conducted in patients with T2DM have informed the Phase 3 clinical plan for evaluation for tirzepatide in this population.

A 26-week Phase 2 Study GPGB assessed the efficacy, tolerability, and safety of QW administration of 4 doses (1 mg, 5 mg, 10 mg, and 15 mg) of tirzepatide versus placebo and an active comparator (dulaglutide 1.5 mg QW) in 318 participants with T2DM with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy. The doses of 10 mg and 15 mg were attained by titration.[11]

Study GPGB demonstrated that tirzepatide 5 mg, 10 mg, and 15 mg doses significantly lowered HbA1c and body weight in a dose-dependent manner in patients with T2DM in comparison to placebo. In addition, reductions in HbA1c in the tirzepatide 5, 10, and 15 mg doses were greater than with dulaglutide 1.5 mg QW. Similar to the GLP-1 receptor agonist class, most of the tirzepatide AEs were GI-related, consisting mainly of nausea, vomiting, and diarrhea and were dose-dependent. The GI AEs were usually mild to moderate in intensity. SAEs were balanced across the treatment groups and none of the groups reported severe hypoglycemia.[11]

As it was recognized that the escalation scheme employed in Study GPGB was unlikely to be optimal for the reduction of GI-related AEs expected with tirzepatide, Study GPGF was designed to explore alternative escalation schemes (longer time intervals between dose escalations and smaller dose escalations) to support evaluation of optimized dosing regimen(s) in Phase 3 clinical studies. This was a 12-week, placebo-controlled study to assess the efficacy and safety of 3 different escalation schemes to attain doses as high as 15 mg of tirzepatide in patients with T2DM. Tirzepatide treatment resulted in clinically significant reductions in HbA1c. The study suggested that lower starting doses and smaller dose increments were associated with a more favorable side-effect profile.[12]

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

A single dose, tirzepatide 5 mg, Phase 1 Study GPGG was conducted in subjects with varying degrees of renal impairment. Tirzepatide exposure in subjects with mild, moderate, and severe renal impairment and end stage renal disease were similar to that in subjects with normal renal function. Since there were no clinically relevant effects of renal impairment on PK of tirzepatide, no dose adjustments may be required in patients with renal impairment or in patients undergoing dialysis.

2.3. Benefit/Risk Assessment

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate noninferiority of tirzepatide (pooled cohort of 5 mg, 10 mg, and 15 mg) QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin, with respect to glycemic control at 52 weeks	• Mean change in HbA1c from baseline
Key Secondary (controlled for type 1 error)	
Efficacy	
• To demonstrate superiority of tirzepatide (pooled cohort 5 mg, 10 mg, and 15 mg) QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks	• Mean change in HbA1c from baseline • Mean change in body weight from baseline • Proportion of participants with HbA1c target values of <7.0% (53 mmol/mol)
• To demonstrate noninferiority of tirzepatide (5 mg, 10 mg, and/or 15 mg) QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks	• Mean change in HbA1c from baseline
• To demonstrate superiority of tirzepatide (5 mg, 10 mg, and/or 15 mg) QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks	• Mean change in HbA1c from baseline • Mean change in body weight from baseline
Additional Secondary (not controlled for type 1 error)	
Efficacy	
• To demonstrate that tirzepatide (pooled cohort of 5 mg, 10 mg, and 15 mg) QW is superior to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks for:	• Proportion of participants achieving HbA1c target ≤6.5% (48 mmol/mol) • Mean change in fasting serum glucose (central laboratory) from baseline • Mean change in daily average 7-point SMBG profiles from baseline • Proportion of participants who achieved HbA1c target value of <7.0% (53 mmol/mol) without hypoglycemia (confirmed glucose <54 mg/dL [3.0 mmol/L] or report of severe hypoglycemia) • Proportion of participants who achieved weight loss of ≥5% from baseline

	• Mean change from randomization in SF-36v2 acute form
	  o Physical Component Summary score
	  o Mental Component Summary score
	  o Physical Functioning domain score
	  o General Health domain score
	  o Vitality domain score
	  o Role-Physical domain score
	  o Bodily Pain domain score
	  o Social Functioning domain score
	  o Role-Emotional domain score
	  o Mental Health domain score

• To demonstrate superiority of tirzepatide (5 mg, 10 mg, and/or 15 mg) QW to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin at 52 weeks	• Proportion of participants with HbA1c target values of <7.0% (53 mmol/mol)
	• Proportion of participants achieving HbA1c target ≤6.5% (48 mmol/mol)
	• Mean change in fasting serum glucose (central laboratory) from baseline
	• Mean change in daily average 7-point SMBG profiles from baseline
	• Proportion of participants who achieved HbA1c target value of <7.0% (53 mmol/mol) without hypoglycemia (confirmed glucose <54 mg/dL [3.0 mmol/L] or report of severe hypoglycemia)
	• Proportion of participants who achieved weight loss of ≥5% from baseline
	• Mean change from randomization in SF-36v2 acute form
	  o Physical Component Summary score
	  o Mental Component Summary score
	  o Physical Functioning domain score
	  o General Health domain score
	  o Vitality domain score

	○ Role-Physical domain score ○ Bodily Pain domain score ○ Social Functioning domain score ○ Role-Emotional domain score ○ Mental Health domain score
Safety • To evaluate the safety of tirzepatide (pooled cohort of 5 mg, 10 mg, and 15 mg) QW to insulin lispro TID, when added to insulin glargine (U100), with or without metformin at 52 weeks, and at the end of the safety follow-up period, with respect to the following outcomes	• TEAEs • SAEs • Early discontinuation of study intervention (tirzepatide or insulin lispro [U100]) due to AEs • Adjudicated pancreatitis • Serum calcitonin • Incidence of treatment-emergent ADAs and systemic hypersensitivity reactions • Mean change in systolic and diastolic blood pressure and heart rate from baseline • Incidence of initiation of rescue therapy for severe, persistent hyperglycemia • Occurrence of hypoglycemic episodes
Tertiary/Exploratory • To compare tirzepatide (pooled cohort of 5 mg, 10 mg, and 15 mg) QW to insulin lispro (U100) TID when added to insulin glargine (U100), with or without metformin at 52 weeks, with respect to the following	• Change in lipids (total cholesterol, high-density lipoproteins, low-density lipoproteins, very low-density lipoproteins, and triglycerides) from baseline • Mean change in body mass index from baseline • Mean change in waist circumference from baseline • Patient-Reported Outcomes: EQ-5D-5L, APPADL, IW-SP

Abbreviations: ADA = anti-drug antibody; AE = adverse event; APPADL= Ability to Perform Physical Activities of Daily Living; HbA1c = hemoglobin A1c; IW-SP = Impact of Weight on Self-perception; QW = once weekly; SAE = serious adverse event; SF-36v2 = Short-Form-36 Health Survey version 2 acute form; SMBG = self-monitored blood glucose; TEAE = treatment-emergent adverse event; TID = three times a day.

4. Study Design

4.1. Overall Design

Study GPHD is a multicenter, multinational, randomized, open-label, Phase 3b study which will assess the safety and efficacy of the addition of tirzepatide (5 mg, 10 mg, or 15 mg QW) versus insulin lispro (U100) TID for change from baseline in HbA1c in participants with T2DM inadequately controlled on insulin glargine (U100) with or without metformin over a 52-week treatment.

Approximately 1182 participants with T2DM will be randomized in this study. Prior to Visit 1, participants will have been treated for at least 90 days

- with once or twice daily doses of basal insulin, either
    - insulin NPH
    - insulin glargine (U100)
    - insulin glargine (U300)
    - insulin detemir (U100)
    - insulin degludec (U100), or
    - insulin degludec (U200)
- with or without
    - oral glucose lowering medications in any combination up to 2 of the following:
        - stable dose of metformin, ≥1500 mg/day and up to maximum approved dose per country specific approved label
        - SUs
        - DPP4is

The study will consist of 3 periods:

- an approximately 12-week screening/insulin optimization period for participants who need insulin glargine (U100) optimization / an approximately 5-week screening period for participants who do not need insulin glargine (U100) optimization (see Section 4.1.1.1.)
- a 52-week treatment period, and
- a 4-week safety follow-up period.

Participants will be randomized in a 1:1:1:3 ratio to

- tirzepatide 5 mg QW
- tirzepatide 10 mg QW
- tirzepatide 15 mg QW, or
- insulin lispro (U100) TID.

Participants will be stratified based on

- country
- pre-randomization HbA1c (≤8.5% or >8.5% [69 mmol/mol]), and
- baseline metformin use (Yes or No).

4.1.1. Overview of Study Periods

On all designated fasting office visits, study participants must report to the site in a fasting condition, after approximately 8 hours without eating, drinking (except water), or performing any significant physical activity. If a participant is adversely affected by the fasting condition, they are allowed to eat; however, specific study procedures need to be completed while fasting.

4.1.1.1. Study Period I - Screening and Insulin Optimization

Visit 1

The purpose of screening procedures at Visit 1 is to

- establish initial eligibility, and
- obtain blood samples for laboratory assessments needed to confirm eligibility at Visit 2.

The participant will sign the ICF before any study procedures are performed.

Procedures at this visit will be performed as shown in Section 1.3.

At Visit 1, participants who meet

- all applicable inclusion criteria, and
- none of the applicable exclusion criteria

will continue on their prestudy therapy doses between Visits 1 and 2.

Visit 2 to Visit 6

Screening laboratory evaluations and fundoscopic examination

At Visit 2, screening laboratory results from Visit 1 will be reviewed.

For those participants meeting all other eligibility requirements, a dilated fundoscopic examination performed by an ophthalmologist or optometrist must be completed within 3 weeks after Visit 2 to ensure identification and exclusion of participants with

- proliferative diabetic retinopathy
- diabetic macular edema, or
- nonproliferative diabetic retinopathy who require acute treatment.

If calcitonin results are unavailable, then Visit 2 can proceed and calcitonin results can be reviewed later before randomization occurs.

Disease management and study procedure training

At Visit 2, participants will undergo training on

- disease management
- study procedures
- management of hypoglycemia, and
- management of severe hyperglycemia.

This training can be repeated at subsequent visits, as deemed appropriate.

Also, at Visit 2, participants and their caregiver(s), if applicable, will receive a glucometer and training on how to perform SMBG.

Participant diary

At Visit 2, participants will be

- provided a diary, and
- trained as appropriate to perform and/or record
    - SMBG, per clinical plan outlined by investigator
    - hypoglycemic events
    - insulin glargine (U100) dose, and
    - insulin glargine (U100) dose adjustments, per clinical plan outlined by investigator.

Treatment

At Visit 2,

- all participants should switch their pre-trial basal insulin therapy to Lilly provided insulin glargine (U100) administered daily at bedtime and at approximately the same time throughout the study
- site personnel will provide appropriate training on instruction for use of the insulin pen for injection of insulin glargine (U100). The training can be provided using a demonstration device, if available. This training will be repeated at subsequent visits, as needed, and
- participant should discontinue other oral glucose lowering agents, SU and/or DPP4i, if used.

Between Visit 2 up to Visit 6, participants should

- continue taking the same dose and formulation of metformin ≥1500 mg/day , if used, unless any contraindication or clinical condition develops that requires adjustment of the dose (see Section 6.5.), and
- receive optimal therapy or clinical care for diabetes related comorbidities.

At Visit 2, the investigator will determine whether the participant belongs to **Group 1** or **Group 2** and follow insulin optimization plan accordingly. Table 4. describes **Group 1** and **Group 2** participants.

Table 4. Descriptions of Group 1 and 2 Participants Determined at Visit 2

Group	Description
1	*Participants who* • *are on pre-trial basal insulin regimen of insulin glargine (U100) daily at bedtime ± metformin (≥1500 mg/day)*
2	*Participants who* • *are on a pre-trial basal insulin regimen **other than** insulin glargine (U100) daily at bedtime ± metformin (≥1500 mg/day)* or • *require discontinuation of SU and/or DPP4i*

Abbreviation: DPP4i = dipeptidyl peptidase 4 inhibitor; SU = sulfonylurea.

Participants from **Group 1** will

- continue on their current dose of insulin glargine (U100) ± metformin (≥1500 mg/day) between Visit 2 and Visit 3, and
- measure FBG everyday between Visit 2 and Visit 3.

Participants from **Group 2** will

- initiate optimization of insulin glargine (U100) for 10 weeks, starting at Visit 2 and up to Visit 6.

At Visit 3, participants from **Group 1**

- who do not require further insulin glargine (U100) optimization **(Group 1A)** (that is, if median of last 3 FBG is ≤125 mg/dL [≤6.9 mmol/L] at Visit 3) should have their randomization visit (Visit 6) within 2 weeks after Visit 3, whenever fundoscopic examination results are available. These participants will skip Visits 4 and 5 (see Section 6.1.2.1.).
- who require further insulin glargine (U100) optimization **(Group 1B)** (that is, if median of last 3 FBG is >125 mg/dL [>6.9 mmol/L] at Visit 3) will initiate optimization of insulin glargine (U100) for 9 weeks, starting at Visit 3 and up to Visit 6 (see Section 6.1.2.1.).

Insulin glargine (U100) optimization for Group 1B and Group 2 participants

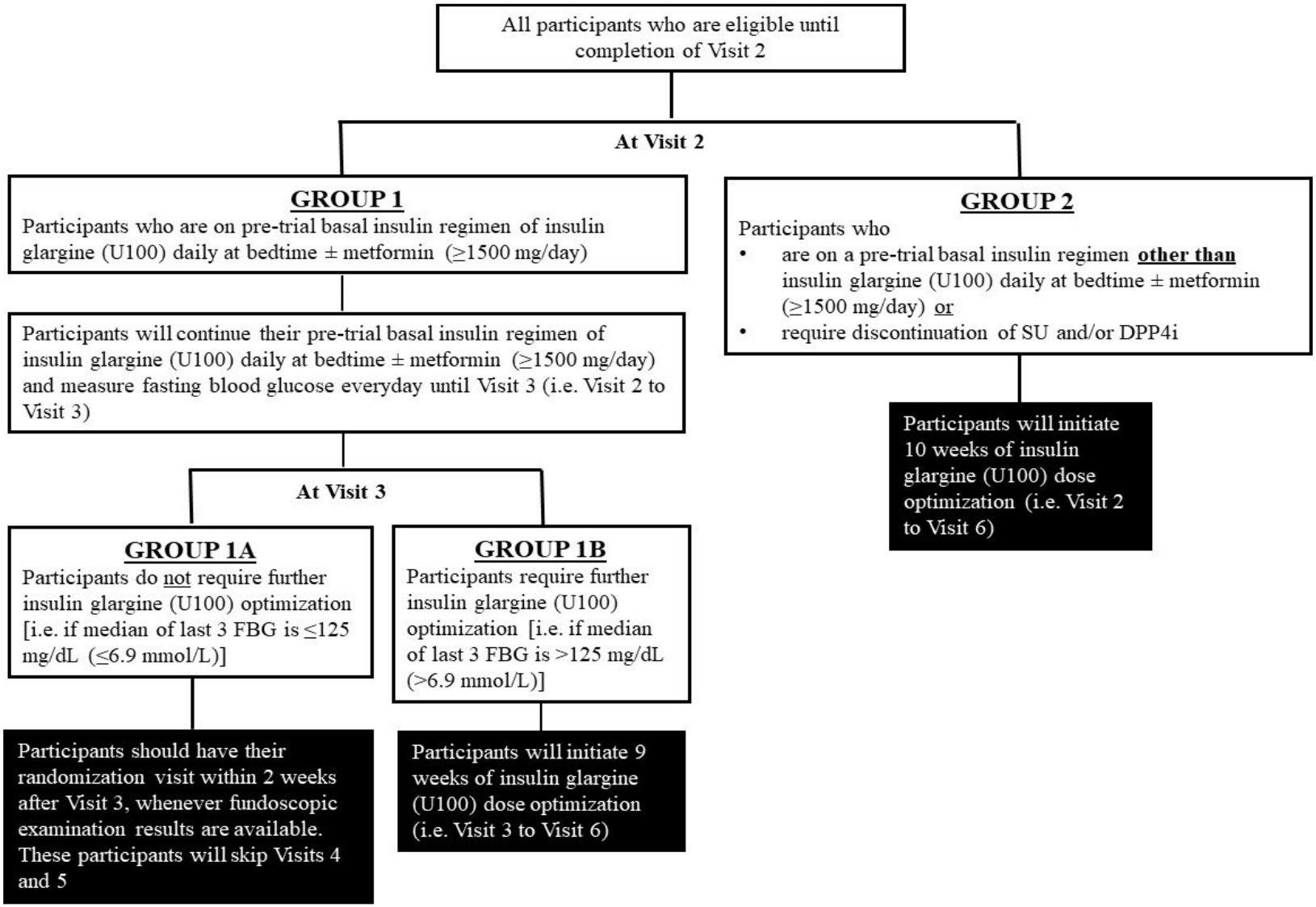
Insulin glargine (U100) dose should be

- titrated per clinical plan outlined by investigator as described in Section 6.1.2.1., and
- monitored by SMBG per clinical plan outlined by investigator as described in Section 6.1.2.1.

