Protocol Amendment I8F-MC-GPHE (c)

A Randomized, Open-Label, Parallel-Group, Two-Arm, Phase 4 Study to Evaluate the Long-Term Efficacy and Safety of Tirzepatide Compared with Intensified Conventional Care in Adults When Initiating Treatment Early in the Course of Type 2 Diabetes (SURPASS-EARLY)

NCT05433584

Approval Date: 15-Mar-2023

Title Page

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Protocol Title: A Randomized, Open-Label, Parallel-Group, Two-Arm, Phase 4 Study to Evaluate the Long-Term Efficacy and Safety of Tirzepatide Compared with Intensified Conventional Care in Adults When Initiating Treatment Early in the Course of Type 2 Diabetes (SURPASS-EARLY)

Protocol Number: I8F-MC-GPHE

Amendment Number: c

Compound: LY3298176

Brief Title: Efficacy and Safety of Tirzepatide Compared with Intensified Conventional Care in Adults when Treatment is Initiated Early for Type 2 Diabetes

Study Phase: 4

Acronym: SURPASS-EARLY

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s):

IND: 128801

EU trial number: 2022-501073-40-00

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

Document ID: VV-CLIN-081316

Medical Monitor Name and Contact Information will be provided separately.

jilhgbProtocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment b	*02-Nov-2022*
Amendment a	*20-Jun-2022*
Original Protocol	*15-Mar-2022*

Amendment (c)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The rationale for amending the protocol is to remove mobile healthcare option due to feasibility issue and provide a few clarifications.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Removed "For participants meeting eligibility requirements,".	For clarification
1.3. Schedule of Activities	Removed "mobile healthcare" and "remote visits" related language.	Feasibility and low expected utilization.
1.3.1. Screening Visits 1-2, and Treatment Visits 3-9	To 'Visit interval tolerance' header row, • Added ±7 day visit interval tolerance to Visit 3. • Added "Visit interval tolerance for Visits 2 and 3 is determined from Visit 1. After Visit 3, the visit interval tolerance is determined from randomization date." in the comments. • To 'Dilated fundoscopic examination' row, removed "if the participant meets all qualifications for the study at Visit 1. An exception may be made for Anti-GAD antibody result if pending at Visit 2." in comments. • To 'Oral glucose tolerance test (OGTT)' row, removed "Perform only if the participant meets all other qualifications for the study at Visit 2."	For clarification.
1.3.1. Screening Visits 1-2, and Treatment Visits 3-9 1.3.2. Treatment Visits 10-25, Early Discontinuation, and the Post-Treatment Follow-up Visit 801	• To '12-lead ECG (local)' row, added "Should" in the beginning of the comments. • To 'Patient-Reported Outcomes' row, changed "Complete PROs" to "PROs should be completed" in the comments.	For clarification.
1.3.2. Treatment Visits 10-25, Early Discontinuation, and the Post-Treatment Follow-up Visit 801	Added "Assess study intervention compliance" at ED visit.	For clarification.
4.1.1. Design Outline	• Removed "For participants meeting eligibility requirements,".	For clarification.

Section # and Name	Description of Change	Brief Rationale
	• Added "should" to Visit 3 Randomization language.	
5.4. Screen Failures	Added "Visit 1 laboratory measures that do not meet inclusion criteria will be considered a screen failure. Retests are NOT ALLOWED except for instances when results from V1 samples are not available from the original samples."	For clarification.
6.1.3. Rescue Therapy 6.5.5. Intensified Conventional Care Dose Modifications 7.1. Discontinuation of Study Intervention 11. References	Updated the citation and reference from "ADA 2022" to "ADA 2023."	Updated the reference.
6.3. Measures to Minimize Bias: Randomization and Blinding 9.3.1. General Considerations 9.3.6. Subgroup Analyses	Considered EU countries and Israel as one region as one of the stratification factors.	To consolidate Western Europe (W-EU), and Eastern Europe + Israel (E-EU + Israel) as a single region (EU+Israel) to minimize the probability of not having enough participants in each stratification factor level.
8.2.4. Dilated Fundoscopic Examination	Removed "if the participant meets all qualifications for the study at Visit 1."	For clarification.
8.3.3.6. Hypoglycemia	Replaced "Site personnel will enter this information into the eCRF at each visit" with "Participants will enter all hypoglycemic episodes in eCOA device."	For clarification.
10.8. Appendix 8: OGTT Test	Added the following: • "approximately" to time • Immediately after collection of the Time 0 sample, a 75-g glucose dose will be given orally. The participant should consume the glucose load within approximately 5 minutes. • The participant should remain minimally active for the duration of the test. Removed the following: • At time zero participants will ingest solution containing 75 g glucose.	For clarification.
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore, not detailed

Table of Contents

1. Protocol Summary 9
1.1. Synopsis 9
1.2. Schema 15
1.3. Schedule of Activities (SoA) 16
1.3.1. Screening Visits 1-2, and Treatment Visits 3-9 17
1.3.2. Treatment Visits 10-25, Early Discontinuation, and the Post-Treatment Follow-up Visit 801 21

2. Introduction 26
2.1. Study Rationale 26
2.2. Background 27
2.3. Benefit/Risk Assessment 28
2.3.1. Risk Assessment for Tirzepatide 28
2.3.2. Benefit Assessment for Tirzepatide 28
2.3.3. Overall Benefit Risk Conclusion 28

3. Objectives, Endpoints, and Estimands 29

4. Study Design 35
4.1. Overall Design 35
4.1.1. Design Outline 35
4.2. Scientific Rationale for Study Design 37
4.3. Justification for Dose 38
4.4. End of Study Definition 38

5. Study Population 39
5.1. Inclusion Criteria 39
5.2. Exclusion Criteria 40
5.3. Lifestyle Considerations 42
5.4. Screen Failures 43
5.5. Criteria for Temporarily Delaying Enrollment of a Participant 43

6. Study Intervention(s) and Concomitant Therapy 44
6.1. Study Intervention(s) Administered 44
6.1.1. Frequency of Tirzepatide Doses and Injection Site 45
6.1.2. Devices 45
6.1.3. Rescue Therapy 46
6.1.4. Background Therapy with Metformin 47
6.2. Preparation, Handling, Storage, and Accountability 48
6.3. Measures to Minimize Bias: Randomization and Blinding 48
6.4. Study Intervention Compliance 48
6.5. Dose Modification 49
6.5.1. Tirzepatide Dose Escalation during the First 24 Weeks 49
6.5.2. Tirzepatide Dose Reductions during the First 24 Weeks 50
6.5.3. Tirzepatide Dose Reductions after Week 24 50
6.5.4. Tirzepatide Dose Re-Escalation 50
6.5.5. Intensified Conventional Care Dose Modifications 50

6.6. Continued Access to Study Intervention after the End of the Study 52
6.7. Treatment of Overdose 52
6.7.1. Tirzepatide Overdose 52
6.7.2. Intensified Conventional Care Overdose 52
6.8. Concomitant Therapy 53
6.8.1. Concomitant Therapy Regimens 53
6.8.2. Changing Concomitant Therapy 53
6.8.3. Concomitant Therapy Data Collection 53
6.8.4. Prohibited Concomitant Medications 53
6.8.5. Allowed Antihyperglycemic Treatments other than Study Interventions 54

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 55
7.1. Discontinuation of Study Intervention 55
7.1.1. Liver Chemistry Stopping Criteria 56
7.1.2. QTc Stopping Criteria 57
7.1.3. Temporary Discontinuation of Study Intervention 57
7.2. Participant Discontinuation/Withdrawal from the Study 58
7.3. Lost to Follow-up 59

8. Study Assessments and Procedures 60
8.1. Efficacy Assessments 60
8.1.1. Self-Monitoring of Blood Glucose (SMBG) 60
8.1.2. β-cell Functions and Insulin Sensitivity Assessed by Oral Glucose Tolerance Test (OGTT) 61
8.1.3. Patient-Reported Outcomes 61
8.2. Safety Assessments 63
8.2.1. Physical Examinations 63
8.2.2. Vital Signs 63
8.2.3. Electrocardiograms 63
8.2.4. Dilated Fundoscopic Examination 64
8.2.5. Clinical Safety Laboratory Tests 64
8.2.6. Pregnancy Testing 64
8.2.7. Hepatic Monitoring 65
8.3. Adverse Events, Serious Adverse Events, and Product Complaints 67
8.3.1. Timing and Mechanism for Collecting Events 68
8.3.2. Pregnancy 69
8.3.3. Safety Topics of Special Interest 70
8.4. Pharmacokinetics 76
8.5. Pharmacodynamics 76
8.6. Genetics 76
8.7. Biomarkers 76
8.8. Immunogenicity Assessments 76
8.9. Health Economics 76