Note: Insulin glargine (U100) dose optimization and SMBG plan for Group 1B and Group 2 participants should be **to target a FBG of 100-125 mg/dL (5.6 to 6.9 mmol/L, inclusive)** and determined by the investigator per clinical judgement and standard of care at study center.

An additional blood sample will be collected for **Group 1B** and **Group 2** participants (see Section 6.1.2.1.) for HbA1c assessment at Visit 5. Only participants with Visit 5 HbA1c ≥7.5% (58 mmol/mol) to ≤11% (97 mmol/mol); determined by the central laboratory, will be eligible for randomization. See Figure 2.

Figure 2. Flowchart to Ascertain Need for Insulin Glargine (U100) Dose Optimization at Visit 2 and Visit 3



Abbreviations: DPP4i=dipeptidyl peptidase-4 inhibitor, FBG= fasting blood glucose, SU=sulfonyl urea

At telephone Visits 3 and 4 and at in-clinic Visit 5, the investigator will ensure that participants are

- appropriately performing their SMBG plan
- accurately using the insulin pen
- adjusting the dose of insulin glargine (U100), as appropriate for **Group 1B** and **Group 2**
- filling out participant diary
- reporting hypoglycemia, and
- reporting AEs.

Those participants who discontinue the study prior to Visit 6 do not need to perform an early termination visit and safety follow-up period.

All participants will need to perform two 7-point SMBG profiles done on 2 nonconsecutive days during the week prior to randomization at Visit 6.

4.1.1.2. Study Period II - 52-Week Treatment Period

Visit 6 (randomization)

At Visit 6, participants should

- arrive at the clinic in the fasting state

  Note: The fasting state should have lasted at least 8 hours without eating, drinking (except water), or performing any significant physical activity.

- complete questionnaires for EQ-5D-5L, APPADL, IW-SP, and SF-36v2 acute form before discussing their medical condition or progress in the study with the investigator and/or site staff and before any other visit procedures, if the participant is not adversely affected by the fasting condition, or after sufficiently recovering from the other visit procedures
- undergo all required baseline study procedures, including the collection of all baseline laboratory measures, ECG, and questionnaires, prior to
  - randomization, and
  - injecting their first dose of study intervention, tirzepatide or insulin lispro [U100]
- be provided a diary, and trained as appropriate to perform and/or record
  - SMBG
  - hypoglycemic events
  - insulin glargine (U100) dose

- insulin glargine (U100) dose adjustments
- tirzepatide injection records or insulin lispro (U100) dose, and
- insulin lispro (U100) dose adjustments, if applicable.

Participants randomized to tirzepatide once weekly

Site personnel will

- provide appropriate training on instruction for use of tirzepatide autoinjector. The training can be provided using a demonstration device, if available. This training will be repeated at subsequent visits, as needed, and
- observe as the participant injects the first dose of tirzepatide.

The autoinjector is also referred to as a single-dose pen.

Participants will **reduce their dose of insulin glargine (U100) by 30% at Visit 6** to reduce the potential risk of hypoglycemia and safely introduce tirzepatide and follow instructions in Section 6.1.2.2. for insulin glargine (U100) treatment thereafter.

Participants randomized to insulin lispro (U100) three times a day

Site personnel will

- provide appropriate training on instruction for use of insulin pen. The training can be provided using a demonstration device, if available. This training will be repeated at subsequent visits, as needed, and
- if feasible, observe as the study participant injects the first dose of insulin lispro (U100) prior to a main meal.

Participants will **reduce their dose of insulin glargine (U100) by 30% at Visit 6** to reduce the potential risk of hypoglycemia and safely introduce insulin lispro (U100) TID and follow instructions in Section 6.1.2.2. for insulin glargine (U100) treatment thereafter.

End of Visit 6 to Visit 23 (post-randomization)

Participants randomized to tirzepatide once weekly

Throughout the treatment period, participants randomized to tirzepatide QW will follow

- the dose escalation schedule as outlined in Section 6.1.1. to reach their maintenance dose of either tirzepatide 5 mg, 10 mg, or 15 mg QW, and
- instructions in Section 6.1.2.2. for insulin glargine (U100) treatment.

At each telephone and in-clinic visit, investigator should assist and guide the participant with regards to insulin glargine (U100) titration algorithm, SMBG measurements, and hypoglycemia.

Participants randomized to insulin lispro (U100) three times a day

Throughout the treatment period, participants randomized to insulin lispro (U100) will follow

- instructions in Section 6.1.2.2. for insulin lispro (U100) treatment, and
- instructions in Section 6.1.2.2. for insulin glargine (U100) treatment.

At each telephone and in-clinic visit, the investigator should assist and guide the participant with regards to insulin glargine (U100) and insulin lispro (U100) titration algorithm, SMBG measurements, and hypoglycemia.

Participant diary

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

- SMBG
- hypoglycemic events
- insulin glargine (U100) doses
- insulin glargine (U100) dose adjustments
- tirzepatide injection records or insulin lispro (U100) dose, and
- insulin lispro (U100) dose adjustments, if applicable.

For that purpose, at each visit,

- study diaries for the period after the previous in-clinic visit will be collected, and
- instructions will be reviewed at each visit.

Telephone visits

In addition to in-clinic visits, 6 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 intervention(s) compliance

- hypoglycemic events
- concomitant medications, and
- AEs.

Study intervention(s) compliance will be re-assessed at the in-clinic visit.

The data obtained from diary at these telephone visits will be entered in the CRFs at the next in-clinic visit.

Study intervention(s) administration

Compliance with study intervention(s) administration schedule and compliance with the insulin titration algorithm will be

- assessed at every in-clinic visit, and
- collected in the eCRF at prespecified visits (see Section 1.3.).

Based on the outcome of these reviews, the site staff should

- discuss additional insulin dose adjustments while the participant is still at the clinic, 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 intervention(s), or
- with the insulin titration algorithms at any time during the study.

Participants should also be advised about the appropriate course of action in the event that study intervention(s) is not taken as instructed, as in the case of missing doses.

Participants should receive optimal therapy/clinical care for diabetes related comorbidities throughout the study. See Section 6.5. for study-approved concomitant medications.

Study intervention(s) and injection supplies will be returned per Section 1.3. and according to local requirements. New supplies will be dispensed as needed.

4.1.1.3. Study Period III - Safety Follow-up Period

Visit 801

All participants who complete the treatment period are required to complete Visit 801, a safety follow-up visit, approximately 4 weeks after their last treatment visit.

Participants discontinuing the study early and performing an early termination visit will also be asked to perform the safety follow-up visit. The safety follow-up visit will be their final visit.

During the safety follow-up period, participants

- will not receive study intervention (tirzepatide or insulin lispro [U100]), and
- may have their anti-hyperglycemic treatment adjusted as decided by the investigator. See Section 6.5. for study-approved medications for use during safety follow-up period

Note:

1. Initiation of new antihyperglycemic therapy for the safety follow-up period will not be classified as “rescue therapy."
2. Insulin glargine (U100) use will be permitted during this period since participants were already on basal insulin regimen prior to Visit 1.

Participants must return any remaining study diaries to the study site at the end of this period.

4.1.2. Study Procedures

Participants will undergo study procedures listed in Section 1.3.

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 interventions (see Section 5.2. and 6.5.).

4.2. Scientific Rationale for Study Design

This study is designed to determine the comparative benefits and risks of tirzepatide 5 mg, 10 mg, and 15 mg QW pooled and individual doses versus insulin lispro (U100) TID in participants with T2DM who are inadequately controlled on insulin glargine (U100) with or without metformin (see Table 5).

Table 5. Scientific Rationale for Study Design

Study Design Element	Scientific Rationale
Open-label study	Due to different mode of administration, frequency and dosing requirements of tirzepatide and insulin lispro (U100), blinding is impractical and open-label design is appropriate.
Parallel-group study	The parallel-group design for comparison of interventions was chosen to avoid any interaction between interventions that may interfere with the interpretation of the study outcome.
Insulin glargine (U100) optimization period	The 10-week optimization period will help to identify participants who require further intensification of insulin therapy.
Study duration	The planned treatment duration of 52 weeks is considered appropriate to assess the full effects and benefit/risk of all doses (that is, 5 mg, 10 mg, and 15 mg) of tirzepatide (pooled and individual) on both glycemic control and body weight. Moreover, the duration of the study is considered sufficient and appropriate for participants to optimize dosing of insulin lispro (U100) for comparison with the tirzepatide intervention groups with respect to change in HbA1c.
Concomitant medications	Medications that may interfere with the assessment of efficacy and safety characteristics of the study interventions will not be allowed **(see Section 6.5)**. Metformin was chosen as allowed concomitant antihyperglycemic medication, as it is commonly used in combination with basal insulin in clinical practice.

4.3. Justification for Dose

Tirzepatide dose justification

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

These doses and associated escalation schemes were selected based on assessments of safety, efficacy (glycemic and weight loss effect), and GI tolerability data, followed by exposure-response modeling of data in participants with T2DM in Phase 1 and 2 studies.

Dosing scheme starting at a low dose of 2.5 mg accompanied by a gradual dose escalation of 2.5-mg increments every 4 weeks should permit time for development of tolerance to GI events and is predicted to minimize GI tolerability concerns.

The maximum proposed dose of 15 mg maintains an exposure multiple of 1.6 to 2.4 to the no-observed adverse-effect level doses in 6-month monkey and rat toxicology studies.

The selected dose and escalation scheme would enable further evaluation of benefit/risk considerations for 5 mg, 10 mg, and 15 mg doses of tirzepatide.

Insulin lispro (U100) dose justification

Insulin lispro (U100) will be administered 3 times a day to address the post-prandial glycemic excursions after the 3 largest meals. This approach was chosen compared to once or twice daily prandial insulin injection to ensure fair comparison between tirzepatide and insulin lispro (U100)

for the primary objective of change in HbA1c from baseline. The dose of insulin lispro (U100) will be adjusted per individualized needs following the standardized titration algorithm. The standardized titration algorithm will ensure uniformity in the way insulin lispro (U100) will be titrated across different study centers and countries to help reduce variability. The approach of starting prandial insulin at a dose of 4 units per meal has been used in other Phase 3 clinical trials; and the titration algorithm has been adapted per glycemic targets (that is, pre-meal and bed-time glucose of 100 to 125 mg/dL) of the current study.[13-15]

4.4. End of Study Definition

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

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

5. Study Population

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if 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 or other locally applicable diagnostic standards.
2. Have been treated for at least 90 days prior to Visit 1

- **with once or twice daily dose of basal insulin, either**
    - insulin NPH
    - insulin glargine (U100)
    - insulin glargine (U300)
    - insulin detemir (U100)
    - insulin degludec (U100), or
    - insulin degludec (U200), and
- **with or without oral glucose lowering medications in any combination up to 2 of the following:**
    - stable daily dose of metformin ≥1500 mg/day and up to maximum approved dose per country specific approved label
    - SUs
    - DPP4is

Note: All basal insulin doses within 90 days prior to Visit 1 should be **at least 30 U/day and ≥0.3 and ≤1.0 U/kg/day**. Metformin dose is considered stable if all doses are ≥1500 mg/day.

Participant Characteristics

3. Have an HbA1c ≥7.5% (58 mmol/mol) to ≤11% (97 mmol/mol), at Visit 1 (determined by central laboratory)

   and

   an HbA1c ≥7.5% (58 mmol/mol) to ≤11% (97 mmol/mol), at Visit 5 (pre-randomization), for those participants that need insulin glargine (U100) optimization (that is, Group 1B and Group 2 participants) determined by the central laboratory.

4. Are of stable weight (± 5%) 90 days or more 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.
5. Have a BMI ≥23 kg/m^2 and ≤45 kg/m^2 at Visit 1.
6. Are male or females at least 18 years of age or of an acceptable age to provide informed consent according to local regulations, whichever is older.

   Participant should be willing to follow contraception requirements as provided in Section 10.5.

   Note: Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

7. In the investigator's opinion, are well-motivated, capable, and willing to

   - perform fingerstick BG monitoring, including scheduled BG profiles with up to 7 measurements in 1 day
   - learn how to self-inject study interventions as required for this protocol. Visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study interventions. Persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study interventions
   - inject study interventions, up to 4 injections per day
   - maintain a study diary, as required for this protocol
   - perform insulin dose adjustments at the frequency outlined in the protocol
   - have a sufficient understanding of 1 of the provided languages of the country such that they will be able to complete the participant questionnaires, and
   - discontinue oral glucose-lowering medications other than metformin, if applicable, and switch their basal insulin therapy to insulin glargine (U100) daily at bedtime, if applicable when entering insulin optimization period.

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

9. Have T1DM.
10. Had chronic or acute pancreatitis any time prior to study entry (Visit 1).
11. Have history of:

    - proliferative diabetic retinopathy, **or**
    - diabetic macular edema, **or**
    - nonproliferative diabetic retinopathy that requires acute treatment.

    Note: A dilated fundoscopic examination performed by an ophthalmologist or optometrist between Visit 2 and within 2 weeks after Visit 3 is required to confirm eligibility.
12. Have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1.
13. Are chronically taking drugs that directly affect GI motility, or have a known clinically significant gastric emptying abnormality, such as severe diabetic gastroparesis or gastric outlet obstruction, or have undergone or plan to undergo weight loss procedure during the study, such as

    - a gastric bypass (bariatric) surgery
    - sleeve gastrectomy, or
    - restrictive bariatric surgery, such as Lap-Band® or gastric banding.
14. Have a history of diabetic ketoacidosis or hyperosmolar state/coma during 6 months prior to Visit 1.
15. Have any of the following CV conditions within 2 months prior to Visit 1:

    - acute myocardial infarction
    - cerebrovascular accident (stroke), or
    - hospitalization due to congestive heart failure.
16. Have New York Heart Association Functional Classification III and IV congestive heart failure.
17. Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than NAFLD, or ALT level >3.0 times the upper limit of the reference range, as determined by

the central laboratory at study entry; participants with NAFLD are eligible for participation in this trial only if their ALT level is ≤3.0 times the ULN for the reference range.

18. Have an estimated glomerular filtration rate <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory at Visit 1; for participants on metformin, have an estimated glomerular filtration rate <45 mL/min/1.73 m^2 (or lower than the country-specific threshold for using the protocol-required dose of metformin per local label).
19. Have evidence of a significant, uncontrolled endocrine abnormality, in the opinion of the investigator.

    Examples: thyrotoxicosis or adrenal crises
20. Have family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
21. Have a serum calcitonin level of 35 ng/L or more, as determined by central laboratory at Visit 1.
22. Known or suspected hypersensitivity to trial intervention(s) or related products.
23. Have evidence of a significant, active autoimmune abnormality that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 18 months.

    Examples: lupus or rheumatoid arthritis
24. Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant.
25. 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.
26. Have a history of any other condition that, in the opinion of the investigator, may preclude the participant from following and completing the protocol.

    Examples: known drug, alcohol abuse, or psychiatric disorder
27. Males with hemoglobin <11.0 g/dL and females with hemoglobin <10.0 g/dL; or any hematological condition that may interfere with HbA1c measurement.

    Examples: hemolytic anemias, sickle cell disease
28. Female participants who are pregnant or breast feeding.

Prior/Concomitant Therapy

29. Treatment with any glucose-lowering agent other than stated in the inclusion criteria 2 in a period of 90 days prior to Visit 1 and use of any other glucose lowering medication except insulin glargine (U100) and metformin (≥1500 mg/day), between Visit 2 and randomization (Visit 6).

    Note: Short-term treatment with a non-study insulin for less than 14 days is allowed for certain clinical situations.

    Examples: elective surgery, during hospitalization

30. Have been treated with prescription drugs that promote weight loss within 90 days prior to Visit 1 and/or between study entry (Visit 1) and randomization (Visit 6)

    Examples:

    - Saxenda (liraglutide 3.0 mg)
    - Xenical® (orlistat)
    - Meridia® (sibutramine)
    - Acutrim® (phenylpropanolamine)
    - Sanorex® (mazindol)
    - Apidex® (phentermine)
    - Qsymia™ (phentermine/topiramate combination)
    - Contrave® (naltrexone/bupropion), or
    - similar other body weight loss medications, including over-the-counter medications such as allī®.

31. Are receiving chronic (greater than 2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, or inhaled preparations) or have received such therapy within 1 month prior to Visit 1 or between Visit 1 and Visit 6.

Prior/Concurrent Clinical Study Experience

32. 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.
33. 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.
34. Have previously completed or discontinued from this study or any other study investigating tirzepatide.

Other Exclusions

35. 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.
36. Are Lilly employees.
37. Are unwilling or unable to comply with the use of a paper diary to directly record data from the participant.

5.3. Lifestyle Considerations

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

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

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

6. Study Intervention

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

6.1. Study Interventions Administered

Table 6. Study Interventions Administered

ARM Name	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Insulin Lispro (U100)	Background Intervention
Intervention Name	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Insulin lispro (U100) [Humalog]	Insulin glargine (U100) [Basaglar/Abasaglar]
Dosage Level	5 mg	10 mg	15 mg	Titrated	Titrated
Route of Administration	SC				
Frequency of Administration	QW			TID	QD
Use	experimental intervention			active comparator	background intervention
Sourcing[a]	Provided centrally by the Sponsor and dispensed via IWRS				
Packaging and Labeling[a]	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 insulin pens in a carton. Each carton will be labeled as required per country requirement. Each pre-filled pen will contain a concentration of 100 U/mL in 3 mL cartridges of insulin lispro (U100).	Will be provided in single-participant-use insulin pens in a carton. Insulin glargine (U100) will be provided by the sponsor.

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

[a] Information provided in this table (sourcing, packaging, and labeling) may change throughout the study or may vary by country.

6.1.1. Tirzepatide

Tirzepatide dose escalation

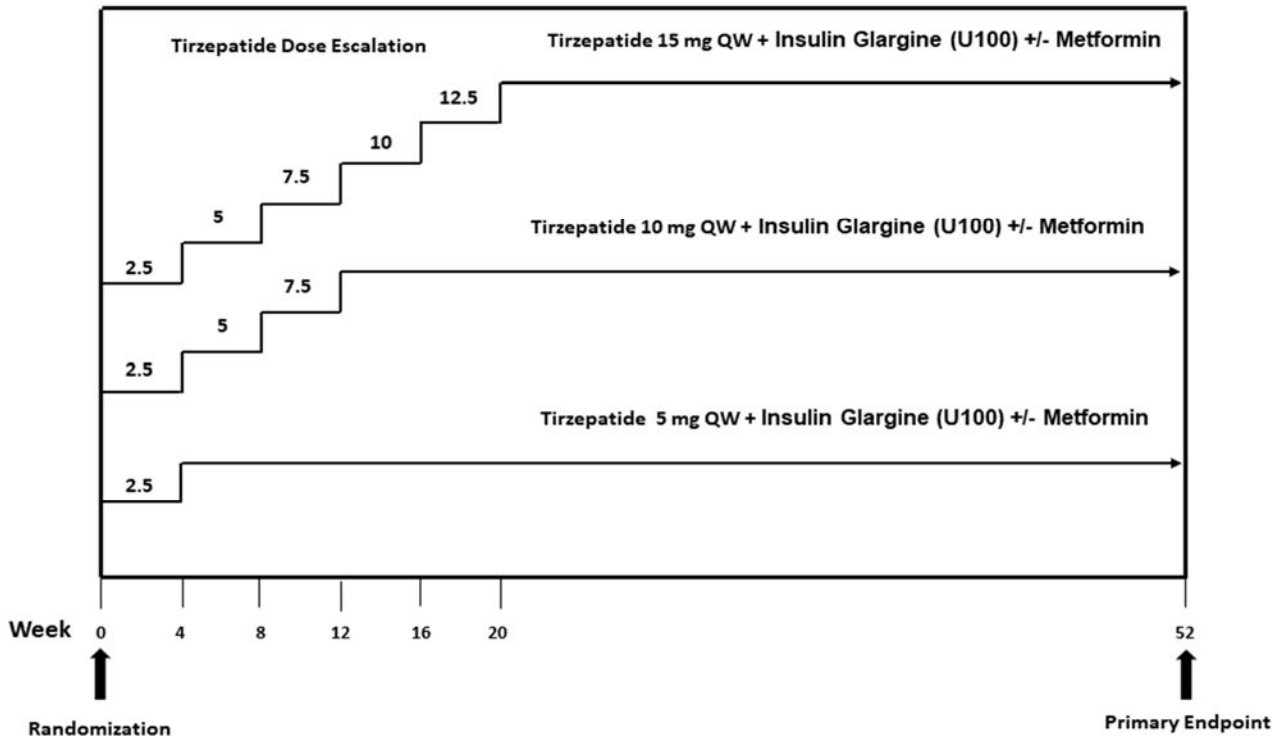
The starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW, for the duration of the study in the 5-mg group.

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 3. illustrates the tirzepatide dose escalation regimen.

Figure 3. Tirzepatide Dose Escalation



Abbreviations: QW = once weekly.

There are no restrictions on the time of day each weekly dose of tirzepatide is given, but it is advisable to administer the SC injections on the same day and same time each week, with or without meals. The actual date and time of all dose administrations will be recorded by the

participant in the diary. If a dose of tirzepatide 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 before 72 hours or more.

All participants will inject tirzepatide SC in the abdomen or thigh. A caregiver may administer the injection in the participant's upper arm. A new single-dose pen will be used for each injection. When tirzepatide is always injected in the same body region, participants should be advised to use a different injection site each week.

6.1.2. Insulin

General guidance on insulin management throughout the study

Site personnel will instruct and educate participants on measuring SMBG, insulin dose adjustments, insulin titration algorithms, and completion of participant diaries. Study-specific training materials will be provided to the study sites.

Participants are responsible for completing the insulin dose adjustments and making the required dose adjustments (self-adjustment). Adjustments of insulin doses per the titration algorithm and administered insulin doses will be recorded by the participants 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(s) at any time during the trial. Site personnel will verify at each office or telephone visit that the adjustment 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 adjustments were not made or the algorithm was not correctly followed, participant will receive additional training and instructions. Additional discussion between visits may be required to enable the participant to reach the target BG ranges.

Investigator should maintain interaction with the participants over the entire study duration to review SMBG values, hypoglycemia risk, and optimize and maintain glycemic control by adjusting the dose of insulin. Clinical judgement must be applied in order to avoid increased risk to the participant’s safety and must always overrule protocol guidelines as deemed appropriate by the investigator.

6.1.2.1. Insulin Treatment during Insulin Optimization Period (Visit 2 to Visit 6)

All participants fulfilling the screening requirement at Visit 2 will discontinue oral glucose lowering agents (except metformin [≥1500 mg/day]), if applicable, and switch their pre-trial basal insulin therapy to Lilly provided insulin glargine (U100) administered daily at bedtime and approximately at the same time throughout the study.

At Visit 2, site personnel will provide appropriate training on instruction for use of the insulin pen for injection of insulin glargine (U100). The training can be provided using a demonstration device, if available. This training will be repeated at subsequent visits, as needed.

Participants receiving

- other once-daily basal insulin, except for insulin glargine (U300), regimen should preferably be switched unit-to-unit from previous basal insulin dose to insulin glargine (U100) at bedtime.
- twice daily basal insulin or insulin glargine (U300) regimens should
    - be switched to a daily bedtime regimen of insulin glargine (U100), and
    - have their pre-trial total basal insulin dose reduced by approximately 20%.

At Visit 2, investigator will determine if the participant belongs to Group 1 or Group 2 based on below criteria:

Group 1 participants: *Participants who are on pre-trial basal insulin regimen of insulin glargine (U100) daily at bedtime ± metformin (≥1500 mg/day)*

- Between Visit 2 and Visit 3, participants should continue on their current dose of insulin glargine (U100) ± metformin (≥1500 mg/day)
- Measure FBG everyday between Visit 2 and Visit 3
- At Visit 3 (telephone visit), investigator will determine if the participant belongs to Group 1A or Group 1B based on below criteria.
    - **Group 1A:** Participant, whose median of last 3 FBG is ≤125 mg/dL (≤6.9 mmol/L)
        - Group 1A participants should have their randomization visit approximately within 2 weeks after Visit 3, whenever fundoscopic examination results are available (Visit 4 and 5 will be skipped). Insulin glargine (U100) dose should not be adjusted unless for safety reasons (i.e. hypoglycemia/severe hyperglycemia). Investigator will establish a SMBG plan in agreement with the participant and based on her/his needs.
    - **Group 1B:** Participant, whose median of last 3 FBG is >125 mg/dL (>6.9 mmol/L)
        - Group 1B participants will optimize their insulin glargine (U100) for 9 weeks, starting at Visit 3 and up to Visit 6.

Group 2 participants: *Participants who are on pre-trial basal insulin regimen* <u>other than</u> *insulin glargine (U100) daily at bedtime ± metformin (≥1500 mg/day) or require discontinuation of sulfonylurea and/or DPP4i.*

- **Group 2** participants will optimize their insulin glargine (U100) for 10 weeks, starting at Visit 2 and up to Visit 6.

Guidance for Group 1B and Group 2 participants on insulin glargine (U100) optimization

- Insulin glargine (U100) should be titrated to reach a FBG target of **100 to 125 mg/dL (5.6 to 6.9 mmol/L)**, inclusive.
- The prescribed insulin glargine (U100) dose during the insulin optimization period is determined by, and the responsibility of, the investigator. Dose adjustments/titration algorithm should be determined by the investigator per clinical judgement and standard of care at study center in discussion with the participant based on switch from other basal insulin regimen and/or discontinued oral glucose lowering medications, available SMBG, and hypoglycemia data.
- Investigator will establish a SMBG plan in agreement with the participant and based on his or her needs to be followed for insulin glargine (U100) optimization.

6.1.2.2. Insulin Treatment during Study Period (Visit 6 to Visit 23)

Participants will collect required FBG for titration of insulin glargine (U100) per Section 6.1.2.2.1. and pre-meals and bedtime BG for titration of insulin lispro (U100), if applicable, per Section 6.1.2.2.2.

Irrespective of SMBGs required for insulin titration, all participants should be collecting at least three FBGs and one 4-point-SMBG (FBG, pre-second meal BG, pre-third meal BG and bedtime BG) per week (these SMBGs could be the same one as used for insulin titration) between Visit 6 and Visit 23 to monitor hypoglycemia and severe hyperglycemia. Investigators should appropriately titrate the dose of insulin glargine (U100) and/or insulin lispro (U100) in case of increased risk of hypoglycemia (see Section 6.6.1.) or severe hyperglycemia.

6.1.2.2.1. Insulin Glargine (U100)

All participants, randomized to either tirzepatide or insulin lispro (U100) TID, will reduce their dose of insulin glargine (U100) by 30% at Visit 6 to reduce the potential risk of hypoglycemia and safely introduce either of the investigational products.

Participants in tirzepatide arms

Dose of insulin glargine (U100) will remain unchanged, after an initial 30% dose reduction at Visit 6, in participants randomized to tirzepatide arm until 4 weeks after randomization (that is, until Visit 10) except for safety reasons (that is, hypoglycemia/severe hyperglycemia). Participants will initiate insulin glargine (U100) titration after Visit 10 per protocol defined titration algorithm.

Participants in the insulin lispro (U100) arm

Participants will initiate titration of insulin glargine (U100) after Visit 6 per protocol defined titration algorithm.

Insulin glargine (U100) titration

Participant should adjust insulin glargine (U100) dose weekly based on the median of last 3 FBG measured, preferably 2 days prior to titration and on the day of titration. If 2 FBG values are available, then the average value will be calculated and will be used to adjust the dose. If none or

only 1 value is available, the participant should contact the investigator site for instructions on adjusting insulin glargine (U100) dose.

Participants will be instructed to adjust insulin glargine (U100) doses to **a target FBG of 100 to 125 mg/dL (5.6 to 6.9 mmol/L), inclusive**, according to Table 7.

Table 7. Insulin Glargine (U100) Titration Algorithm

If median fasting blood glucose is...		Then adjust insulin glargine (U100) bedtime dose by...
mg/dL	mmol/L	
≤70	≤3.9	Decrease by 4 units
71 to 99	4.0 to 5.5	Decrease by 2 units
100 to 125	5.6 to 6.9	No adjustment
126 to 149	7.0 to 8.3	Increase by 2 units
150 to 179	8.4 to 9.9	Increase by 4 units
≥180	≥10.0	Increase by 6 units

Insulin glargine (U100) dose should be decreased by 4 units for any dose adjustment, if participant experienced any episode that either,
1) met the criteria for severe hypoglycemia (events requiring assistance of a third person to administer therapy)
or
2) was associated with FBG value <54 mg/dL (<3.0 mmol/L)
during the adjustment period.

If the participant achieves the target FBG per titration algorithm for 2 consecutive weeks and the dose of insulin glargine (U100) is low, (that is, less than 10 units), investigator may choose to temporarily interrupt insulin glargine (U100) injection. Participant should continue to measure required FBG for insulin glargine (U100) dose adjustment and be re-evaluated every 2 weeks. Insulin glargine (U100) should be restarted, if participant is not at target FBG.

6.1.2.2.2. Insulin Lispro (U100)

Participants randomized to insulin lispro (U100) arm will start administering **4 U** of insulin lispro (U100), prior to the 3 most significant meals of the day, that is, the 3 largest meals.

Participants are expected to eat 3 main meals per day (for example, morning/breakfast, midday/lunch, and evening/dinner) on a regular basis.

At Visit 6, site personnel will provide appropriate training on instruction for use of the insulin pen for injection of insulin lispro (U100). The training can be provided using a demonstration device, if available. This training will be repeated at subsequent visits, as needed.

Participant should adjust insulin lispro (U100) dose twice weekly until Week 24 after randomization (that is, Visit 20). After Visit 20, the investigator may choose to reduce the frequency of insulin lispro (U100) dose adjustment to once weekly per clinical judgment and pre-meal/bedtime SMBG values.

The dose adjustment for a particular injection of the day of insulin lispro (U100) will be based upon the median of the previous 3 SMBG values for each corresponding referenced time point as indicated in Table 8.

Table 8. Insulin Lispro (U100) Dose Adjustments

For dose adjustment of insulin lispro (U100) at...	use...
First meal (e.g. pre-breakfast dose)	pre-second meal SMBG values (e.g. pre-lunch SMBG values)
Second meal (e.g. pre-lunch dose)	pre-third meal SMBG values (e.g. pre-dinner SMBG values)
Third meal (e.g. pre-dinner dose)	bedtime SMBG values

If 2 SMBG values are available, then the average value will be calculated and will be used to adjust the dose. If none or only 1 value is available, the participant should contact the investigator site for instructions on adjusting insulin lispro (U100) dose.

Participants will be instructed to adjust insulin lispro (U100) doses to **a target pre-meal and bedtime SMBG of 100 to 125 mg/dL (5.6 to 6.9 mmol/L), inclusive** according to Table 9.