9. Statistical Considerations 77
9.1. Statistical Hypotheses 77
9.1.1. Multiplicity Adjustment 77
9.2. Analyses Sets 78
9.3. Statistical Analyses 78
9.3.1. General Considerations 78
9.3.2. Primary Endpoint Analysis 79
9.3.3. Secondary Endpoints Analysis 80
9.3.4. Exploratory Endpoints Analysis 81
9.3.5. Safety Analyses 81
9.3.6. Subgroup Analyses 82
9.4. Interim Analysis 82
9.5. Sample Size Determination 82

10. Supporting Documentation and Operational Considerations 84
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 84
10.1.1. Regulatory and Ethical Considerations 84
10.1.2. Financial Disclosure 85
10.1.3. Informed Consent Process 85
10.1.4. Data Protection 85
10.1.5. Committees Structure 85
10.1.6. Dissemination of Clinical Study Data 86
10.1.7. Data Quality Assurance 86
10.1.8. Source Documents 88
10.1.9. Study and Site Start and Closure 88
10.1.10. Publication Policy 89
10.1.11. Investigator Information 89
10.1.12. Sample Retention 89
10.2. Appendix 2: Clinical Laboratory Tests 90
10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event 93
10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 94
10.3.1. Definition of AE 94
10.3.2. Definition of SAE 95
10.3.3. Definition of Product Complaints 96
10.3.4. Recording and Follow-up of AE and/or SAE and Product Complaints 97
10.3.5. Reporting of SAEs 99
10.3.6. Regulatory Reporting Requirements 100
10.4. Appendix 4: Contraceptive and Barrier Guidance 101
10.4.1. Definitions 101
10.4.2. Contraception Guidance 102
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 104

10.6. Appendix 6: 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....106
10.7. Appendix 7: Country-Specific Requirements....107
10.7.1. Germany....107
10.8. Appendix 8: OGTT Test....112
10.9. Appendix 9: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, BMI, and Vital Signs....113
10.10. Appendix 10: Provisions for Changes in Study Conduct During Exceptional Circumstances....115
10.11. Appendix 11: Abbreviations and Definitions....120
10.12. Appendix 12: Protocol Amendment History....125
11. References....129

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Randomized, Open-Label, Parallel-Group, Two-Arm, Phase 4 Study to Evaluate the Long-Term Efficacy and Safety of Tirzepatide Compared with Intensified Conventional Care in Adults When Initiating Treatment Early in the Course of Type 2 Diabetes (SURPASS-EARLY)

Brief Title:

Efficacy and Safety of Tirzepatide Compared with Intensified Conventional Care in Adults when Treatment is Initiated Early for Type 2 Diabetes

Regulatory Agency Identifier Number(s):

IND: 128801

EU trial number: 2022-501073-40-00

Rationale:

Results of Phase 3 SURPASS studies show that tirzepatide may potentially address an important clinical care gap in the treatment of type-2 diabetes (T2D).

This study aims to test the hypothesis that, during the course of T2D, when compared to other existing treatment options, early initiation of tirzepatide treatment may improve glycemic control and lower body weight during the first 2 years. Moreover, these improvements may be maintained through 4 years without the need to initiate additional glucose-lowering therapy as well as delay the deterioration of β-cell function. Existing treatment options are represented in this trial by the intensified conventional care. Treatments in the intensified conventional care arm include a range of glucose-lowering medications used in clinical practice and supported by treatment guidelines.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To demonstrate that tirzepatide is non-inferior to intensified conventional care in hemoglobin A1c (HbA1c) change from baseline to Week 104 in participants with type-2 diabetes (T2D)	o Change in HbA1c from baseline
Key Secondary	
To demonstrate that tirzepatide is superior to intensified conventional care at Week 104	o Change in HbA1c from baseline o Change in weight from baseline o Change in waist circumference from baseline

Objectives	Endpoints
To demonstrate that tirzepatide is non-inferior to intensified conventional care at Week 208	o Change in HbA1c from baseline
To demonstrate that tirzepatide is superior to intensified conventional care at Week 208	o Change in HbA1c from baseline o Change in weight from baseline o Change in waist circumference from baseline
Additional Secondary	

To assess the clinical effect of tirzepatide compared to intensified conventional care at Week 104	o Change in FSG (via central lab) from baseline
	o Change in lipids from baseline (total cholesterol, HDL, LDL, VLDL, and TG)
	o HbA1c <5.7%, ≤6.5%, and <7%
	o Weight loss from baseline of ≥5%, ≥10%, and ≥15%
	o A composite endpoint defined as
	  o HbA1c ≤6.5%
	  o weight loss ≥10%, and
	  o no hypoglycemia, defined as BG <54 mg/dL (<3.0 mmol/L) and/or severe hypoglycemia
	o Change in β-cell function and insulin sensitivity from baseline assessed in OGTT
	  o β-cell glucose sensitivity based on the modeling analysis
	  o Insulin secretion rate at a fixed glucose concentration (adjusted and unadjusted for basal potentiation) from modeling analysis
	  o postprandial insulin sensitivity indices (for example, Matsuda index and OGIS)
	  o fasting and post-challenge glucose (total and incremental $AUC_{0\text{-}240min}$)
	  o fasting and post-challenge insulin (total and incremental $AUC_{0\text{-}240min}$)

Objectives	Endpoints
	○ Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) – Physical-Functioning domain

To assess the clinical effect of tirzepatide compared to intensified conventional care at Week 208	○ Change in FSG (via central lab) from baseline
	○ Change in lipids from baseline (total cholesterol, HDL, LDL, VLDL, and TG)
	○ HbA1c <5.7%, ≤6.5%, and <7%
	○ Weight loss from baseline of ≥5%, ≥10%, and ≥15%
	○ A composite endpoint defined as
	  ○ HbA1c ≤6.5%
	  ○ weight loss ≥10%, and
	  ○ no hypoglycemia, defined as BG <54 mg/dL (<3.0 mmol/L) and/or severe hypoglycemia
	○ Change in β-cell function and insulin sensitivity from baseline of the following parameters assessed in OGTT:
	  ○ β-cell glucose sensitivity based on modeling analysis
	  ○ Insulin secretion rate at a fixed glucose concentration (adjusted and unadjusted for basal potentiation) from modeling analysis
	  ○ postprandial insulin sensitivity indices (for example, Matsuda index and OGIS)
	  ○ fasting and post-challenge glucose (total and incremental $AUC_{0\text{-}240min}$)
	  ○ fasting and post-challenge insulin (total and incremental $AUC_{0\text{-}240min}$)
	○ IWQOL-Lite-CT – Physical-Functioning domain

Abbreviations: AUC = area under the curve; BG = blood glucose; FSG = fasting serum glucose; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OGIS = oral glucose insulin sensitivity; OGTT = oral glucose tolerance test; TG = triglyceride; VLDL = very-low-density lipoprotein.

Primary and key secondary endpoints are controlled for multiplicity.

Overall Design:

SURPASS-EARLY is a randomized, open-label, parallel-group, two-arm, multicenter, multinational, Phase 4 study to investigate the long-term efficacy and safety of tirzepatide 15 mg or maximum tolerated dose compared to intensified conventional care in participants with up to 4 years of T2D history. This study will enroll participants with T2D inadequately controlled with diet, exercise, and metformin.

This study includes an approximate 3-week screening period, a 208-week treatment period, and a 4-week safety follow-up.

Brief Summary:

Period I: Screening

Visit 1

Interested individuals will sign the appropriate informed consent document(s) prior to initiating any procedure.

The investigator will review medical history and other inclusion and exclusion criteria prior to any diagnostic procedures. If the participant is eligible after this review, then the site will perform the diagnostic procedures to confirm eligibility.