Table 9. Insulin Lispro (U100) Titration Algorithm

If median pre-meal/bed-time blood glucose is...		Then adjust dose of insulin lispro (U100) for respective meal by...
mg/dL	mmol/L	
≤70	≤3.9	Decrease by 2 units
71 to 99	4.0 to 5.5	Decrease by 1 unit
100 to 125	5.6 to 6.9	No adjustment
≥126	≥7.0	Increase by 2 units

Insulin lispro (U100) dose should be decreased by 2 units (for a particular meal) for any dose adjustment, if participant experienced any episode that either,
1) met the criteria for severe hypoglycemia (events requiring assistance of a third person to administer therapy)
or
2) was associated with respective pre-meal/bedtime BG value <54 mg/dL (<3.0 mmol/L)
during the adjustment period.

If the participant achieves the glycemic goal per titration algorithm for 2 consecutive weeks and the dose of insulin lispro (U100) for corresponding meal is low (that is, less than 4 units), investigator may choose to temporarily interrupt insulin lispro (U100) injections related to that mealtime. Participant should continue to measure required pre-meal/bedtime glucose for insulin lispro (U100) dose adjustment and be re-evaluated every 2 weeks. Respective mealtime Insulin lispro (U100) should be restarted, if participant is not at target glucose level.

6.1.3. Medical Devices

The combination products provided for use in the study is the tirzepatide autoinjector and a marketed insulin pen.

The intended autoinjector configuration includes 0.5 mL of the sterile drug product contained in a 1-mL glass syringe with a plunger, which is assembled into a single-use, prefilled pen designed to administer the 0.5-mL dose. Different doses are being considered to allow for escalation to the efficacious dose, and these doses will be achieved by manufacturing the drug product at different drug substance concentrations while maintaining the 0.5-mL injection volume. The prefilled pen is intended for self-administration as well as administration via another person depending on the injection site chosen. The prefilled pen being used in the tirzepatide clinical programs is the same prefilled pen used in the marketed product platform device.

The prefilled insulin pen injector is designed to provide subcutaneous injection of insulin lispro (U100) and/or insulin glargine (U100) for treatment of diabetes mellitus. The device is previously marketed and is not an investigational device. The pen may be used for self-administration by the participant or by health care providers or caregivers to administer the medicine. The product can be used more than once with the same drug cartridge and is discarded after the cartridge is empty.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention(s) received, and any discrepancies are reported and resolved before use of the study intervention(s).
2. Only participants enrolled in the study may receive study intervention(s), and only authorized site staff may supply or administer study intervention(s). All study intervention(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 site staff.
3. The investigator, institution, or the head of the medical institution, where applicable, is responsible for study intervention(s) accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention(s) are provided in the study training documents.

6.3. Measures to Minimize Bias: Randomization and Blinding

This study is designed as open-label due to different mode of administration, frequency, and dosing requirements of tirzepatide and insulin lispro (U100). However, the specific intervention to be taken by a participant will be assigned using an IWRS. The site will contact the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required. Potential bias will be reduced due to centralized randomization.

6.4. Study Intervention Compliance

Participant compliance with study intervention(s) will be assessed at each visit. Compliance will be assessed by direct questioning and counting of unused study intervention(s) and/or empty cartons returned. Study intervention(s) compliance will be determined by the following:

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

Study intervention(s) compliance for each visit interval is defined as taking at least 75% of the required injections of study intervention(s).

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

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

6.5. 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 intervention(s) (see Table 10).

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

Any medication or vaccine, including over-the-counter or prescription medicines and vitamins, or other specific categories of interest, that the participant is receiving at the time of enrollment or receives during the study, must be recorded on the "Concomitant Medications" section of the eCRF, along with

- reason for use
- dates of administration, including start and end dates, and
- dosage information, including dose and frequency for concomitant therapy of special interest (that is, any other glucose lowering medication).

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

Antihyperglycemic medications other than study intervention(s) and metformin, if applicable, are not allowed at any time during the study except

- as allowed for those participants who require permanent discontinuation of study intervention (that is, tirzepatide or insulin lispro [U100]), but remain in the study
- as rescue therapy, 24 weeks after randomization due to severe, persistent hyperglycemia (see Section 8.3.6.2.), or
- during the safety follow-up period.

Glucagon-like peptide-1 receptor agonist, DPP-4is, pramlintide, other basal insulins (except insulin glargine [U100]), and other prandial insulins (except insulin lispro [U100]) are prohibited medications and are not allowed as rescue therapies. Short-term treatment with a nonstudy insulin for less than 14 days is allowed for certain clinical situations, such as elective surgery, during hospitalization, or hyperosmolar states.

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

1. Dose may be reduced or discontinued if increased hypoglycemia risk persists, but only after appropriate adjustment of insulin glargine (U100) and/or insulin lispro (U100), if applicable.
2. In certain situations that require short-term discontinuation (less than 14 days) in line with the product labeling for each respective country (for example, severe dehydration, elective surgery, or need for radiologic examination involving IV iodinated contrast dye). Once the situation that led to temporary discontinuation of the drug resolves, metformin treatment should be restarted at investigator discretion.
3. If a participant develops contraindications to metformin such that the use of the drug is contraindicated according to the country-specific label.
4. If a participant meets the criteria for severe, persistent hyperglycemia (Section 8.3.6.2.), or discontinues study intervention(s), then metformin dose may be increased according to country-specific label as long as that is not the sole intervention.

All concomitant medications will be recorded on the eCRF at all visits.

Table 10. Criteria for Use of Concomitant Medications that May Interfere with Efficacy and Safety Assessments in Study I8F-MC-GPHD

Drug Class	Use between Visit 2 to Visit 6	Conditions for Use after Randomization		
		Acute Therapy[a]	Rescue Therapy/Post Study Intervention Discontinuation	During Safety Follow-Up Period
Drugs with approved weight loss indication[b]	Excluded	N	N/A	Y
Systemic glucocorticoid therapy[c]	Excluded except for acute therapy[a]	Y	N/A	Y
Antihyperglycemia medications				
GLP-1 RA	Excluded	N	N	N
DPP4i	Excluded	N	N	N
Pramlintide	Excluded	N	N	N
SGLT-2i	Excluded	N	Y	Y
Insulin glargine (U100)	Required	Y	N/A	Y
Basal insulins except insulin glargine (U100)	Excluded except for acute therapy[a]	Y	N	Y
Insulin lispro (U100)	Excluded except for acute therapy[a]	Y	(Y or N/A)[d]	Excluded except for acute therapy[a]
Prandial insulins except insulin lispro (U100)	Excluded except for acute therapy[a]	Y	N	Excluded except for acute therapy[a]
Other insulins	Excluded except for acute therapy[a]	Y	N	Excluded except for acute therapy[a]
Meglitinides	Excluded	N	Y	Y
Alpha-glucosidase inhibitors	Excluded	N	Y	Y
Sulfonylureas	Excluded	N	Y	Y
Thiazolidinediones	Excluded	N	Y	Y
Metformin[e]	Y[f]	N/A	Y[g]	Y

Note: Local country availability and labeling requirements should be followed for any concomitant medication used during the study.

Abbreviations: DPP4i = dipeptidyl peptidase 4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; N = no; N/A = not applicable; SGLT-2i = sodium-glucose co-transporter 2 inhibitor; Y = yes.

[a] Acute therapy = treatment for up to 14 days.

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

[c] From 1 month prior to Visit 1 or between Visits 1 and 6; does not apply to topical, intraocular, intranasal, intra-articular, or inhaled preparations.

[d] Y for participants on tirzepatide arm, NA for participants on insulin lispro (U100)

[e] Metformin pre-screening dose and formulation (short-acting or long-acting) should be maintained throughout the study, except as specified in Section 6.5.

[f] Only if participant was on metformin (≥1500 mg/day) at Visit 1

[g] Increasing the metformin dose should not be used as the sole intervention for rescue therapy or after premature study intervention discontinuation.

6.6. Dose Modification

6.6.1. Management of Increased Hypoglycemia Risk

If a hypoglycemic event occurs,

- participant should record in the study diary
    - BG level measured prior to administration of treatment, if taken
    - associated symptoms, and
    - treatment administered
- site personnel should educate and encourage participants to measure and record BG values during the symptoms of hypoglycemia in their study diaries, if safe to do so, and
- participants should be instructed to call the investigative site, as soon as possible, if they experience a hypoglycemic event that requires treatment assistance.

If a hypoglycemic event occurs, the investigator should

- use definitions and criteria provided in Section 8.3.7. to diagnose hypoglycemia
- properly categorize the suspected or confirmed event
- assess the effect and timing of the intervention(s)
- evaluate the frequency of the event
- establish the role of dietary changes in the development of the event
- establish the role of physical exercise, or any other contributing factor, in the development of the event, and

- provide participant additional education, if deemed appropriate.

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

Management of hypoglycemia in participants in tirzepatide arms

- In the absence of obvious causes (such as dietary or physical activity changes) of hypoglycemia, dose of insulin glargine (U100) should be adjusted first to manage increased risk of hypoglycemia. In case of repeated hypoglycemic events, even with a low insulin glargine (U100) dose (that is, less than 10 units/day) and despite insulin glargine (U100) dose decreases per the titration algorithm, administration of insulin glargine (U100) may be temporarily or permanently discontinued.
- Participant should be restarted on insulin glargine (U100), whenever it is safe to do so per clinical judgement of investigator.
- Metformin dose, if applicable, may also be reduced or discontinued if increased hypoglycemia risk persists, but only after appropriate adjustment of insulin glargine (U100).

Management of hypoglycemia in participants in the insulin lispro (U100) three times a day arm

- In the absence of obvious causes (such as dietary or physical activity changes) of hypoglycemia, timing of the hypoglycemic event(s) should be consulted and dose of insulin glargine (U100) and/or insulin lispro (U100) should be adjusted first to manage increased risk of hypoglycemia.
- If the participant experiences repeated hypoglycemia in spite of decreasing insulin glargine (U100) dose to a low level (less than 10 units), investigator may choose to temporarily or permanently discontinue insulin glargine (U100).
- If the participant experiences repeated hypoglycemia in spite of decreasing the relevant insulin lispro (U100) dose of the day to a low level (less than 4 units), investigator may choose to temporarily interrupt that particular dose of insulin lispro (U100). Remaining doses of insulin lispro (U100) for the day may be continued based on the clinical judgement of the investigator.
- Participant should be restarted on insulin glargine (U100) and/or regular TID regimen of insulin lispro (U100), whenever it is safe to do so per clinical judgement of investigator.
- Metformin dose, if applicable, may also be reduced or discontinued if increased hypoglycemia risk persists, but only after appropriate adjustment of insulin glargine (U100) and/or insulin lispro (U100).

6.6.2. Tirzepatide Dose Modifications

Dose modification for tirzepatide is not permitted.

6.6.3. Management of Participants with Gastrointestinal Symptoms

The tirzepatide dose escalation scheme has been designed to minimize the development of GI symptoms. During the dose escalation period, every effort should be made by the investigator to escalate and maintain participants on the corresponding tirzepatide dosage.

Dose escalation period for different doses of tirzepatide is defined as

- Weeks 0 to 8 for maintenance dose of tirzepatide 5 mg
- Weeks 0 to 16 for maintenance dose of tirzepatide 10 mg
- Weeks 0 to 24 for maintenance dose of tirzepatide 15 mg

To mitigate GI symptoms and manage participants with intolerable GI AEs during the escalation period for respective maintenance doses of tirzepatide, the investigator should follow these steps (see Table 11):

Table 11. Mitigation of Gastrointestinal Symptoms

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

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

In the event of intolerable persistent GI symptoms that occur after the escalation period, the investigator should take the above measures to keep the participant on tirzepatide before stopping permanently and initiating another glucose-lowering agent. All dose adjustments will be managed through IWRS.

If a participant misses 3 or more consecutive doses of tirzepatide due to intolerable GI symptoms (that is, nausea, vomiting, or diarrhea) that could be reasonably attributed due to tirzepatide, despite following the mitigation steps above, tirzepatide should be discontinued. Participant will continue to titrate insulin glargine (U100) and receive another glucose-lowering intervention (if needed per clinical judgement of investigator) and will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements.

6.6.4. Insulin Lispro (U100) and Insulin Glargine (U100) Dose Modifications

After randomization, it is recommended that the insulin glargine (U100) and insulin lispro (U100) titration algorithm is followed. However, it is also important that the decision of adjustment of insulin doses is based on all available information, such as

- symptoms of hypo- and/or hyperglycemia
- previous responses to dose adjustments, and
- SMBG values other than those required as per protocol.

A reason for deviating from the insulin glargine (U100) and insulin lispro (U100) algorithm should be entered in eCRF.

6.7. Intervention after the End of the Study

The following interventional products will not be made available to participants after the conclusion of the study:

- tirzepatide, and
- insulin lispro (U100)
- insulin glargine (U100)

Participants may continue treatment with insulin glargine (U100) available locally or return to their pre-study basal insulin at investigator discretion.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study and complete all study visits and procedures.

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

Participants who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF. Discontinuation of the investigational product for abnormal liver tests **should be** considered by the investigator when a participant meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or AST >8 times ULN
- ALT or AST >5 times ULN for more than 2 weeks
- ALT or AST >3 times ULN and TBL >2 times ULN or INR >1.5
- ALT or AST >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3 times ULN
- ALP >2.5 times ULN and TBL >2 times ULN
- ALP >2.5 times ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Additional circumstances in which participants will be discontinued from the investigational product

A participant will be discontinued from investigational product due to any of the following:

- If a participant is inadvertently enrolled and it is determined that continued treatment with study intervention would not be medically appropriate
- Acute or chronic pancreatitis

- If a participant is diagnosed with MTC after randomization, or has postrandomization calcitonin value 35 ng/L or more 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, in situ, or grade group 1 [that is, Gleason 6 or lower] prostate cancer) after randomization
- Any significant study intervention-related hypersensitivity reaction
- Any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken
- If a participant misses 3 or more consecutive doses of tirzepatide due to intolerable GI symptoms (that is, nausea, vomiting, or diarrhea) that could be reasonably attributed to tirzepatide, despite following the mitigation steps per Section 6.6.3.
- If female participant becomes pregnant (see Section 8.3.5.)

  Note: Participant will be discontinued from the study, as well.
- If a participant is diagnosed with T1DM

  Note: Participant will be discontinued from the study, as well.

Participants who permanently stop tirzepatide or insulin lispro (U100) will continue to titrate insulin glargine (U100) and receive another glucose-lowering intervention, if needed per clinical judgment of investigator, and will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements.

Participants discontinuing tirzepatide or insulin lispro (U100) prematurely for any reason should complete AE and other follow-up procedures per this protocol.

See Section 1.3. for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

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

The data related to temporary interruption of study intervention(s) will be documented in source documents and entered on the eCRF.

Temporary discontinuation of tirzepatide

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

Table 12. Managing Missed Tirzepatide Doses

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

Abbreviations: IWRS = interactive web-response system.

If tirzepatide interruption is due to intolerable persistent GI AE, such as nausea, vomiting, or diarrhea, the participant should be treated as suggested in Section 6.6.3.

Temporary discontinuation of insulin lispro (U100) three times a day

See Section 6.6.1. for management of increased hypoglycemia risk and temporary discontinuation of insulin lispro (U100).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

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

A participant will be withdrawn from the study:

- if a female participant becomes pregnant
- if a participant is diagnosed with T1DM.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SoA. See Section 1.3. for data to be collected at the time of study

discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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, he or she 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 should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow-up is as outlined in Section 1.3., Section 8.2., and Section 8.3. of the 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 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.

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessments

The primary efficacy measurement in this study is mean change in HbA1c values from baseline to 52 weeks, as determined by the central laboratory. Blood samples for HbA1c measurements will be collected at specific in-clinic visits as summarized in the SoA (Section 1.3.).

8.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be assessed at 52 weeks based on data collected at times shown in Section 1.3.

- Key secondary efficacy assessment, controlled for type 1 error
    - mean change in HbA1c from baseline
    - mean change in body weight from baseline
    - proportion of participants with HbA1c target value of <7.0% (53 mmol/mol)
- Additional secondary efficacy assessment, not controlled for type 1 error
    - proportion of participants achieving HbA1c target value of ≤6.5% (48 mmol/mol)
    - proportion of participants with HbA1c target value of <7.0% (53 mmol/mol)
    - mean change in FSG (central laboratory) from baseline
    - proportion of participants who achieved HbA1c target value of <7.0% (53 mmol/mol) without hypoglycemia (confirmed glucose <54 mg/dL [3.0 mmol/L] or report of severe hypoglycemia)

- mean change in daily average 7-point SMBG profiles from baseline
- proportion of participants who achieved weight loss of ≥5% from baseline
- mean change from baseline in SF-36v2 acute form
  - Physical Component Summary score
  - Mental Component Summary score
  - Physical Functioning domain score
  - General Health domain score
  - Vitality domain score
  - Role-Physical domain score
  - Bodily Pain domain score
  - Social Functioning domain score
  - Role-Emotional domain score
  - Mental Health domain score

8.1.3. Exploratory Assessments and Procedures

The following exploratory measures will be calculated based on data collected at the times shown in Section 1.3.

- Patient-reported outcomes (see Section 8.1.4.):
  - EQ-5D-5L
  - APPADL
  - IW-SP
- Change from baseline in lipids, specifically
  - total cholesterol
  - high-density lipoproteins
  - low-density lipoproteins
  - very low-density lipoproteins, and
  - triglycerides
- Mean change from baseline in BMI

- Mean change from baseline in waist circumference

8.1.4. Patient Reported Outcomes Assessments

The self-reported questionnaires will be

- translated into the native language of the region
- linguistically validated, and
- administered according to the SoA (Section 1.3.).

At the visits where patient reported outcomes will be administered, the questionnaires should be completed before the participant has discussed their medical condition or progress in the study with the investigator and/or site staff. The questionnaires should be completed before any other study procedures, if the participant is not adversely affected by the fasting condition or completed after the participant has sufficiently recovered from the preceding visit procedures.

8.1.4.1. Short Form 36 Version 2, Acute, 1-week Recall Version

The SF-36v2 acute, 1-week recall version is a 36-item, generic, participant-administered measure designed to assess the following 8 domains:

- Physical Functioning
- Role-Physical
- Bodily Pain
- General Health
- Vitality
- Social Functioning
- Role-Emotional
- Mental Health

Each domain is scored individually and information from these 8 domains are further aggregated into 2 health-component summary scores: Physical-Component Summary and Mental-Component Summary. The Physical-Functioning domain assesses limitations due to health "now" while the remaining domains assess functioning "in the past week".

Items are answered on Likert scales of varying lengths (3-, 5-, or 6- point scales). Scoring of each domain and both summary scores are norm-based and presented in the form of T-scores, with a mean of 50 and standard deviation of 10. Higher scores indicate better levels of function and/or better health.[16]

8.1.4.2. EQ-5D-5L

Generic health-related quality of life will be assessed using the EQ-5D-5L User Guide.[17] 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, namely

- mobility
- self-care
- usual activities
- pain/discomfort, and
- anxiety/depression.

The 5L version, introduced in 2005, scores each dimension at 5 levels, namely

- no problems
- slight problems
- moderate problems
- severe problems, and
- 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 <0 (where 0 is a health-state equivalent to death; negative values are valued as worse than dead), to 1 (perfect health).[18] In addition, the EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated, 0 to 100 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 170 different languages. Details on the instrument, and scoring, organizing, and presenting the data collected can be found in the EQ-5D-5L User Guide.[17]

8.1.4.3. Impact of Weight on Self-perception

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.[19] 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.[19]

8.1.4.4. 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.[20,21] 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.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Height, weight, and waist circumference will be measured and recorded, per Section 10.8.

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

- skin, including feet
- CV
- respiratory
- GI
- neurological systems, and
- thyroid exam.

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 Section 1.3. and following the study-specific recommendations included in Section 10.8.

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

8.2.3. Electrocardiograms

For each participant, a 12-lead ECG should be collected locally according to Section 1.3. Electrocardiogram should be recorded after the participant has been supine for 5 minutes in a quiet room.

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. Copies of ECGs collected on thermal paper should be made as source data and stored.

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2. for the list of clinical laboratory tests to be performed and Section 1.3. for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2., must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE, AE, or dose modification) then the results must be recorded in the CRF.

8.2.5. Hepatic Safety Monitoring

Close hepatic monitoring

Laboratory tests, as defined in Section 10.6., 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 1 or more conditions occur that are listed in Table 13.

Table 13. Hepatic Safety Monitoring Tests

If a participant with baseline results of...	develops an elevation of...
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants 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, and
    - recent illnesses, for example, heart failure, systemic infection, hypotension, or seizures
- recent travel
- history of concomitant medications, including
    - over-the-counter, and
    - herbal and dietary supplements
- history of alcohol drinking, and
- other substance abuse.

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

Table 14. Comprehensive Hepatic Evaluation

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

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

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

At a minimum, this evaluation should include

- physical examination
- a thorough medical history, as outlined above
- tests for PT-INR
- tests for viral hepatitis A, B, C, or E
- tests for autoimmune hepatitis, and
- an abdominal imaging study.

  Examples: ultrasound, CT scan

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease

- blood alcohol levels
- urinary ethyl glucuronide, and
- serum phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for

- a hepatologist or gastroenterologist consultation
- magnetic resonance cholangiopancreatography
- endoscopic retrograde cholangiopancreatography
- cardiac echocardiogram, or
- a liver biopsy.

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

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

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT is <1.5x ULN)
    - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests

2. Elevated TBL to ≥2x ULN (if baseline TBL <1.5x ULN (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline

3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests

4. Hepatic event considered to be an SAE

5. Discontinuation of study intervention(s) due to a hepatic event

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

8.2.6. Safety Surveillance

The sponsor has robust safety surveillance processes based on recommendation made by the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI - Management of Safety Information from Clinical Trials Report. These processes are in line with

the FDA's expectations for Safety Assessment Committees and EMA expectations for monitoring safety in clinical trials.

Each investigational product has a DSST which is responsible for monitoring the safety of participants and overseeing the evolving safety profile of investigational products.

The DSST will review all available data including but not limited to

- clinical trial data, cumulative AE and SAE data and laboratory data
- non-clinical data, toxicology studies
- epidemiology studies, and
- literature.

The team will conduct real time review of all SAEs and other incoming expedited safety reports. The DSST is also responsible for review of accumulating safety data across all trials for the investigational product. The DSST will meet in a timely manner at pre-defined intervals or on an ad-hoc basis as required.

The DSST is a multidisciplinary team which includes a physician/scientist who are well versed in pharmacovigilance and with the therapeutic area for which the investigational product is being developed. The roles and responsibilities of this team and the processes are clearly defined in Lilly's internal Standard Operating Procedures.

Each investigational product has a DSMT which is a cross-functional, multidisciplinary team and includes DSST members, study team physicians and other members depending on the necessity such as epidemiologist, clinical pharmacologist, toxicologist, or statistician. The DSST and DSMT work together to review clinical data from the clinical trial.

The DSST can make recommendations to the DSMT in order to minimize risk to participants in clinical trials. Such recommendations will include, but are not limited to, changes to conduct of the trial, determination of new adverse drug reactions, and determining if event(s) meet the criteria for expedited reporting to regulators, such as investigational new drug safety reports, and investigators.

In addition, each individual clinical trial study team has clearly defined processes to review all relevant safety data at cohort level and trial level in order to monitor safety of participants in clinical trials and enable trial level decisions.

Lilly Global Patient Safety has a robust process for expedited communication of SAEs and SUSARs per regulatory requirements and other important study information, as needed. The protocol gives detailed information to study sites for collection and reporting of AEs and SAEs (see Section 10.4.).

8.3. Adverse Events and Serious Adverse Events

The definitions of device-related safety events (adverse device effects, unanticipated adverse device effects, and serious adverse device effects) can be found in Section 10.7. Device deficiencies are covered in Section 10.7.3.

Adverse 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 designee are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7.).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs will be collected from the signing of the ICF until participation in study has ended.

All AEs will be collected from the signing of the ICF until participation in study has ended.

Adverse events that begin before the start of study intervention, but after signing of the ICF, will be recorded on the AE CRF.

Although all AEs after signing the ICF are recorded by the site in the eCRF, SAE reporting to sponsor begins after the participant has signed the ICF and has received study intervention. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.4.

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

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE 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 8.3.7.) 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.). Further information on follow-up procedures is provided in Section 10.4.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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

8.3.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 30 days after the last dose.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

8.3.6.1. 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 Section 1.3.). Site personnel will enter this information into the eCRF at each visit.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia. The BG/serum values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips which are provided to the participant by the study sponsor.[22,23]

Glucose alert value - level 1

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of ≤70 mg/dL (≤3.9 mmol/L).

- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG ≤70 mg/dL (≤3.9 mmol/L).

- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured BG ≤70 mg/dL (≤3.9 mmol/L).

Clinically significant hypoglycemia - level 2

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of <54 mg/dL (<3.0 mmol/L).

- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG <54 mg/dL (<3.0 mmol/L).

- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured BG <54 mg/dL (<3.0 mmol/L).

Severe hypoglycemia - level 3

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

  All severe hypoglycemia episodes should be reported as an SAE.

Other hypoglycemia categories

- **Nocturnal hypoglycemia** is defined as any hypoglycemic event that occurs between bedtime and waking.

- **Severe hypoglycemia requiring hospitalization, documented medical help, or is life threatening**

If a hypoglycemic event meets the criteria of severe, it needs to be recorded as serious on the AE CRF and reported to Lilly as an SAE.

To avoid duplicate reporting, all consecutive BG values ≤70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event.[24,25]

In each case of suspected or confirmed hypoglycemia, it is important that the event be properly categorized, the effect of the intervention be assessed, and the frequency of hypoglycemia be evaluated. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established. The participant should receive additional education, if deemed appropriate. Please refer to Section 6.6.1. for guidance on management of increased hypoglycemia risk.

8.3.6.2. Severe, Persistent Hyperglycemia

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

Note: The criteria for evaluation of severe, persistent hyperglycemia will only be applicable after Week 24.

Investigators will be trained on the application of criteria for deciding when and how to intervene with participants experiencing severe persistent hyperglycemia. Evaluation should be made if participant is compliant to study intervention(s) and has appropriately titrated the dose of insulin glargine (U100) and/or insulin lispro (U100), if applicable, prior to asserting if severe, persistent hyperglycemia criteria has been met. Insulin glargine (U100) and/or insulin lispro (U100), if applicable should be titrated first before adding any rescue therapy. Protocol allowed rescue therapies may be added thereafter in participants who meet the severe, persistent hyperglycemia criteria at the discretion of investigator in accordance with American Diabetes Association/European Association for the Study of Diabetes guidance.[26] Rescue medication will be prescribed as add-on to study intervention(s), and participants will continue to follow the protocol-specified visit schedule.

Add-on glycemic rescue therapy will be allowed for participants who met any 1 of the following prespecified criteria for severe, persistent hyperglycemia and no intercurrent cause of the hyperglycemia 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:

- average daily BG from the weekly 4-point SMBG (fasting BG, pre-second meal BG, pre-third meal BG, and bedtime BG) profile is >200 mg/dL (>11.1 mmol/L) over a consecutive 2-week period at any time beyond the first 24 weeks post-randomization, or

- HbA1c ≥8.5% (69 mmol/mol) after 24 weeks, with inadequate response to the existing regimen defined as improvement in HbA1c over the last 3 months that is, <0.3%

Rescue therapy option:

Rescue treatment with pramlintide, DPP-4is, GLP-1 RAs, other basal insulins (except insulin glargine [U100]), or other prandial insulins (except insulin lispro [U100]), will not be allowed (see Section 6.5.).

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.

8.3.6.3. Pancreatitis

Diagnosis of acute 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.[27] 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;[27,28] the pain is often associated with nausea and vomiting)
- serum pancreatic amylase and/or lipase ≥3X ULN, and
- characteristic findings of acute pancreatitis on CT scan or magnetic resonance imaging.

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including levels of pancreatic amylase and lipase, via the central laboratory and, if needed, via a local laboratory as well, and
- perform imaging studies, such as abdominal CT scan with or without contrast, magnetic resonance imaging, or gallbladder ultrasound.

Discontinuation and rescue intervention for acute pancreatitis

If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the participant must discontinue therapy with investigational product(s),but will continue in the study on another glucose-lowering regimen (details on rescue intervention will be provided). The most appropriate diabetes therapeutic regimen will be decided by the investigator, based on the participant's clinical status. A review of the participant's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Reporting adverse events and serious adverse events of acute pancreatitis

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

The investigator must report the event as an SAE if the typical signs and/or symptoms of pancreatitis

- are present, and
- are confirmed by

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

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

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

Pancreatic hyperenzymemia

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

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic participants.[29-31] Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia, lipase and/or pancreatic amylase 3X ULN or more, is not mandated, but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

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

Case adjudication and data entry

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

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

8.3.6.4. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of medullary thyroid carcinoma and/or multiple endocrine neoplasia type 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 medullary thyroid carcinoma and papillary carcinoma and measurements of calcitonin. These 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 or more 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 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.

8.3.6.5. Major Adverse Cardiovascular Events

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

- 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, or stroke, and transient ischemic attack.

8.3.6.6. Supraventricular Arrythmias and Cardiac Conduction Disorders

Participants who develop any event from these groups of disorders should undergo an ECG. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 10.4. must be reported as SAEs.

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

8.3.6.7. Hypersensitivity Events

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

The sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention(s). It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

In the case of generalized urticaria or anaphylaxis, additional blood samples should be collected as described in Section 10.3. Laboratory results are provided to the sponsor via the central laboratory. Investigational product should be temporarily interrupted in any individual suspected

of having a severe or serious allergic reaction to investigational product. Investigational product may be restarted when/ if it is safe to do so, in the opinion of the investigator. If investigational product is permanently discontinued, the participant will continue to adjust the dose of insulin glargine (U100) and may 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.

8.3.6.8. Injection Site Reactions

Injection site reactions will be collected on the eCRF separate from the hypersensitivity reaction eCRF. At the time of AE occurrence in the tirzepatide group, samples will be collected for measurement of tirzepatide ADA and tirzepatide concentration.

8.3.6.9. Anti-Drug Antibodies

The occurrence of ADA formation will be assessed as outlined in Section 8.9.

8.3.6.10. 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 within 2 weeks after Visit 3, and prior to randomization, to exclude participants with

- proliferative diabetic retinopathy
- diabetic macular edema, or
- nonproliferative diabetic retinopathy that requires acute treatment.

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.

8.3.6.11. 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 10.6.

8.3.6.12. 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, refer to Section 6.6.3.

8.3.6.13. 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.[32] 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.

8.3.6.14. 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 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. Routine bicarbonate assessment will be performed during the course of the study. If lactic acidosis is suspected, metformin, if used, should be temporarily discontinued until the resolution of the event.

8.3.6.15. Amputation/Peripheral Revascularization

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

8.3.7. Product Complaints

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 trial intervention. Refer to Section 10.7. for definition and discussion of product complaints related to devices (device deficiencies).

Sponsor 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 or drug delivery system, so that the situation can be assessed.

Note: Adverse events and SAEs that are associated with a product complaint will also follow the processes outlined in Sections 8.3.3. and 10.4.

8.3.7.1. Time Period for Detecting Product Complaints

- Product complaints that result in an adverse event will be detected, documented, and reported to the sponsor during all periods of the study in which the drug/device is used.

- If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug/device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Deficiency is provided in Section 10.7.

8.3.7.2. Prompt Reporting of Product Complaints to Sponsor

- Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.
- Device deficiencies will be reported to the sponsor within 72 hours after the investigator determines that the event meets the definition of a medical device deficiency.
- Product complaints will be reported by the investigator to the sponsor per instructions provided on the study specific Product Complaint Form.

8.3.7.3. Follow-up of Product Complaints

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.7.4. Regulatory Reporting Requirements for Product Complaints

- The investigator will promptly report all device related product complaints to the sponsor to facilitate timely regulatory reporting.
- As required by local regulations, the investigator will report to their IRB/IEC any unanticipated adverse device effect or UADE (unanticipated problem that resulted in an SAE), or any product complaint that could have led to an SAE had precautions not been taken.