Visit 2

The investigator will review the results of the screening laboratory measures if available to further assess participant eligibility.

Participants arrive to the clinic in the fasting state.

An Oral Glucose Tolerance Test to assess β-cell function will be performed at Visit 2.

A dilated fundoscopic examination will be scheduled and completed between Visit 2 and Visit 3.

Participants or caregivers, if applicable, will receive a blood glucose (BG) meter and electronic Clinical Outcome Assessment device.

Participants will be asked to monitor 7-point self-monitoring of blood glucose profiles, prior to and 2 hours after the 3 main meals and at bedtime, on 2 nonconsecutive days during the 2-weeks preceding prespecified visits.

At investigator's and participant's discretion, participants should monitor BG any time a hypoglycemic event is suspected or unusual symptoms are present.

Participants should continue their diet and exercise routine and must not use any glucose-lowering treatment other than metformin taken prior to the screening visit or change their metformin dose or formulation.

Period II: Treatment period

Visit 3 Randomization

All screening laboratory test results and screening dilated fundoscopic examination results must be reviewed for exclusion criteria prior to randomization and dosing at Visit 3.

Study personnel will provide appropriate training for use of the tirzepatide autoinjector and observe the participant inject the first dose of tirzepatide.

Study personnel will provide appropriate instruction for treatment with the antihyperglycemic medication selected as the study intervention in the intensified conventional care treatment group.

Visit 25 (Week 208) or early discontinuation (ED) visit

The investigator will determine a participant's transition from study treatment to another diabetes treatment.

Period III: Safety follow-up visit

All participants who complete the treatment period or discontinue the study early (ED) are required to complete the safety follow-up visit approximately 4 weeks after their last study visit.

Participants will return study e-diaries to the study site.

Study Population:

In general, participants may take part in the study if they

- Are 18 years of age or older
- Have, within the last 4 years, been diagnosed with T2D
- Have HbA1c ≥7% to ≤9.5%
- Have been on a stable treatment of metformin ONLY and no other antihyperglycemic medication for at least 90 days preceding Visit 1
    - with the minimum effective dose of ≥1500 mg/day, but not higher than the maximum approved dose per country-specific label, OR
    - <1500 mg/day in case of intolerance of full therapeutic dose
- Are reliable and willing to make themselves available for the duration of the study and are willing and able to follow study procedures as required.

In general, participants may not take part in the study if they

- Have a history of
    - proliferative diabetic retinopathy
    - diabetic maculopathy, or
    - nonproliferative diabetic retinopathy that requires acute treatment.
- Are at high-risk for CVD in the investigator's opinion or have a history of any of these CV conditions prior to Visit 1
    - myocardial infarction
    - percutaneous coronary revascularization procedure
    - carotid stenting or surgical revascularization
    - nontraumatic amputation

  - peripheral vascular procedure (e.g., stenting or surgical revascularization)
  - cerebrovascular accident (stroke), or
  - congestive heart failure

- At the investigator's opinion, participants for whom an HbA1c ≤ 6.5% goal is not appropriate, considering expected benefits and risks of therapy.
- Have a history or presence of an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with the interpretation of data.
- Have been treated with any injectable GLP-1 receptor agonists and insulin prior to screening.

  Exception: use of insulin for gestational diabetes or short-term use (<14 days) for acute conditions such as acute illness, hospitalization, or elective surgery.
- Have within 90 days prior to screening received treatment with medications intended to promote weight loss. This includes prescribed, over-the-counter, or alternative remedies.

  Examples include, but are not limited to

  - Liraglutide 3.0 mg
  - Semaglutide 2.4 mg
  - Sibutramine
  - Mazindol
  - Lorcaserin
  - Naltrexone/bupropion
  - Zonisamide
  - Topiramate
  - Orlistat
  - Phenylpropanolamine
  - Phentermine
  - Phentermine/topiramate combination, or
  - Pramlintide.

Number of Participants:

A sample size of approximately 780 participants will be randomly assigned in a 1:1 ratio to tirzepatide or intensified conventional care.

Intervention Groups and Duration:

The planned treatment groups are tirzepatide and intensified conventional care.

Tirzepatide is administered once-weekly by subcutaneous injection, and the dose will be escalated to 15 mg or the MTD.

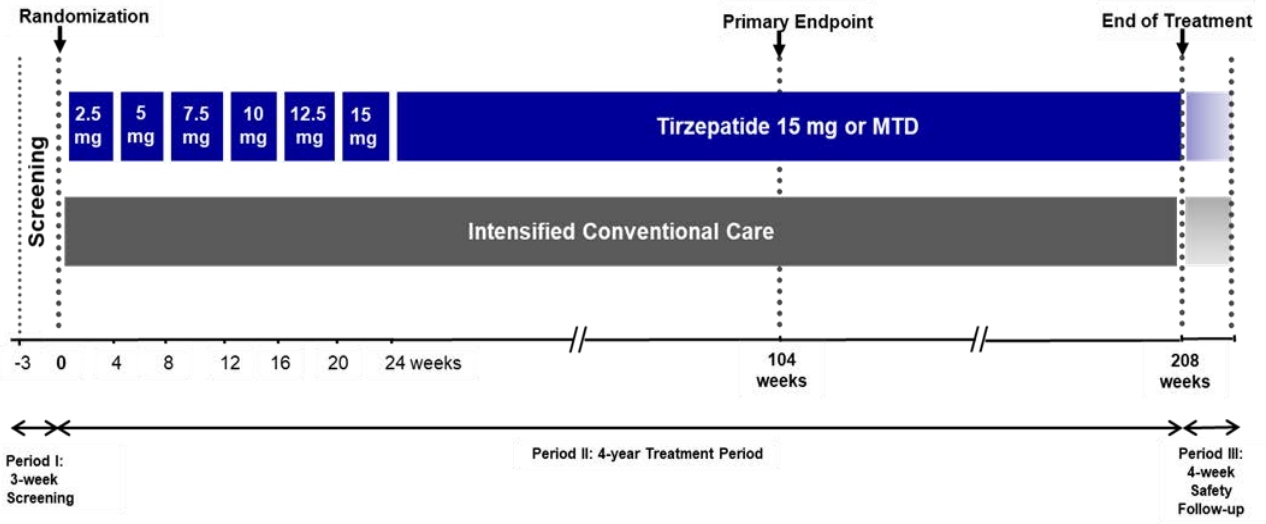
Treatments in the intensified conventional care arm include a range of glucose-lowering medications used in clinical practice and supported by treatment guidelines. They will be used in accordance with the product labels approved locally.

Ethical Considerations of Benefit/Risk:

Considering the data that are available to date from previous clinical studies, and the measures taken to ensure the safety of the participants in this study, the potential risks related with tirzepatide are justified by the anticipated benefits a participant with T2D may experience in the study.

Data Monitoring Committee: No

1.2. Schema



Abbreviation: MTD = maximum tolerated dose.

1.3. Schedule of Activities (SoA)

Two tables describe the schedule of activities.

Table 1 (Section 1.3.1) describes procedures for Screening Visits 1-2, and Treatment Visits 3-9.

Table 2 (Section 1.3.2) describes procedures for Treatment Visits 10-25, Early Discontinuation, and the Safety Follow-up Visit 801.

Fasting Visits

Participants should fast at least 8 hours without eating, drinking (except water), or performing any significant physical activity before the visit.

If a participant attends these visits in a non-fasting state, the sample should still be collected except for Visits 2, 16, and 25.

If participant attends Visits 2, 16, and 25 in the non-fasting state, these visits must be rescheduled. If a participant attends other visits in a non-fasting state, the samples should be collected as non-fasting and this will not be considered a protocol deviation.

Early Discontinuation

See the activities listed for ED in Section 1.3.2 for participants that discontinue from the study prior to the last scheduled visit.

1.3.1. Screening Visits 1-2, and Treatment Visits 3-9

Study I8F-MC-GPHE	Period I Screening		Period II – Treatment Period							Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	-3	-2	—	4	8	12	16	20	24	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	Visit interval tolerance for Visits 2 and 3 is determined from Visit 1. After Visit 3, the visit interval tolerance is determined from randomization date.
Fasting visit		X	X			X			X	
Informed consent	X									Participant signs ICF before any tests or procedures are performed. See Section 10.1.3 for additional details.
Inclusion and exclusion criteria, review and confirm	X	X	X							Confirm inclusion and exclusion criteria prior to randomization and first dose of intervention.
Demographics	X									Includes ethnicity (where permissible), year of birth, gender (sex), and race.
Preexisting conditions and medical history, including relevant surgical history	X									Collect all ongoing conditions and relevant past surgical and medical history.
Prespecified medical history (indication and history of interest)	X									Collect additional data for the indication and comorbidities of interest. See Section 4.1.1.
Substance use (tobacco or nicotine)	X									
Prior treatments for indication	X									Add details of T2D medication. Includes medications used for T2D since diagnosis.
Concomitant medications	X	X	X	X	X	X	X	X	X	See Section 6.8.
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	AEs are any events that occur after signing the informed consent. Collect additional data for safety topics of special interest. See Section 8.3.3.
Physical Evaluation										
Height	X									
Weight	X		X	X	X	X	X	X	X	
Waist circumference	X		X	X	X	X	X	X	X	
Vital signs	X		X	X	X	X	X	X	X	Includes pulse rate and blood pressure. Measure after participant has been sitting for at least 5 minutes and before obtaining an ECG tracing and before collection of blood samples for laboratory testing. See Section 8.2.2.
Physical examination	X									See Section 8.2.1.

Study I8F-MC-GPHE	Period I Screening		Period II – Treatment Period							Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	-3	-2	—	4	8	12	16	20	24	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	Visit interval tolerance for Visits 2 and 3 is determined from Visit 1. After Visit 3, the visit interval tolerance is determined from randomization date.
Fasting visit		X	X			X			X	
Symptom-directed physical assessment		X								Symptom-directed physical assessment will be conducted at the discretion of the PI or qualified personnel per local regulations, as indicated based on participant status and standard of care.
12-lead ECG (local)			X							Should perform prior to collection of blood samples for laboratory testing. Participants should be supine for approximately 5 to 10 minutes before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit. See Section 8.2.3.
Dilated fundoscopic examination		X								Schedule dilated fundoscopic examination between Visits 2 and 3. A previous examination ≤90 days of screening meeting study requirements is acceptable to confirm eligibility. An ophthalmologist or optometrist, if allowed by country, will perform the examination. Perform additional examinations when clinically indicated.
Participant Education and Supplies										
Diabetes counseling, training, and education		X								Includes counseling on diet and exercise, symptoms and management of hypoglycemia and hyperglycemia, etc. See Sections 5.3 and 8.3.3. After Visit 2, conduct as needed.
BG meter, SMBG training		X								Participant will be trained at randomization. Additional training may occur as needed.
Dispense BG meter/supplies		X	X	X	X	X	X	X	X	
Study intervention injection training with demo device			X							Train participant prior to starting any new injectable type.
Remind participants about 7-point SMBG		X								
Review 7-point SMBG values collected in the eDiary			X							
Review hypoglycemic events			X	X	X	X	X	X	X	
Participant Diary (Electronic)										
Participant eDiary dispensed		X								eDiary includes blood glucose values, collection of intervention administration information on dosing days, and hypoglycemia. See Section 8.1.
eDiary compliance check			X	X	X	X	X	X	X	
Patient-Reported Outcomes (Electronic) *Complete prior to any clinical administered assessments*										PROs should be completed before any other study procedures if the participant is not adversely affected by the fasting condition or after the participant has

Study I8F-MC-GPHE	Period I Screening		Period II – Treatment Period							Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	-3	-2	—	4	8	12	16	20	24	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	Visit interval tolerance for Visits 2 and 3 is determined from Visit 1. After Visit 3, the visit interval tolerance is determined from randomization date.
Fasting visit		X	X			X			X	
										sufficiently recovered from the preceding visit procedures. Must be completed on eCOA device.
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36 v2, Acute)			X							
Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT)			X							
Ability to Perform Physical Activities of Daily Living (APPADL)			X							
Impact of Weight on Self Perception (IW-SP)			X							
Laboratory Tests and Sample Collections										
Oral glucose tolerance test (OGTT)		X								Collect glucose, C-peptide, insulin, intact proinsulin, and glucagon at each timepoint. See Sections 8.1.2 and 10.8.
Hematology	X									
Clinical chemistry	X		X			X			X	
Hemoglobin A1c (HbA1c)	X		X			X			X	
Glucose	X		X			X			X	
Pancreatic amylase	X		X						X	
Lipase	X		X						X	
Calcitonin	X								X	
Lipid panel			X			X			X	
Serum pregnancy	X								X	Only for WOCBP and females with a history of tubal ligation. See Section 10.4.2.
Urine pregnancy (local)			X	X	X	X	X	X	X	Collect for WOCBP only. The result must be available prior to first dose of intervention. Monthly home urine pregnancy test is required in between visits after Visit 9. Perform additional pregnancy tests if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation.
Follicle-stimulating hormone (FSH)	X									Optional; perform as needed to confirm postmenopausal status. See Section 10.4.

Study I8F-MC-GPHE	Period I Screening		Period II – Treatment Period							Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	-3	-2	—	4	8	12	16	20	24	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	Visit interval tolerance for Visits 2 and 3 is determined from Visit 1. After Visit 3, the visit interval tolerance is determined from randomization date.
Fasting visit		X	X			X			X	
Microalbumin			X							
C-reactive protein, high-sensitivity (hsCRP)			X							
Anti-GAD antibody	X									
Cystatin-c	X									
Estimated glomerular filtration rate (eGFR)	X									Calculate using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) method.
Urinary albumin/creatinine ratio (UACR)	X								X	
Stored Samples										
Exploratory biomarker samples			X						X	
Randomization and Dosing via IWRS										
Register visit	X	X	X	X	X	X	X	X	X	
Randomization			X							
Dispense study intervention			X	X	X	X	X	X	X	Dispense to participant or caregiver, as necessary.
Observe participant administer intervention			X							For tirzepatide home dosing.
Dispense ancillary supplies			X	X	X	X	X	X	X	
Participant or caregiver returns unused study intervention and ancillary supplies				X	X	X	X	X	X	Where applicable as per local regulations.
Assess study intervention compliance				X	X	X	X	X	X	

Abbreviations: Anti-GAD = anti-glutamic acid decarboxylase; BG = blood glucose; ECG = electrocardiogram; eCOA = electronic clinical outcome assessment; ICF = informed consent form; IWRS = interactive web-response system; PI = Principal Investigator; PRO = patient-reported outcomes; SMBG = self-monitoring of blood glucose; T2D = type-2 diabetes; WOCBP = women of childbearing potential.

1.3.2. Treatment Visits 10-25, Early Discontinuation, and the Post-Treatment Follow-up Visit 801

Study I8F-MC-GPHE	**Period II – Treatment Period**																	**Period III Safety Follow-up**	**Comments**
Visit number	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	ED	801	ED = early discontinuation
Weeks from randomization	32	44	56	68	80	92	104	116	128	140	152	164	176	188	200	208	—		
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Fasting visit	X		X		X		X		X		X		X		X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 6.8.
Substance use (tobacco or nicotine)							X									X	X		
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collect additional data for safety topics of special interest. See Section 8.3.3.
Physical Evaluation																			
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Waist circumference	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes pulse rate and blood pressure. Measure after participant has been sitting for at least 5 minutes and before obtaining an ECG tracing and before collection of blood samples for laboratory testing. See Section 8.2.2.
Physical examination			X				X				X					X	X		See Section 8.2.1.
Symptom-directed physical assessment	X																		Symptom-directed physical assessment will be conducted at the discretion of the PI or qualified personnel per local regulations, as indicated based on participant status and standard of care. Excluding Visits 12, 16, 20, 25 and ED as they include a physical examination.