8.4. Treatment of Overdose

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until tirzepatide can no longer be detected systemically (at least 30 days).

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

In the event of overdose, refer to the Investigator's Brochure for tirzepatide and/or product label for insulin glargine (U100) and/or insulin lispro (U100), as applicable.

8.5. Pharmacokinetics

Tirzepatide PK samples may be analyzed. If PK analysis is planned, then analysis will be conducted as needed at a laboratory approved by the sponsor. Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry (LC/MS) method. Bioanalytical samples collected to measure tirzepatide concentrations will be retained for a maximum of 1 year following last participant visit for the study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

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

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

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

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

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

In addition, samples will be stored and analysis may be performed on immunogenicity along with a paired sample for PK analysis (see Section 8.9.), and biomarker variants thought to play a role in T2DM including, but not limited to, serum/plasma analytes to evaluate their association with observed clinical responses to tirzepatide.

8.9. Immunogenicity Assessments

Exploratory biomarker samples collected during the study will be used to perform any immunogenicity related assessments as deemed appropriate.

Treatment-emergent ADAs are defined in Section 9.4.6.

Samples with tirzepatide ADA detected will be titered and may then be evaluated for their ability to neutralize the activity of assigned treatment, tirzepatide-neutralizing antibodies. Samples with ADA detected will also be tested for cross-reactive binding to native GIP and GLP-1, and, if such is detected, may then be tested for neutralizing antibodies against native GIP and GLP-1.

8.10. Health Economics

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

9. Statistical Considerations

9.1. Statistical Hypotheses

The alternative hypothesis for the primary objective is the following:

- $H_{p,1}$: The pooled cohort of tirzepatide (5 mg, 10 mg, and 15 mg) QW is noninferior to insulin lispro (U100) TID, relative to the mean change in HbA1c from baseline to 52 weeks.

The alternative hypotheses for the key secondary objectives controlled for type 1 error rate are the following:

- $H_{p,2}$: The pooled cohort of tirzepatide (5 mg, 10 mg, and 15 mg) QW is superior to insulin lispro (U100) TID, relative to mean change in HbA1c from baseline to 52 weeks.

- $H_{p,3}$: The pooled cohort of tirzepatide (5 mg, 10 mg, and 15 mg) QW is superior to insulin lispro (U100) TID, relative to mean change in body weight from baseline to 52 weeks.

- $H_{p,4}$: The pooled cohort of tirzepatide (5 mg, 10 mg, and 15 mg) QW is superior to insulin lispro (U100) TID, relative to proportion of participants achieving target value of HbA1c < 7% at 52 weeks.

- $H_{5,1}$, $H_{10,1}$, $H_{15,1}$: Each of tirzepatide (5 mg, 10 mg, and 15 mg) QW is noninferior to insulin lispro (U100) TID, relative to mean change in HbA1c from baseline to 52 weeks.

- $H_{5,2}$, $H_{10,2}$, $H_{15,2}$: Each of tirzepatide (5 mg, 10 mg, and 15 mg) QW is superior to insulin lispro (U100) TID, relative to mean change in HbA1c from baseline to 52 weeks.

- $H_{5,3}$, $H_{10,3}$, $H_{15,3}$: Each of tirzepatide (5 mg, 10 mg, and 15 mg) QW is superior to insulin lispro (U100) TID, relative to mean change in body weight from baseline to 52 weeks.

The details of family-wise type I error rate control strategy and methods for the aforementioned hypotheses will be provided in the SAP.

9.2. Sample Size Determination

Participants will be randomized in a 1:1:1:3 ratio to tirzepatide (5 mg, 10 mg, 15 mg) QW or insulin lispro (U100) TID. The randomization ratio is determined to optimize safety assessment between the pooled cohort of tirzepatide (5 mg, 10 mg, and 15 mg) QW and insulin lispro (U100).

Although the primary objective of the trial is to demonstrate that the pooled cohort of tirzepatide (5 mg, 10 mg, and 15 mg) QW is noninferior to insulin lispro (U100) TID, relative to the primary endpoint (mean change in HbA1c from baseline to 52 weeks) with a 0.3% noninferiority margin, sample size selection is guided by establishing noninferiority of each tirzepatide dose, tested against insulin lispro (U100), relative to the primary endpoint (mean change in HbA1c from baseline to 52 weeks).

The sample size determination assumes that evaluation of noninferiority of individual tirzepatide dose to insulin lispro (U100) will be conducted, each at a one-sided significance of 0.025, using a two-sample t-test. Additionally, a 0% difference in mean change in HbA1c from baseline to 52 weeks for each tirzepatide arm compared with insulin lispro (U100); a common SD of 1.3% (accounting for increase in SD due to the inclusion of data on rescue medications and after premature treatment discontinuation and imputation of missing data) and a noninferiority margin of 0.3% are assumed for statistical power calculations. On the basis of these assumptions, randomizing 1182 participants in a 1:1:1:3 ratio to tirzepatide 5 mg (197 participants), tirzepatide 10 mg (197 participants), tirzepatide 15 mg (197 participants) and insulin lispro (U100) (591 participants) provides 80% power to demonstrate noninferiority of each tirzepatide dose to insulin lispro (U100).

Furthermore, this sample size will ensure 97% power to establish noninferiority of the pooled cohort of tirzepatide (5 mg, 10 mg, and 15 mg) compared to insulin lispro (U100), using a 2-sample t-test at 1-sided significance level of 0.025, provided a 0.0% difference in mean change in HbA1c from baseline to 52 weeks for the pooled cohort of tirzepatide doses compared with insulin lispro (U100), a common SD of 1.3% and noninferiority margin of 0.3%.

9.3. Populations for Analyses

Table 15. Populations for Analyses

Population	Description
Screened participants	All participants who sign informed consent.
Randomized participants	All participants who are randomly assigned to a treatment arm.
mITT population	All randomly assigned participants who are exposed to at least 1 dose of study intervention, that is, tirzepatide or insulin lispro (U100). In the event of a treatment error, participants will be analyzed according to the treatment they were randomized.
EAS	Data obtained during Study Period II from the mITT population, excluding data after initiating rescue antihyperglycemic medication or stopping study intervention.
FAS	Data obtained during Study Period II from the mITT population, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.
SS	Data obtained during Study Periods II or III from the mITT population, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.

Abbreviations: EAS = efficacy analysis set; FAS = full analysis set; mITT = modified intention-to-treat; SS = safety analysis set.

9.4. Statistical Analyses

9.4.1. General Considerations

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

Any change to the data analysis methods described in the protocol will require an amendment ONLY, if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or Clinical Study Report. 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 CI will be calculated at 95%, 2-sided. In statistical summaries and analyses, participants will be analyzed as randomized.

There will be 2 estimands of interest in comparing efficacy of tirzepatide doses with insulin lispro (U100). The first estimand, the “efficacy” estimand, represents efficacy prior to discontinuation of study intervention without the confounding effects of antihyperglycemic rescue therapy. The second estimand, the “treatment-regimen” estimand, represents the efficacy irrespective of adherence to study intervention or initiation of rescue antidiabetic drugs.

The primary efficacy assessment, guided by the “efficacy” estimand, will be conducted using the EAS. The primary efficacy assessment, guided by the “treatment-regimen” estimand, will be conducted using the FAS. As they are intended for different purposes, no multiplicity adjustments will be made for conducting the 2 primary efficacy assessments.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide (5 mg, 10 mg, and 15 mg) with insulin lispro (U100), irrespective of adherence to study intervention or initiation of antihyperglycemic rescue therapy. Thus, the safety analysis will be conducted using the 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 arms relative to continuous measurements assessed over time will be an MMRM, with terms of treatment, visit and treatment-by-visit interaction, country, metformin use (Yes or No), and baseline measurement as a covariate. An unstructured covariance matrix will model the relationship of within-participant errors.

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

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

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

9.4.2. Treatment Arm Comparability

9.4.2.1. Participant Disposition

Frequency counts and percentages of all participants screened, randomized, and receiving at least 1 dose of study intervention (tirzepatide or insulin lispro [U100]), will be presented by treatment arm. Of the participants in the mITT population, frequency, counts and percentages of participants completing the study, prematurely discontinuing the study, including the reason for premature discontinuation, will be presented by treatment arm. A Kaplan-Meier analysis of time from randomization to premature discontinuation from study by treatment arm will be provided.

9.4.2.2. Participant Characteristics

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

9.4.2.3. Concomitant Therapy

Concomitant medications, including previous therapy for diabetes, will be summarized by anatomical therapeutic chemical classification and treatment arm 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 arms.

9.4.2.4. Treatment Compliance

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

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

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

As indicated in Section 9.4.1., there will be 2 primary efficacy analyses conducted to establish noninferiority of the pooled cohort of tirzepatide at 5 mg, 10 mg, and 15 mg to insulin lispro (U100) relative to mean change in HbA1c from baseline to the 52-week visit.

The primary efficacy analysis regarding the "treatment-regimen" estimand, defined in Section 9.4.1., will analyze change in HbA1c values obtained at the 52-week visit using an ANCOVA with terms of treatment, country, metformin use (Yes or No), and baseline HbA1c as a covariate. Missing change in HbA1c from baseline values at the 52-week visit will be imputed based on observed changes in HbA1c from baseline values at the visit from participants in the same treatment arm who had their efficacy assessed after early discontinuation of study intervention and/or initiation of rescue antihyperglycemic medication. Analysis will be conducted with multiple imputations, and statistical inference over multiple imputations will be guided by the method proposed by Rubin.[33]

The ANCOVA analysis will report least square means and standard error values for the pooled cohort of tirzepatide doses and insulin lispro (U100) as well as the difference in mean change in HbA1c from baseline to the 52-week visit. Two-sided 95% CI for the difference in mean change in HbA1c from baseline to 52-week visit between the pooled cohort of 5 mg, 10 mg, and 15 mg tirzepatide and insulin lispro (U100) will be constructed. The mean change in HbA1c from baseline to the 52-week visit will be calculated as subtracting the baseline HbA1c from the 52-week HbA1c. The difference between the pooled tirzepatide cohort and insulin lispro (U100) will be calculated as subtracting the mean change in HbA1c for insulin lispro (U100) from the mean change of HbA1c for the pooled tirzepatide cohort. If the upper limit of the CI is below 0.3%, the pooled cohort of 5 mg, 10 mg, and 15 mg QW tirzepatide will be declared noninferior to insulin lispro (U100).

The primary efficacy analysis regarding the "efficacy" estimand, defined in Section 9.4.1., will be conducted using the EAS. The primary analysis model for HbA1c measurements over time will be an MMRM. The response variable of MMRM will be change in HbA1c from baseline values obtained at each scheduled postbaseline visit. The independent variables of the MMRM model are treatment (pooled cohort of 5 mg, 10 mg, and 15 mg QW tirzepatide, and insulin lispro [U100]), visit, and treatment-by-visit interaction, country, metformin use (Yes or No), and baseline HbA1c as a covariate. An unstructured covariance structure will model the relationship of within-participant 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.

The MMRM analysis will report least square means and standard error values for the pooled cohort of tirzepatide doses and insulin lispro (U100) as well as the difference in mean change in HbA1c from baseline to the 52-week visit. With the aid of the MMRM analysis, 2-sided 95% CI for the difference in mean change in HbA1c from baseline to the 52-week visit between the pooled cohort of 5 mg, 10 mg, and 15 mg tirzepatide, and insulin lispro (U100) will be constructed. The mean change in HbA1c from baseline to 52-week visit will be calculated as subtracting the baseline HbA1c from the 52-week HbA1c. The difference between the pooled tirzepatide cohort and insulin lispro (U100) will be calculated as subtracting the mean change in HbA1c for insulin lispro (U100) from the mean change of HbA1c for the pooled tirzepatide cohort. If the upper limit of the CI is below 0.3%, the pooled tirzepatide cohort will be declared noninferior to insulin lispro (U100).

9.4.3.2. Secondary Analyses

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

- superiority of pooled tirzepatide (5 mg, 10 mg, and 15 mg) QW to insulin lispro (U100) TID, relative to mean change in HbA1c from baseline to 52 weeks
- superiority of pooled tirzepatide (5 mg, 10 mg, and 15 mg) QW to insulin lispro (U100) TID, relative to mean change in body weight from baseline to 52 weeks
- superiority of pooled tirzepatide (5 mg, 10 mg, and 15 mg) QW to insulin lispro (U100) TID, relative to proportion of participants achieving target value of HbA1c < 7% at 52 weeks
- noninferiority of each tirzepatide dose to insulin lispro (U100), relative to mean change in HbA1c from baseline to 52 weeks
- superiority of each tirzepatide dose to insulin lispro (U100), relative to mean change in HbA1c from baseline to 52 weeks
- superiority of each tirzepatide dose to insulin lispro (U100), relative to mean change in body weight from baseline to 52 weeks

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 both estimands, the “efficacy” estimand and the “treatment-regimen” estimand.

Analysis of change from baseline in body weight at the 52-week visit will be conducted in a manner similar to the primary efficacy analyses with change in body weight from baseline as the response variable, baseline body weight as a covariate, and HbA1c (≤ 8.5% or >8.5% [69 mmol/mol]) as a stratification factor.

Comparisons among treatments relative to the proportion of participants achieving the HbA1c target value of <7.0% (53 mmol/mol) at the 52-week visit will be conducted using a logistic regression analysis with terms of treatment, country, metformin use (Yes or No), and baseline HbA1c as a covariate. In the analysis of participants achieving the HbA1c target value relative to the "efficacy" estimand, subjects with missing values at the 52-week visit will be excluded. In the analysis of participants achieving the HbA1c target value relative to the "treatment-regimen" estimand, missing values at the 52-week visit will be imputed based on observed data at respective visits from participants in the same treatment arm who had their efficacy assessed after early discontinuation of study intervention and/or initiation of rescue medication. The analysis will be conducted with multiple imputations and statistical inference over multiple imputations will be guided by the method proposed by Rubin.[33]

Analyses of actual and change from baseline in 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.

9.4.3.3. Tertiary/Exploratory Analyses

All exploratory 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.

9.4.4. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of the pooled cohort of tirzepatide doses with insulin lispro (U100) irrespective of adherence to study intervention(s) 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.

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

9.4.4.1. Hypoglycemic Events

Incidence of documented symptomatic hypoglycemia events and severe hypoglycemia will be compared between the pooled cohort of tirzepatide doses and insulin lispro (U100) using negative binomial regression analysis. Selected safety analyses may be conducted excluding data after introduction of another antihyperglycemic therapy, for example, rescue therapy.

9.4.4.2. Gastrointestinal Events

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

9.4.4.3. 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 intervention, and time from randomization to the event will be listed.

9.4.4.4. Central Laboratory Measures and Vital Signs

Values and change from baseline to postbaseline values of central laboratory measures and vital signs will be summarized at each scheduled visit. The analysis model to make comparisons among treatment arms, 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-participant errors.

The percentages of participants with TE abnormal, high, or low laboratory measures at any time will be summarized and compared between treatment arms 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.

9.4.5 Pharmacokinetic/Pharmacodynamic Analyses

Exploratory biomarker samples collected during the study may be used to perform any PK/PD related assessments as deemed appropriate.

If tirzepatide PK samples are analyzed to determine tirzepatide concentration, then subsequently the concentration data may be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM® software. The relationships between tirzepatide dose and/or concentration and efficacy, tolerability, and safety endpoints may be characterized. Additionally, the impact of intrinsic and extrinsic participant factors such as age, weight, gender, and renal function on PK may be examined as needed. If ADA titers are detected from immunogenicity testing, then the impact of immunogenicity titers on tirzepatide PK may also be examined.

9.4.6 Evaluation of Immunogenicity

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

9.4.7. Other Analyses

9.4.7.1. Subgroup Analyses

Subgroup analyses of mean change in HbA1c from baseline to the 52-week visit will be provided by age, race, ethnicity, gender, duration of diabetes, baseline HbA1c (≤8.5% or >8.5% [69 mmol/mol]), and baseline metformin use.

9.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

9.6. Data Monitoring Committee

There will be no Data Monitoring Committee.