Study I8F-MC-GPHE	Period II – Treatment Period																	Period III Safety Follow-up	Comments
Visit number	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	ED	801	ED = early discontinuation
Weeks from randomization	32	44	56	68	80	92	104	116	128	140	152	164	176	188	200	208	—		
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Fasting visit	X		X		X		X		X		X		X		X	X	X		
12-lead ECG (local)							X									X	X	X	Should perform prior to collection of blood samples for laboratory testing. Participants should be supine for approximately 5 to 10 minutes before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit. See Section 8.2.3.
Dilated fundoscopic examination							X									X	X		An ophthalmologist or optometrist, if allowed by country, will perform the examination.
Participant Education and Supplies																			
Diabetes counseling, training, and education	X				X				X						X				Includes counseling on diet and exercise, symptoms and management of hypoglycemia and hyperglycemia, etc. See Sections 5.3 and 8.3.3. After Visit 2, conduct as needed.
BG meter, SMBG training	X				X				X						X				Additional training may occur as needed.
Dispense BG meter/supplies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Return BG meter/supplies																	X	X	
Remind participants about 7-point SMBG		X				X				X					X				
Review 7-point SMBG values collected in the eDiary			X				X				X					X			
Review hypoglycemic events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant Diary (Electronic)																			

Study I8F-MC-GPHE	**Period II – Treatment Period**																	**Period III Safety Follow-up**	**Comments**
Visit number	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	ED	801	ED = early discontinuation
Weeks from randomization	32	44	56	68	80	92	104	116	128	140	152	164	176	188	200	208	—		
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Fasting visit	X		X		X		X		X		X		X		X	X	X		
eDiary compliance check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
eDiary return																	X	X	
Patient-Reported Outcomes (Electronic) *Complete prior to any clinical administered assessments*																			PROs should be completed before any other study procedures if the participant is not adversely affected by the fasting condition or after the participant has sufficiently recovered from the preceding visit procedures. Must be completed on eCOA device.
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36 v2, Acute)			X				X				X					X	X		
Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT)			X				X				X					X	X		
Ability to Perform Physical Activities of Daily Living (APPADL)			X				X				X					X	X		
Impact of Weight on Self Perception (IW-SP)			X				X				X					X	X		
Laboratory Tests and Sample Collections																			
Oral glucose tolerance test (OGTT)							X									X	X		Collect glucose, C-peptide, insulin, intact proinsulin, and glucagon at each timepoint. See Sections 8.1.2 and 10.8.
Hematology			X				X				X					X	X		
Clinical chemistry	X		X		X		X		X		X		X		X	X	X	X	

Study I8F-MC-GPHE	**Period II – Treatment Period**																	**Period III Safety Follow-up**	**Comments**
Visit number	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	ED	801	ED = early discontinuation
Weeks from randomization	32	44	56	68	80	92	104	116	128	140	152	164	176	188	200	208	—		
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Fasting visit	X		X		X		X		X		X		X		X	X	X		
Hemoglobin A1c (HbA1c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Glucose	X		X		X				X		X		X		X				
Pancreatic amylase	X		X		X		X		X		X		X		X	X	X	X	
Lipase	X		X		X		X		X		X		X		X	X	X	X	
Calcitonin			X				X				X					X	X	X	
Lipid panel	X		X		X		X		X		X		X		X	X	X		
Urine pregnancy (local)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Collect for WOCBP only. Monthly home urine pregnancy test is required in between visits. Perform additional pregnancy tests if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation.
Microalbumin			X				X				X					X	X		
C-reactive protein, high-sensitivity (hsCRP)			X				X				X					X	X		
Cystatin-c			X				X				X					X	X	X	
Estimated glomerular filtration rate (eGFR)			X				X				X					X	X	X	Calculate using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) method.
Urinary albumin/creatinine ratio (UACR)	X		X		X		X		X		X		X		X	X	X	X	
Stored Samples																			

Study I8F-MC-GPHE	**Period II – Treatment Period**																	**Period III Safety Follow-up**	**Comments**
Visit number	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	ED	801	ED = early discontinuation
Weeks from randomization	32	44	56	68	80	92	104	116	128	140	152	164	176	188	200	208	—		
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Fasting visit	X		X		X		X		X		X		X		X	X	X		
Exploratory biomarker samples			X				X				X					X	X		
Randomization and Dosing using IWRS																			
Register visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study intervention	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				Dispense to participant or caregiver, as necessary.
Dispense ancillary supplies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Participant or caregiver returns unused tirzepatide and ancillary supplies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Participant or caregiver returns unused study intervention and ancillary supplies from the intensified conventional care treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Where applicable as per local regulations.
Assess study intervention compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Abbreviations: BG = blood glucose; ECG = electrocardiogram; eCOA = electronic clinical outcome assessment; IWRS = interactive web-response system; PI = Principal Investigator; PRO = patient-reported outcomes; SMBG = self-monitoring of blood glucose; WOCBP = women of childbearing potential.

2. Introduction

Importance of achieving and maintaining glycemic control when treatment is initiated early for T2D

Several studies in T2D (UK Prospective Diabetes Study 1998a, 1998b; Holman et al. 2008) and in T1D (DCCT 1993, DCCT/EDIC 2015) have demonstrated the clinical importance of achieving and maintaining glycemic control during the first years following clinical diagnosis.

The UKPDS study showed that intensive glucose control in participants with newly diagnosed T2D lowered the risk of microvascular complications during the originally planned study period. In addition, participants in the intensive treatment group demonstrated a continued reduction in microvascular risk, a reduction of risk for myocardial infarction, and death from any cause during 10 years of post-study follow-up.

Normalizing blood glucose early during T2D might improve longer-term glycemic control as demonstrated in the studies evaluating impact of short-term intensive insulin therapy (Wajchenberg 2007; Brown and Rother 2008).

The clinical care gap in diabetes therapy for participants with T2D

Despite the availability of several classes of antihyperglycemic agents, studies continue to show that substantial numbers of participants with T2D do not reach their goals for glycemic control, weight loss, blood pressure control, or lipid control (Ali et al. 2013; Stark Casagrande et al. 2013; Van Gaal and Scheen 2015; Blonde et al. 2019; Fang et al. 2021). Even if the desired glycemic control is achieved, limited data exist for available antihyperglycemic medicines to provide long-term glycemic control or delay the progression of the disease, that is, deterioration of β-cell function (Li et al. 2021).

Tirzepatide

Tirzepatide is a QW dual GIP and GLP-1 receptor agonist developed for the treatment of T2D. The structure of tirzepatide is engineered from the GIP sequence and includes a C20 fatty diacid moiety. Tirzepatide has a mean half-life of approximately 5 days, which enables QW dosing (Coskun et al. 2018).

2.1. Study Rationale

Results of Phase 3 SURPASS studies show that tirzepatide may potentially address an important clinical care gap in the treatment of T2D.

This study aims to test the hypothesis that, during the course of T2D, when compared to other existing treatment options, early initiation of tirzepatide treatment may improve glycemic control and lower body weight during the first 2 years. Moreover, these improvements may be maintained through 4 years without the need to initiate additional glucose-lowering therapy as well as delay the deterioration of β-cell function. Existing treatment options are represented in this trial by the intensified conventional care. Treatments in the intensified conventional care arm include a range of glucose-lowering medications used in clinical practice and supported by treatment guidelines.

2.2. Background

Tirzepatide: Mechanism of Action

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

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

Phase 3 clinical studies

Clinical reductions in HbA1c and body weight

In a series of 5 global Phase 3 SURPASS studies, tirzepatide demonstrated clinically meaningful reductions in HbA1c and body weight, which were greater than placebo, semaglutide 1 mg, titrated insulin degludec, and titrated insulin glargine (Rosenstock et al. 2021; Frías et al. 2021; Ludvik et al. 2021; Del Prato et al. 2021; Dahl et al. 2022. These treatment effects were sustained up to 104 weeks (Del Prato et al. 2021).

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

Improvements in metabolic endpoints

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

Common adverse events

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

Hypoglycemia events

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

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of tirzepatide may be found in the IB and that of the intensified conventional care treatments may be found in the patient information leaflet.

2.3.1. Risk Assessment for Tirzepatide

The most commonly reported TEAEs observed in the tirzepatide clinical studies, in healthy participants and participants with T2D, are GI effects, including nausea, diarrhea, and vomiting.

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

Potential risks associated with tirzepatide include:

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

2.3.2. Benefit Assessment for Tirzepatide

The potential benefits from participation in this study include improved glycemic control, weight loss, delayed deterioration of β-cell function, and continued expert medical care of T2D for the study duration.

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

2.3.3. Overall Benefit Risk Conclusion

The safety and efficacy profile seen to date for tirzepatide, supports the overall benefit risk for participants in this study. Considering the measures taken to minimize risk to participants in this study as outline in the protocol, the potential risks identified in association with tirzepatide are justified by the anticipated benefits that may be afforded to participants living with T2D.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate that tirzepatide is non-inferior to intensified conventional care in HbA1c change from baseline to Week 104 in participants with T2D	o Change in HbA1c from baseline
Key Secondary	
To demonstrate that tirzepatide is superior to intensified conventional care at Week 104	o Change in HbA1c from baseline o Change in weight from baseline o Change in waist circumference from baseline
To demonstrate that tirzepatide is non-inferior to intensified conventional care at Week 208	o Change in HbA1c from baseline
To demonstrate that tirzepatide is superior to intensified conventional care at Week 208	o Change in HbA1c from baseline o Change in weight from baseline o Change in waist circumference from baseline
Additional Secondary	

To assess the clinical effect of tirzepatide compared to intensified conventional care at Week 104	o Change in FSG (via central lab) from baseline
	o Change in lipids from baseline (total cholesterol, HDL, LDL, VLDL, and TG)
	o HbA1c <5.7%, ≤6.5%, and <7%
	o Weight loss from baseline of ≥5%, ≥10%, and ≥15%
	o A composite endpoint defined as
	  o HbA1c ≤ 6.5%
	  o weight loss ≥10%, and
	  o no hypoglycemia, defined as BG <54 mg/dL (<3.0 mmol/L) and/or severe hypoglycemia
	o Change in β-cell function and insulin sensitivity from baseline assessed in OGTT
	  o β-cell glucose sensitivity based on the modeling analysis

Objectives	Endpoints
	○ Insulin secretion rate at a fixed glucose concentration (adjusted and unadjusted for basal potentiation) from modeling analysis ○ postprandial insulin sensitivity indices (for example, Matsuda index and OGIS) ○ fasting and post-challenge glucose (total and incremental $AUC_{0-240min}$) ○ fasting and post-challenge insulin (total and incremental $AUC_{0-240min}$) ○ Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) – Physical-Functioning domain
To assess the clinical effect of tirzepatide compared to intensified conventional care at Week 208	○ Change in FSG (via central lab) from baseline ○ Change in lipids from baseline (total cholesterol, HDL, LDL, VLDL, and TG) ○ HbA1c <5.7%, ≤6.5%, and <7% ○ Weight loss from baseline of ≥5%, ≥10%, and ≥15% ○ A composite endpoint defined as ○ HbA1c ≤6.5% ○ weight loss ≥10%, and ○ no hypoglycemia, defined as BG <54 mg/dL (<3.0 mmol/L) and/or severe hypoglycemia ○ Change in β-cell function and insulin sensitivity from baseline of the following parameters assessed in OGTT: ○ β-cell glucose sensitivity based on modeling analysis ○ Insulin secretion rate at a fixed glucose concentration (adjusted and unadjusted for basal potentiation) from modeling analysis ○ postprandial insulin sensitivity indices (for example, Matsuda index and OGIS) ○ fasting and post-challenge glucose (total and incremental $AUC_{0-240min}$)

Objectives	Endpoints
	○ fasting and post-challenge insulin (total and incremental $AUC_{0-240min}$) ○ IWQOL-Lite-CT – Physical-Functioning domain
Exploratory	
To assess the clinical effect of tirzepatide compared to intensified conventional care at Week 104	○ Change in daily average 7-point self-monitored blood glucose profiles ○ Change in BMI from baseline ○ Change in urinary albumin to creatinine ratio from baseline ○ Change in eGFR from baseline ○ Change in number of antihyperglycemic medications from baseline ○ Slope of HbA1c following the initial nadir ○ Biomarkers ○ Time to treatment failure, defined as HbA1c ≥7% confirmed at 2 consecutive study visits after Week 32 ○ The change from baseline in the following parameters assessed during OGTT: ○ glucagon concentration at fasting and post-challenge (total and incremental $AUC_{0-240min}$) ○ insulin/glucagon ratios at fasting and post-challenge (total and incremental $AUC_{0-240min}$) ○ C-peptide concentration at fasting and post-challenge (total and incremental $AUC_{0-240min}$) ○ insulinogenic index ○ insulin clearance ○ SF-36 (standard version) ○ IWQOL-Lite-CT (Total, Physical, and Psychosocial) ○ Ability to Perform Physical Activities of Daily Living (APPADL) ○ Impact of Weight on Self Perception (IW-SP)

Objectives	Endpoints
To assess the effect of tirzepatide compared to intensified conventional care at Week 208	o Change in daily average 7-point self-monitored blood glucose profiles o Change in BMI from baseline o Change in urinary albumin to creatinine ratio from baseline o Change in eGFR from baseline o Change in number of antihyperglycemic medications from baseline o Slope of HbA1c following the initial nadir o Time-averaged HbA1c over the entire study period o Biomarkers o Time to treatment failure, defined as HbA1c ≥7% confirmed at 2 consecutive study visits after Week 32 o The change from baseline in the following parameters assessed during OGTT: o glucagon concentration at fasting and post-challenge (total and incremental $AUC_{0\text{-}240min}$) o insulin/glucagon ratios at fasting and post-challenge (total and incremental $AUC_{0\text{-}240min}$) o C-peptide concentration at fasting and post-challenge (total and incremental $AUC_{0\text{-}240min}$) o insulinogenic index o insulin clearance o SF-36 (standard version) o IWQOL-Lite-CT (Total, Physical, and Psychosocial) o APPADL o IW-SP

Abbreviations: AUC = area under the curve; BG = blood glucose; BMI = body mass index; eGFR = estimated glomerular filtration rate; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OGIS = oral glucose insulin sensitivity; OGTT = oral glucose tolerance test; SF-36 = 36-item short-form health survey; T2D = type-2 diabetes; TG = triglyceride; VLDL = very-low-density lipoprotein.

Primary and key secondary endpoints are controlled for multiplicity.

Primary estimands

There will be 2 primary estimands evaluated in this study:

- The treatment-regimen estimand is accepted by the FDA and is consistent with the expected US Prescribing Information. This estimand aims at reflecting how participants with T2D are treated in clinical practice and takes into account both tolerability and efficacy.
- The efficacy estimand focuses on the treatment effect if participants who underwent randomization continued to receive the study treatment without rescue antihyperglycemic medication for severe, persistent hyperglycemia and/or prohibited medications. This estimand will be used in publications to inform prescribers/physicians and may be submitted to other regulatory agencies outside the US.

Treatment-regimen estimand

The treatment-regimen estimand answers the following question of interest for the primary objective: What is the treatment difference in change from baseline in HbA1c after 104 weeks of treatment in participants with T2D regardless of treatment discontinuation for any reason and regardless of initiation of antihyperglycemic rescue treatment or prohibited medication (except for non-study tirzepatide) or change in the background metformin treatment?

The treatment-regimen estimand is described by the following attributes.

- *Population*: Participants with T2D inadequately controlled with diet and exercise with a background of metformin at a stable dose. Further details can be found in Section 5.
- *Endpoint*: Change from baseline to Week 104 after randomization in HbA1c.
- *Treatment condition*: The randomized treatment regardless of adherence to treatment with or without antihyperglycemic rescue medication or prohibited medication, except for non-study tirzepatide, or change in background metformin medication. Further details on study treatment and concomitant therapy, including rescue, treatments can be found in Section 6.
- *Intercurrent events*: Intercurrent events of interest: “treatment discontinuation for any reason” and “initiation of rescue antihyperglycemic treatment or prohibited medication (except for non-study tirzepatide), or change in background metformin medication” are addressed by the treatment condition. Initiation of non-study tirzepatide is addressed by the hypothetical strategy; that is, as if participants had not taken non-study tirzepatide.
- *Population-level summary*: Difference in mean changes between treatment conditions.

Efficacy estimand

The efficacy estimand answers the following question of interest for the primary objective: What is the treatment difference in HbA1c change from baseline to Week 104 after randomization in participants with T2D regardless of changes in background metformin medication assuming that participants had stayed on treatment and not taken antihyperglycemic rescue or prohibited medication?