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 GCP guidelines, and
    - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's 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.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, and

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, if applicable, and all other applicable local regulations.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his or her representative will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements (HIPPA), 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 re-consented 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 his or her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

Reports

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

Data

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

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal.

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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF 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 entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records 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 Trials Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

Data collected via the sponsor-provided data capture system(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 an archival copy of pertinent data for retention.

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

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

10.1.7. Source Documents

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

10.1.8. Study and Site Start and Closure

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

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, IRBs/IECs, regulatory authorities, and any contract research organizations 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.

10.1.9. 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.

10.1.10. Investigator Information

Physicians with a specialty in diabetes, endocrinology, internal medicine, family medicine, general medicine, or any other specialty physician who have experience treating T2DM and clinical research in T2DM and clinical trials involving insulin will participate as investigators in this clinical study.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in this section will be performed by the central laboratory, unless specified otherwise.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing will be performed as detailed in Section 1.3.

Investigators must document their review of each laboratory safety report.

Table 16. Clinical Laboratory Tests-Hematology

Hematology	Notes
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Differential:	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	

Table 17. Clinical Laboratory Test-Clinical Chemistry

Clinical Chemistry	Notes
Sodium	
Potassium	
Bicarbonate	
Total bilirubin	

Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Blood urea nitrogen (BUN)	
Creatinine	
Uric acid	
Calcium	
Glucose	
HbA1c	
Calcitonin	

Table 18. Clinical Lab Tests-Urine Chemistry

Urine Chemistry	Notes
Albumin	
Creatinine	

Table 19. Clinical Lab Tests-Lipids

Lipid Panel	Notes
Total cholesterol	
Low density lipoprotein (LDL)	
High density lipoprotein (HDL)	
Very low-density lipoprotein (VLDL)	
Triglycerides	

Table 20. Clinical Lab Test-Hormones

Hormones (female)	Notes
Serum pregnancy	• Must be performed only for women of childbearing potential at Visit 1 and Visit 5 (for Group 1B and Group 2 participants). • May be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period.
Urine pregnancy	• Evaluated locally. • Must be performed only for women of childbearing potential at Visit 6, Visit 16, Visit 20, Visit 22, Visit 23 and Visit 801. • At Visit 6, result should be available prior to administration of first injection of tirzepatide or insulin lispro (U100). • May be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period.
Follicle stimulating hormone	• Used to confirm post-menopausal status of subset of women participants

Table 21. Clinical Lab Tests-Pancreas

Pancreas (Exocrine panel)	Notes
Pancreatic amylase	
Lipase	

Table 22. Clinical Lab Tests-Exploratory Stored Samples

Exploratory Stored Samples	Notes
Exploratory stored samples:	
Serum	• Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Plasma (EDTA)	• Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Plasma (P800)	• Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Table 23. Clinical Lab Tests-Immunogenicity

Immunogenicity Assessments	Notes
Tirzepatide anti-drug antibody	• Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tirzepatide PK sample for immunogenicity	• Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Table 24. Clinical Lab Tests-Calculations

Calculations	Notes
eGFR (CKD-EPI)	• Will be calculated by the central laboratory and included in laboratory result reports
Urinary albumin/creatinine ratio	• Will be calculated by the central laboratory and included in laboratory result reports

10.3 Appendix 3: Laboratory Assessments for Hypersensitivity Events

Guidance for laboratory assessments for hypersensitivity events

- Laboratory assessments should be performed if the participant experiences generalized urticaria or if anaphylaxis is suspected
- Collect sample after the participant has been stabilized, and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

Table 25. summarizes the laboratory parameters that will be evaluated. These laboratory tests are bundled in the hypersensitivity laboratory testing kit.

Table 25. Clinical Lab Tests for Hypersensitivity Events

Hypersensitivity Tests	Notes Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.
Tirzepatide anti-drug antibodies (immunogenicity/ADA)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tirzepatide concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **Note:** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine sample for N-methylhistamine testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine N-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for N-methylhistamine testing at the next regularly scheduled visit or after 4 weeks, whichever is later.
N-methylhistamine	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Drug-specific IgE	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Basophil activation test	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **Note:** The basophil activation test is an in vitro cell based assay that only requires a serum sample. It is a surrogate assay for drug specific IgE, but is not specific for IgE.
Complement (C3, C3a, and C5a)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Cytokine panel	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Abbreviations: ADA = anti-drug antibody; IgE = immunoglobulin E; PK = pharmacokinetic.

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow up and Reporting

10.4.1. Definition of Adverse Event

Adverse Event Definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

Note: An AE can, therefore, be any unfavorable and unintended sign, including an abnormal laboratory finding; symptom; or disease, new or exacerbated, temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

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

"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 an AE or SAE, if they fulfill the definition of an AE or SAE.

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events Not Meeting the Adverse Event Definition

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

10.4.2. Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

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 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

f. Other situations:

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

10.4.3. Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording

- When an AE/SAE 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 information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the 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 the 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 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 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.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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 and/or Product Information, for marketed products, in his or her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he or 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 the 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 the sponsor or designee.
- The investigator may change his or her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the 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 the sponsor with a copy of any post-mortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.4.4. Reporting of Serious Adverse Events

Serious Adverse Event 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 paper SAE data collection tool (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 paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in site training documents.

Serious Adverse Event Reporting via Paper Case Report Form

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- 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.

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

General Definitions

General definitions for contraceptive guidance can be found in Table 26.

Table 26. General Definitions

Word/Phrase	Definition
Women not of childbearing potential	Females are considered women not of childbearing potential • after menopause • before the menarche • if they have a congenital anomaly such as Mullerian agenesis with primary amenorrhea, **or** • who are infertile due to surgical sterilization. Examples of surgical sterilization include • hysterectomy • bilateral oophorectomy, and • tubal ligation.
Post-menopausal state	The post-menopausal state is defined as: • A woman at any age with at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note, **or** • A woman who is 40 to less than 55 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 12 months without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL, **or** • A woman 55 years 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

Contraception Guidance

Contraception Requirements for Male Participants

All men should refrain from sperm donation and follow the contraception guidance in Table 27. for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days following the last dose of study intervention.

Table 27. Contraception Requirements for Male Participants

Category	Guidance
Men who remain abstinent as their preferred usual lifestyle	remain abstinent
Men in exclusively same sex relationships, as their preferred and usual lifestyle	are not required to use contraception
Men with partners of childbearing potential (nonpregnant)	1) use condoms with spermicide, **and** 2) A) use an additional highly effective (less than 1% failure rate) method of contraception **Examples:** • combination oral contraceptives, • implanted contraceptives, or • intrauterine devices **OR** B) use an additional effective method of contraception **Examples:** • diaphragms with spermicide, or • cervical sponges
Men with partners of non- childbearing potential (postmenopausal females or females with tubal ligation or hysterectomy or bilateral oophorectomy or has congenital anomaly, for example, Mullerian agenesis)	use condoms with spermicide
Men who had vasectomy or testicular removal surgery or who are sterile due to other medical condition	use condoms with spermicide
Men with pregnant partners	use condoms with spermicide

Contraception Requirements for Female Participants

All females should follow the contraception guidance in Table 28. for the entirety of the study and 30 days thereafter.

Table 28. Contraception Requirements for Female Participants

Category	Guidance
Women who remain abstinent as their preferred usual lifestyle	remain abstinent
Women in exclusively same sex relationships, as their preferred and usual lifestyle	are not required to use contraception
Women of non-childbearing potential	are not required to use contraception
Women of childbearing potential (nonpregnant)	must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit and Visit 5, if applicable, followed by a negative urine pregnancy test at Visit 6. **AND** Use 2 forms of effective contraception. At least 1 form should be highly effective such as combination oral contraceptives, implanted contraceptives, or intrauterine devices. Effective contraception such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges may be used as the second method.

Classification of Contraceptive Methods based on their Effectiveness

Table 29. provides examples of effective contraceptive methods.

Table 29. Classification of Contraceptive Methods based on their Effectiveness

Effectiveness	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence (if this is their preferred usual lifestyle) • vasectomy • 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
	  o female condom with spermicide
	Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective

Ineffective/unacceptable forms of contraception	• barrier protection methods without concomitant use of a spermicide
	• use of male and female condoms as a double barrier method due to the high failure rate when these methods are combined
	• spermicide alone
	• immunocontraceptives
	• periodic abstinence
	• fertility awareness or post-ovulation methods
	  o calendar method
	  o temperature method
	  o combination of above 2
	  o cervical mucus
	  o symptothermal
	• withdrawal
	• post coital douche
	• lactational amenorrhea

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 interventions.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy.

Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of 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 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 <22 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. 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 intervention and be withdrawn from the study.

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

Hepatic evaluation testing

- Refer to Section 8.2.5. for guidance on appropriate test selection.
- For testing selected, analysis is required to be completed by the Lilly designated central laboratory, except for microbiology.
- Local testing may be performed in addition to central testing when required for immediate participant management.
- Results will be reported if a validated test or calculation is available.

Table 30. Hepatic Evaluation Labs

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

Hepatitis B core IgM antibody	**Other Serology**
Hepatitis B core IgG antibody	Anti-nuclear antibody (ANA)
HBV DNA[a]	Anti-smooth muscle antibody (ASMA) [b]
Hepatis C Virus (HCV) Testing:	Anti-actin antibody[c]
HCV antibody	Epstein-Barr Virus (EBV) Testing:
HCV RNA[a]	EBV antibody
Hepatitis D Virus (HDV) Testing:	EBV DNA[a]
HDV antibody	Cytomegalovirus (CMV) Testing:
Hepatitis E Virus (HEV) Testing:	CMV antibody
HEV IgG antibody	CMV DNA[a]
HEV IgM antibody	Herpes Simplex Virus (HSV) Testing:
HEV RNA[a]	HSV (Type 1 and 2) antibody
Microbiology[d]	HSV (Type 1 and 2) DNA[a]
Culture:	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Blood	
Urine	

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

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

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

[d] Assayed by investigator-designated local laboratory ONLY. No central testing available.

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

10.7.1. Definition of Adverse Event and Adverse Device Event

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization (ISO) 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. (See Section 6.1.3. for the list of sponsor medical devices.)

Adverse Event and Adverse Drug Event Definition

- An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.
- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, any malfunction of the investigational medical device, as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of Serious Adverse Event, Serious Adverse Device Event and Unanticipated Serious Adverse Device Event

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is an AE that:

a. Led to death.

b. Led to serious deterioration in the health of the participant, that either resulted in:

1. A life-threatening illness or injury. 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.

2. A permanent impairment of a body structure or a body function.
3. Inpatient or prolonged hospitalization planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

c. Led to fetal distress, fetal death, or a congenital abnormality or birth defects.

d. Any device deficiency that might have led to an SAE, if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Serious Adverse Device Event Definition

An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

Unanticipated Adverse Device Event Definition

A UADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3.)

10.7.3. Definition of Device Deficiency

Device Deficiency Definition

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.7.4. Recording and Follow-Up of Adverse Event and/or Serious Adverse Event and Device Deficiencies

Adverse Event, Serious Adverse Event and Device Deficiency Recording

- When an AE/SAE/device deficiency 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/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate CRF or the Product Complaint Form.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE/device deficiency CRF or the Product Complaint Form.
- There may be instances when copies of medical records for certain cases are requested by the 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 the 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/SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 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
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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 and/or product information (for marketed products) in his or her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he or 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 the 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 the sponsor or designee.
- The investigator may change his or her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE/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 the sponsor or designee with a copy of any post-mortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.7.5. Reporting of Serious Adverse Events

Serious Adverse Event 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 paper SAE data collection tool, (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 paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in site training documents.

Serious Adverse Event Reporting via Paper Case Report Form

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor.
- 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.

10.7.6. Reporting of Serious Adverse Device Events

Serious Adverse Device Event Reporting

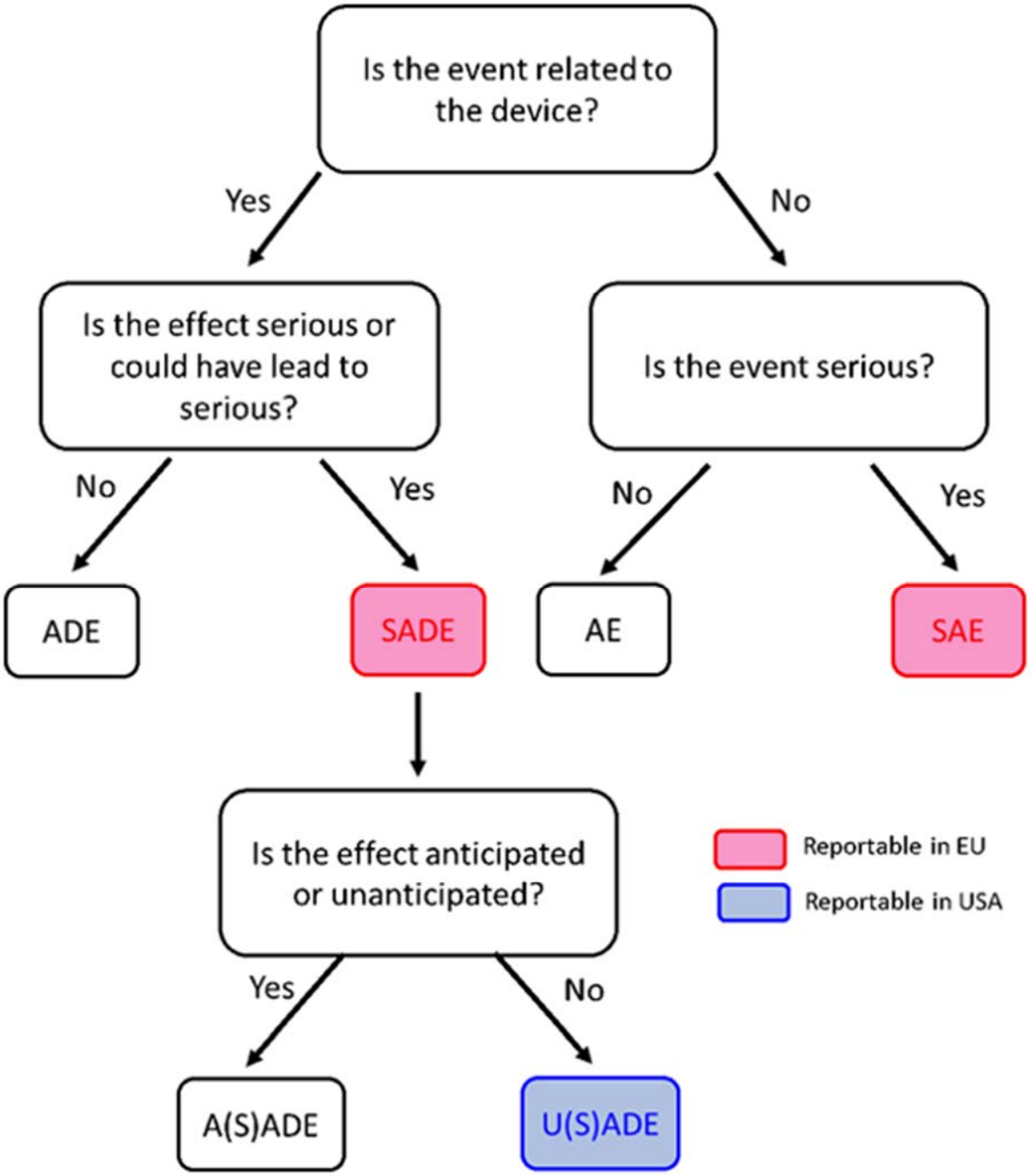
Note: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in site training documents.

10.7.7. Adverse Event, Adverse Device Event, Serious Adverse Event, Serious Adverse Device Event Determination Flow Chart

Note: Adverse event reporting for countries other than the US and EU must follow the regulatory and ethical requirements for that country.

Figure 4. Adverse Event, Adverse Device Event, Serious Adverse Event, Serious Adverse Device Event Determination Flow Chart



Abbreviations: AE = adverse event; ADE = adverse device event; SADE = serious adverse device event; SAE = serious adverse event

10.8. Appendix 8: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, Vital Signs

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) Manual.[34]

Measuring Height

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

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

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

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

Measuring Weight

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

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

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

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

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

Measuring Waist Circumference

- Waist circumference should be measured at midpoint, between lower margin of least palpable rib and top of iliac crest (~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.