The efficacy estimand is described by the following attributes.

- *Population*: Participants with T2D inadequately controlled with diet and exercise with a background of metformin. Further details can be found in Section 5.
- *Endpoint*: HbA1c change from baseline to Week 104 after randomization.
- *Treatment condition*: The randomized treatment, regardless of changes to the background metformin medication. Further details on study treatment can be found in Section 6.
- *Intercurrent event*: Intercurrent events of interest: "Treatment discontinuation for any reason" and "Initiation of antihyperglycemic rescue treatment or prohibited medication" will be addressed using the following strategies:
    - Had participants stayed on treatment (hypothetical strategy).
    - Had participants not taken antihyperglycemic rescue or prohibited medication (hypothetical strategy).
- *Population-level summary:* Difference in mean changes between treatment conditions.

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

4. Study Design

4.1. Overall Design

SURPASS-EARLY is a randomized, open-label, parallel-group, two-arm, multicenter, multinational, Phase 4 study to investigate the long-term efficacy and safety of tirzepatide 15 mg or MTD compared to intensified conventional care in participants with up to 4 years of T2D history. This study will enroll participants with T2D inadequately controlled with diet, exercise, and metformin.

This study includes an approximate 3-week screening period, a 208-week treatment period, and a 4-week safety follow-up.

See the SoA (Section 1.3) for additional details about the study periods and visit-specific assessments, including assessments needed at an ED visit.

4.1.1. Design Outline

Period I: Screening

Visit 1

Interested individuals will sign the appropriate informed consent document(s) prior to initiating any procedure.

The investigator will review medical history and other inclusion and exclusion criteria prior to any diagnostic procedures. If the participant is eligible after this review, then the site will perform the diagnostic procedures to confirm eligibility.

Visit 2

The investigator will review the results of the screening laboratory measures if available to further assess participant eligibility.

Participants arrive to the clinic in the fasting state as specified in Section 10.8, Appendix 8.

An OGTT test to assess β-cell function will be performed at Visit 2.

A dilated fundoscopic examination will be scheduled and completed between Visit 2 and Visit 3.

Participants or caregivers, if applicable, will receive a BG meter and eCOA device.

Participants and their caregiver(s), if applicable, will receive training on

- eCOA device, including the eDiary data collection and the electronic PRO data collection
- diabetes self-monitoring and management, including instructions on diet and exercise, education about the signs, symptoms, and treatment of hypoglycemia and hyperglycemia
- recording blood glucose measurements, and
- study requirements.

Participants will be asked to monitor 7-point SMBG profiles, prior to and 2 hours after the 3 main meals and at bedtime, on 2 nonconsecutive days during the 2-weeks preceding prespecified visits, as shown in the SoA (Section 1.3).

At investigator's and participant's discretion, participants should monitor BG any time a hypoglycemic event is suspected or unusual symptoms are present. Additional measurements might be used to monitor trends in BG.

Participants should continue their diet and exercise routine and must not use any glucose-lowering treatment other than metformin taken prior to the screening visit or change their metformin dose or formulation.

Period II: Treatment period

Visit 3 Randomization

See Section 6.1 for intervention details, and Section 6.3 for randomization and stratification factors.

All screening laboratory test results and screening dilated fundoscopic examination results must be reviewed for exclusion criteria prior to randomization and dosing at Visit 3.

This is the general flow for Visit 3:

- Participants arrive to the clinic in the fasting state
- Study personnel confirm enrollment criteria
- Participants are randomly assigned to an intervention group
- Participants should complete PRO questionnaires before any other study procedures if the participant is not adversely affected by the fasting condition or complete after the participant has sufficiently recovered, and
- Study personnel complete all required visit procedures, including the collection of vital signs, all baseline procedures and sample collection.

Study intervention training

Study personnel will provide appropriate training for use of the tirzepatide autoinjector. The training can be provided using a demonstration device, if available. This training will be repeated at subsequent visits, as needed.

In addition, study personnel will provide product-specific "instructions for use" information to the participants upon request, if available.

First tirzepatide dose

Study personnel will observe as the participant injects the first dose of tirzepatide. The autoinjector is also referred to as an SDP. The date and time of the first dose of tirzepatide should be recorded on the CRF.

First intensified conventional care dose

Study personnel will provide appropriate instruction for treatment with the antihyperglycemic medication selected as the study intervention. Additional training may be provided at subsequent visits, as needed.

Study personnel will provide product-specific injectable "instructions for use" information to the participants upon request.

Visit 4 through Visit 24 (Week 4 through Week 200) Treatment period

Participants complete all visit procedures described in the SoA.

Visit 25 (Week 208) or ED visit

Participants complete all visit procedures described in the SoA.

The investigator will determine a participant's transition from study treatment to another diabetes treatment.

Period III: Safety follow-up visit

All participants who complete the treatment period or discontinue the study early (ED) are required to complete the safety follow-up visit approximately 4 weeks after their last study visit.

Participants complete all visit procedures described in the SoA. Participants will return study e-diaries to the study site.

4.2. Scientific Rationale for Study Design

This study is designed to determine long-term efficacy and safety of tirzepatide 15 mg or MTD compared with intensified conventional care in adults with a short history of T2D.

Primary endpoint

The primary endpoint of the study is the change in HbA1c from baseline to 104 weeks. HbA1c was chosen as the primary endpoint because it is an accepted and well understood endpoint reflecting glycemic control over extended periods of time.

Duration of treatment period and safety follow-up

Duration of the study has been selected based on learnings from the ADOPT study evaluating the impact of antihyperglycemic therapies on T2D disease progression (Kahn et al. 2006). The planned treatment duration of 104 weeks as the primary endpoint will allow assessment of near-term benefits and risks of early initiation of therapy with tirzepatide in participants with T2D.

The entire 208 weeks treatment period provides more insight into long-term effects including durability of glycemic control and the ability of tirzepatide to modify the course of the disease. The 208 weeks will enable meaningful conclusions regarding durability of glycemic control and the ability of tirzepatide to modify the course of the disease.

The 104-week and 208-week durations are important to fully evaluate the scientific hypothesis and clinical relevance of the study.

Intensified conventional care as a comparator

Treatments in the intensified conventional care arm include a range of glucose-lowering medications used in clinical practice and supported by treatment guidelines. They will be used in accordance with the product labels approved locally.

Intensified conventional care provides participants and investigators an opportunity to achieve best treatment results with existing therapies.

Open-label design

An open-label design was chosen due to the different dosage forms, dosing frequency, titration schemes, and injection devices available for intensified conventional care compared with tirzepatide. The open-label design prevents the risk of concomitant use of tirzepatide and GLP-1 RAs, which are a frequently prescribed treatment for T2D.

Demographics collection

In this study, collection of demographic information includes race and ethnicity (where permissible). The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

4.3. Justification for Dose

Tirzepatide

Tirzepatide at 15 mg or MTD, administered subcutaneously QW, will be evaluated in this study.

To mitigate the potential occurrence of GI AEs associated with tirzepatide and permit time for the development of tolerance to GI effects, a dose escalation scheme will be used in tirzepatide arm. The treatment starts at a low dose of 2.5 mg QW for 4 weeks and then escalates by 2.5 mg increments every 4 weeks until tirzepatide 15 mg or MTD is reached (Section 6.5.1).

Participants may be treated with lower dose if they do not achieve full dose escalation to 15 mg.

These doses and associated escalation schemes were selected based on the results of global registration Phase 3 studies in people with T2D. The requirement to escalate the dose to 15 mg or MTD is based on the finding that tirzepatide lowers blood glucose but also provides other metabolic benefits such as weight loss and increase in insulin sensitivity, in a dose-dependent manner. Since these metabolic benefits may play a role in a long-term treatment effect, it is important to use the highest possible dose of tirzepatide.

Intensified Conventional Care

Dosing of study intervention will be used in accordance with the locally accepted treatment guidelines and the approved product label. Doses will be chosen to achieve and maintain glycemic control that is considered optimal, without compromising participants' safety, primarily without increasing the risk of hypoglycemia.

4.4. End of Study Definition

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

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

5. Study Population

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

5.1. Inclusion Criteria

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

Age

- Are 18 years old or of an acceptable age to provide informed consent according to local regulations, whichever is older.