Vital Sign Measurements (blood pressure and heart rate)

- Vital sign measurements (blood pressure and heart rate, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing.
- The participant should sit quietly for 5 minutes before vital signs measurements are taken.
- For each parameter, 2 measurements will be taken using the same arm, preferably the nondominant arm.
- The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and blood pressure needs to be recorded in the eCRF.
- Blood pressure must be taken with an automated blood pressure instrument.
- If blood pressure and pulse measurements are taken separately, pulse should be taken prior to blood pressure.

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

10.9. Appendix 9: 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"
- 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.

1. Remote Visits

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

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

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

- AEs and product complaints
- concomitant medications
- review of study participant diary (including compliance to self-monitored blood glucose monitoring, insulin glargine [U100], insulin lispro [U100] and tirzepatide treatment [including insulin titration], and hypoglycemia)
- administration of patient-reported outcomes, and
- other potential assessments if needed (i.e., urinary pregnancy test).

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

- weight and waist circumference measurements
- collecting blood samples
- brief physical assessment, including collection of vital signs or general wellness check
- patient-reported outcome measures administration, and
- collecting health information, including AEs, hypoglycemia events, concomitant medications.

Other alternative locations: During exceptional circumstances, laboratory samples may be drawn locally, if needed outside of mobile healthcare visits.

ADDITIONAL CRITERIA WHEN INCORPORATING REMOTE VISITS:

- **Participants on Tirzepatide:**

  Between Visit 6 and Visit 20 (i.e. week 0 to week 24 post-randomization), maximum duration for which a participant can continue tirzepatide without an on-site visit is 16 weeks. Tirzepatide should be interrupted otherwise until an in-clinic visit is conducted as soon as reasonably possible.

  Participants should contact the site for safety concerns related to hypoglycemia or severe hyperglycemia and Insulin glargine (U100) dose should be adjusted appropriately.

- **Participants on Insulin Lispro (U100):**

  Between Visit 6 and Visit 20 (i.e. week 0 to week 24 post-randomization), maximum duration for which a participant can continue uptitration of insulin lispro (U100) without an on-site visit is 12 weeks. Insulin lispro (U100) dose should not be uptitrated otherwise until an in-clinic visit is conducted as soon as reasonably possible.

  Participants should contact the site for safety concerns related to hypoglycemia or severe hyperglycemia and Insulin lispro (U100) and/or Insulin glargine (U100) dose should be adjusted appropriately.

  Between Visit 6 and Visit 10, if a participant is unable to come for on-site visits and needs additional training for following insulin lispro (U100) titration algorithm, investigator can ask participant to adjust dose once weekly for each of the three major meals during telemedicine visits while providing sufficient training for self-titration. As soon as investigator feels that participant will be able to self-titrate insulin lispro (U100) dose, twice weekly titration schedule should be resumed.

- **Safety Lab Assessments and Study Drug Continuation:**

  Safety lab assessments (including hematology, clinical chemistry, and urine pregnancy test) are performed at Visits 16, 20, 22, and 23 during the treatment period to ensure overall safety of participant while continuing study drug.

  The following guidelines must be followed for study drug continuation if safety lab assessments cannot be performed at routine schedule.

Study drug	Maximum duration for which study drug can be continued without safety lab assessment (either via central lab or local lab)
Insulin glargine (U100)	6 months
Insulin lispro (U100)	6 months
Tirzepatide	Between 0 to 24 weeks (Visit 6 to Visit 20) post-randomization: 16 weeks Between 24 to 52 weeks (Visit 21 to Visit 23) post-randomization: 20 weeks

Study drug should be interrupted otherwise until safety lab assessments are conducted as soon as reasonably possible.

2. Local Laboratory Testing Option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for clinical lab tests in Tables 22, 23, and 24 and exploratory stored samples as described in Appendix 2. The local laboratory must be qualified in accordance with applicable local regulations.

3. Study Intervention and Ancillary Supplies (including Participant Diaries)

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

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

These requirements must be met before action is taken:

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

4. Screening and Insulin Glargine (U100) Optimization Period Guidance

The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

Screening period (Visit 1 to Visit 2)

A) If participation was paused for less than 30 days between Visit 1 and Visit 2:
The participant will proceed to Visit 2 per the usual Schedule of Activities, provided that Visit 2 must be conducted within 30 days from Visit 1. The site should conduct Visit 2 if the participant's eligibility criteria are confirmed, and the site should document the reason for delay in the CRF. Due to the pause after Visit 1, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.

B) If participation was paused for more than 30 days between Visit 1 and Visit 2:
The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual Schedule of Activities should be followed, starting at Visit 1 to ensure participant eligibility by Visit 2. Any potential need to rescreen a participant more than once must be approved by sponsor.

NOTE: Rescreening of same participant is not allowed under normal circumstances. It is only allowed as outlined above in exceptional circumstances.

Insulin glargine (U100) optimization period (Visit 2 to Visit 6)

Visit 2 can be a telephone visit assuming all supplies like insulin glargine (U100), participant diary, glucometer, glucose test strips, etc. can be made available to participants. Site staff must ensure that participant has received sufficient training and is confident about self-administering insulin glargine (U100) using Kwikpen® device.

A) Group 1A participants:
If the participant is unable to come for onsite Visit 6 per original protocol schedule, then:

- Visit 6 may occur any time within 4 weeks after Visit 3, whenever fundoscopic examination results are available.
- Insulin glargine (U100) dose should not be adjusted until Visit 6 except for safety reasons (i.e. hypoglycemia or severe hyperglycemia).
- If the participant cannot come for onsite Visit 6 despite above mitigation step, he/she should be discontinued from the study.

B) Group 1B and Group 2 participants:
If the participant is unable to come for onsite Visit 5 or Visit 6 per original protocol schedule, then:

- Insulin glargine (U100) optimization period can be extended up to 14 weeks (total duration between Visit 2 and Visit 6).

- Visit 6 can be extended up to 2 weeks after Visit 5.
- If the participant cannot come for onsite Visit 5 or Visit 6 despite the above visit window extensions, he/she should be discontinued from the study.

5. 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	**Acceptable Tolerance** **(instead of what is mentioned in the Schedule of Activities)**
Visit 7 to Visit 14	± 4 days
Visit 15 to Visit 18	± 6 days
Visit 19 and Visit 20	± 10 days
Visit 21 and Visit 22	±14 days
Visit 23 (primary endpoint visit)	±28 days (i.e. the visit may be brought forward no sooner than 28 days [Week 48] or extended up to 28 days [Week 56])
Visit 801	±14 days

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

Documentation

Changes to study conduct will be documented:

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

10.10. Appendix 10: Abbreviations

Term	Definition
ADA	anti-drug antibody
ADE	adverse device event
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
BMI	body mass index
CEC	clinical endpoint committee
CI	confidence interval
CK	creatine kinase
CRF	case report form
CRP	clinical research physician
CT	computed tomography
CV	cardiovascular
D. Bil	direct bilirubin
DPP4i	dipeptidyl peptidase 4 inhibitors
DSMT	Developmental Safety Management Team
DSST	Developmental Safety Surveillance Team
EAS	efficacy analysis set
ECG	electrocardiogram
eCRF	electronic case report form
ERB	ethical review board
FAS	full analysis set
FBG	fasting blood glucose

FSG	fasting serum glucose
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIP-R	glucose-dependent insulinotropic polypeptide receptor
GIP/GLP-1 RA	glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonist
GLP-1	glucagon-like peptide-1
GLP-1 R	glucagon-like peptide-1 receptor
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	International Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web-response system
IW-SP	Impact of Weight on Self-perception
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MTC	medullary thyroid cancer
NAFLD	nonalcoholic fatty liver disease
NPH	Neutral Protamine Hagedorn
PD	pharmacodynamics
PK	pharmacokinetics
PT	prothrombin time
QW	once weekly
RA	receptor agonist
SADE	serious adverse device event
SAE	serious adverse event
SAP	statistical analysis plan

SC	subcutaneous
SD	standard deviation
SF-36v2	short form health survey version 2
SMBG	self-monitored blood glucose
SoA	schedule of activities
SS	safety analysis set
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TE	treatment emergent
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.
TID	three times a day
UADE	unanticipated adverse device effect
ULN	upper limit of normal

10.11. Appendix 11: Protocol Amendment History

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

Amendment [a]:

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

The overall changes and rationale for the changes made to this protocol are described in the following table. Note 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
Section 5.2, Exclusion Criteria	Corrected exclusion criterion 33 that describes participation in a clinical study. The last statement was updated to include the following missing information: “days (whichever is longer) should have passed”.	This statement was corrected to include all details for this exclusion criterion.
Section 10.8, Appendix 8	Added description of vital sign measurements	Text added for clarification
Section 1.1, Synopsis, Section 3.0, Objectives and Endpoints, Section 10.9, Appendix 9	Minor errors in abbreviations	Corrected errors

Amendment (b)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:
The overall changes and rationale for the changes made to this protocol are described in the following table. Note 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
Section 10.9. Appendix 9: Provisions for Changes in Study Conduct during Exceptional Circumstances	An appendix has been added describing the temporary measures intended to be used only in the case of exceptional circumstances during specific time periods as directed by the sponsor in partnership with the investigator.	The added language provides guidance when a participant's ability and/or willingness to attend their onsite study visit is impacted by exceptional circumstances, e.g., the global restrictions enacted in response to the COVID-19 pandemic.
Section 5.2. Exclusion Criteria; Section 10.1.5 – 10.1.10; 1.2 Schema, Section 6.5	Minor errors in units, section numbering, abbreviations, and incorrect references have been corrected.	Corrected errors

11. References

1. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32(1):193-203. https://doi.org/10.2337/dc08-9025
2. Dale J, Martin S, Gadsby R. Insulin initiation in primary care for patients with type 2 diabetes: 3-year follow-up study. *Prim Care Diabetes*. 2010;4(2):85-89. https://doi.org/10.1016/j.pcd.2010.03.001
3. Kunt T, Snoek FJ. Barriers to insulin initiation and intensification and how to overcome them. *Int J Clin Pract Suppl*. 2009;63(suppl 164):6-10. https://doi.org/10.1111/j.1742-1241.2009.02176.x
4. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26(11):3080-3086. https://doi.org/10.2337/diacare.26.11.3080
5. Davies M, Evans R, Storms F, et al. Initiation of insulin glargine in suboptimally controlled patients with type 2 diabetes: sub-analysis of the AT.LANTUS trial comparing treatment outcomes in subjects from primary and secondary care in the UK. *Diabetes Obes Metab*. 2007;9(5):706-713. https://doi.org/10.1111/j.1463-1326.2006.00652.x
6. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia*. 2006;49(3):442-451. https://doi.org/10.1007/s00125-005-0132-0
7. Gerstein HC, Yale JF, Harris SB, et al. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. *Diabet Med*. 2006;23(7):736-742. https://doi.org/10.1111/j.1464-5491.2006.01881.x
8. Hollander P, Cooper J, Bregnhøj J, Pedersen CB. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. *Clin Ther*. 2008;30(11):1976-1987. https://doi.org/10.1016/j.clinthera.2008.11.001
9. Raskin P, Gylvin T, Weng W, Chaykin L. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2009;25(6):542-548. https://doi.org/10.1002/dmrr.989

10. Tomlinson B, Hu M, Zhang Y, et al. An overview of new GLP-1 receptor agonists for type 2 diabetes. *Expert Opin Investig Drugs*. 2016;25(2):145-158. https://doi.org/10.1517/13543784.2016.1123249

11. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet*. 2018;392(10160):2180-2193. https://doi.org/10.1016/S0140-6736(18)32260-8

12. Frias JP, Nauck MA, Van J, et al. Efficacy and tolerability of tirzepatide, a dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes: a 12-week, randomized, double-blind, placebo-controlled study to evaluate different dose-escalation regimens. *Diabetes Obes Metab*. Published online January 27, 2020. https://doi.org/10.1111/dom.13979

13. Marso SP, McGuire DK, Zinman B,et al. Design of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events) - DEVOTE 1. *Am Heart J*. 2016;179:175-183. https://doi.org/10.1016/j.ahj.2016.06.004

14. Billings LK, Doshi A, Gouet D, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: the DUAL VII randomized clinical trial. *Diabetes Care*. 2018;41(5):1009-1016. https://doi.org/10.2337/dc17-1114

15. Bowering K, Case C, Harvey J, et al. Faster aspart versus insulin aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes: the onset 2 trial. *Diabetes Care*. 2017;40(7):951-957. https://doi.org/10.2337/dc16-1770

16. Maruish ME, editor. *User's Manual for the SF-36v2 Health Survey*. 3rd ed. QualityMetric Incorporated; 2011.

17. EuroQol Research Foundation. EQ-5D-5L User Guide, Version 3.0. Updated September 2019. Accessed March 13, 2020. https://euroqol.org/publications/user-guides

18. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997;35(11):1095-1108. https://doi.org/10.1097/00005650-199711000-00002

19. Hayes RP, DeLozier AM. Reliability, validity, and responsiveness of the Impact of Weight on Self-Perceptions Questionnaire (IW-SP) in individuals with type 2 diabetes and obesity. *Diabetes Technol Ther*. 2015;17(3):210-214. https://doi.org/10.1089/dia.2014.0142

20. Hayes RP, Nelson DR, Meldahl ML, Curtis BH. Ability to perform daily physical activities in individuals with type 2 diabetes and moderate obesity: a preliminary validation of the Impact of Weight on Activities of Daily Living Questionnaire. *Diabetes Technol Ther*. 2011;13(7):705-712. https://doi.org/10.1089/dia.2011.0027

21. Hayes RP, Schultz EM, Naegeli AN, Curtis BH. Test-retest, responsiveness, and minimal important change of the ability to perform physical activities of daily living

questionnaire in individuals with type 2 diabetes and obesity. *Diabetes Technol Ther*. 2012;14(12):1118-1125. https://doi.org/10.1089/dia.2012.0123

22. American Diabetes Association. 3. Comprehensive medical evaluation and assessment of comorbidities. *Diabetes Care*. 2017;40(suppl 1):S25-S32. https://doi.org/10.2337/dc17-S006 Published correction appears in *Diabetes Care*. 2017;40(7):985. https://doi.org/10.2337/dc17-er07

23. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2020. *Diabetes Care*. 2020;43(suppl 1):S66-S76. https://doi.org/10.2337/dc20-S006

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

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

26. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38(1):140-149. https://doi.org/10.2337/dc14-2441

27. Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology . Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379-2400. https://journals.lww.com/ajg/Fulltext/2006/10000/Practice_Guidelines_in_Acute_Pancreatitis.31.aspx

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

29. Nauck MA, Meier JJ, Schmidt WE. Incretin-based glucose-lowering medications and the risk of acute pancreatitis and/or pancreatic cancer: reassuring data from cardio-vascular outcome trials. *Diabetes Obes Metab*. 2017;19(9):1327-1328. https://doi.org/10.1111/dom.12981

30. Steinberg WM, Buse JB, Ghorbani MLM, et al. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: results from the LEADER randomized trial. *Diabetes Care*. 2017;40(7):966-972. https://doi.org/10.2337/dc16-2747

31. Steinberg WM, Rosenstock J, Wadden TA, et al. Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: secondary analyses of pooled data

from the SCALE clinical development program. *Diabetes Care*. 2017;40(7):839-848. https://doi.org/10.2337/dc16-2684

32. Aroda VR, Ratner R. The safety and tolerability of GLP-1 receptor agonists in the treatment of type 2 diabetes: a review. *Diabetes Metab Res Rev*. 2011;27(6):528-542. https://doi.org/10.1002/dmrr.1202

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

34. World Health Organization. The WHO STEPWise approach to noncommunicable disease risk factor surveillance. WHO STEPS Surveillance Manual. Updated January 26, 2017. Accessed March 13, 2020. https://www.who.int/ncds/surveillance/steps/STEPS_Manual.pdf

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