Type of Participant and Disease Characteristics

1. Have, within the last 4 years, been diagnosed with T2D based on the World Health Organization classification, ADA classification, or other locally applicable diagnostic standards.
2. Have HbA1c ≥7% to ≤9.5% as determined by the central laboratory.
3. Have been on a stable treatment of metformin ONLY and no other antihyperglycemic medication for at least 90 days preceding Visit 1
    - with the minimum effective dose of ≥1500 mg/day, but not higher than the maximum approved dose per country-specific label, or
    - <1500 mg/day in case of intolerance of full therapeutic dose.

Weight

4. Have had stable body weight (±5%) during the 90 days preceding screening and agree to not initiate a new intensive 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 BMI ≥25 kg/m^2 and ≤45 kg/m^2 at screening.

Sex and Contraceptive/Barrier Requirements

6. Contraceptive use by participants:

    Male participants must be willing to use reliable contraceptive methods as provided in Section 10.4, Appendix 4.

    Both women of childbearing potential (WOCBP) and women not of childbearing potential (WNOCBP) may participate in the study.

    WOCBP participant should be willing to follow contraception requirements as provided in Section 10.4, Appendix 4.

Informed Consent

7. Are capable of giving signed informed consent as described in Section 10.1.3, Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other Inclusions

8. Are reliable and willing to make themselves available for the duration of the study and are willing and able to follow study procedures as required, including, but not limited to
    - Self-inject intervention or injection by a caregiver when applicable
    - Take provided study interventions as directed
    - Maintain an eDiary, and
    - Complete electronic patient-reported questionnaires.

5.2. Exclusion Criteria

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

Medical Conditions

9. Have T1D.
10. Have a history of chronic or acute pancreatitis any time prior to screening.
11. Have a history of
    - proliferative diabetic retinopathy
    - diabetic maculopathy, or
    - nonproliferative diabetic retinopathy that requires acute treatment.
12. Have a history of ketoacidosis or hyperosmolar state/coma.
13. Have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1.
14. Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction), have undergone or plan to have during the course of the study: gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or chronically take drugs that directly affect GI motility.
15. Have acute or chronic hepatitis, signs and symptoms of any liver disease other than NAFLD, or ALT level >3.0 times the ULN for the reference range, as determined by the central laboratory at study entry. Participants with NAFLD are eligible to participate in this study if their ALT level is ≤3.0 times the ULN for the reference range.
16. Have an eGFR <30 mL/min/1.73 m^2 (or lower than the country-specific threshold for discontinuing metformin therapy per local label), calculated by Chronic Kidney Disease-Epidemiology equation as determined by central laboratory at screening.
17. Have evidence of a significant, uncontrolled endocrine abnormality (for example, thyrotoxicosis or adrenal crises), in the opinion of the investigator.
18. Have family or personal history of MTC or MEN2.
19. Have a serum calcitonin level of ≥35 ng/L, as determined by central laboratory at screening.
20. Have known or suspected hypersensitivity to study product(s) or related products.

21. Have evidence of a significant, active autoimmune abnormality, for example, lupus or rheumatoid arthritis, that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 2 years.
22. Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant.
23. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy for less than 5 years.

    Exceptions:

    - basal or squamous cell skin cancer
    - *in situ* carcinomas of the cervix, and
    - *in situ* or grade 1 (for example, Gleason 6 or lower) prostate cancer.
24. Have a history of any other condition such as known drug, alcohol abuse, or psychiatric disorder that, in the opinion of the investigator, may preclude the participant from following and completing the protocol.
25. Have any chronic hematological condition that may interfere with HbA1c measurement. For example, hemolytic anemias and sickle cell disease.
26. At the investigator's opinion, participants for whom an HbA1c ≤ 6.5% goal is not appropriate, considering expected benefits and risks of therapy.
27. Have a history or presence of an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with the interpretation of data.

Prior/Concomitant Therapy

28. Have been treated with any injectable GLP-1 receptor agonists and insulin prior to screening.

    Exception: use of insulin for gestational diabetes or short-term use (<14 days) for acute conditions such as acute illness, hospitalization, or elective surgery.
29. Have within 90 days prior to screening received treatment with medications intended to promote weight loss. This includes prescribed, over-the-counter, or alternative remedies. See Section 6.8.4 for list of prohibited medications.
30. Are receiving chronic (>2 weeks or 14 days) systemic glucocorticoid therapy or have received such therapy within 1 month of Visit 1 or between Visits 1 and 3.

    Exceptions: topical, intraocular, intranasal, or inhaled preparations.

Prior/Concurrent Clinical Study Experience

31. 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.
32. 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 prior to Visit 1.

33. Have previously completed or withdrawn from this study or any other study investigating tirzepatide.

Other Exclusions

34. Are Lilly employees or are employees of any third-party involved in study who require exclusion of their employees.
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. Female participants who are pregnant or breastfeeding or intending to become pregnant.
37. Are at high risk for CVD in the investigator's opinion or have a history of any of these CV conditions prior to Visit 1
    - myocardial infarction
    - percutaneous coronary revascularization procedure
    - carotid stenting or surgical revascularization
    - nontraumatic amputation
    - peripheral vascular procedure (e.g., stenting or surgical revascularization)
    - cerebrovascular accident (stroke), or
    - congestive heart failure

5.3. Lifestyle Considerations

Diabetes management counseling

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

Participant exercise and diet

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.

Per Inclusion Criterion [4] (Section 5.1), participants should not initiate an organized diet and/or exercise (weight reduction) program during the study other than the lifestyle and dietary measures for diabetes treatment.

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

Blood product donation

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

5.4. Screen Failures

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

Visit 1 laboratory measures that do not meet inclusion criteria will be considered a screen failure. Retests are NOT ALLOWED except for instances when results from V1 samples are not available from the original samples.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened on 1 occasion. Rescreened participants should be assigned a new participant number.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable to this study. All entry criteria must be met within the specified visit intervals in the SoA (Section 1.3).

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

The planned treatments are tirzepatide and intensified conventional care.

For tirzepatide, the dose will be escalated to 15 mg or MTD (Section 6.5).

Treatments in the intensified conventional care arm include a range of glucose-lowering medications used in clinical practice and supported by treatment guidelines. They will be used in accordance with the product labels approved locally (Section 6.5).

This table lists the interventions used in this clinical study.

Intervention Name	Tirzepatide (LY3298176)	Country-specific medications approved for T2D that may be used in this study include: • Sulfonylurea • Thiazolidinedione • DPP-4 inhibitor • SGLT-2 inhibitor • GLP-1 RA (oral and injectable), and • Insulin.	Metformin as background therapy
Dosage Level(s)	2.5 mg 5 mg 7.5 mg 10 mg 12.5 mg 15 mg	Refer to prescribing information as appropriate	Refer to prescribing information as appropriate
Route of Administration	SC	Refer to prescribing information as appropriate	Refer to prescribing information as appropriate
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized and used according to EU authorization	Authorized and used according to EU authorization

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SC = subcutaneous; SGLT-2 = sodium-glucose cotransporter-2; T2D = type-2 diabetes.

Packaging and labeling

Tirzepatide

Tirzepatide will be supplied by the sponsor in SDPs in accordance with current Good Manufacturing Practice. These will be dispensed via an IWRS. SDPs will be packaged in cartons to be dispensed and will be labeled as appropriate for country requirements.

Tirzepatide will be dispensed at the study visits summarized in SoA (Section 1.3).

Returned tirzepatide should not be re-dispensed to the participants.

Intensified conventional care

Study intervention will be prescribed by the study investigator under locally approved labeling and packaging.

6.1.1. Frequency of Tirzepatide Doses and Injection Site

Tirzepatide

Tirzepatide is administered QW by SC injection. There are no restrictions on the time of day each weekly dose of study intervention is given, but it is advisable to administer the SC injections on the same day and same time each week, with or without meals.

If a dose is missed, it should be administered as soon as possible, within 4 days (96 hours) after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, participants can then resume their regular once weekly dosing schedule.

All participants will inject tirzepatide subcutaneously of the stomach area (abdomen) or upper leg (thigh) using the SDPs provided. If the injection is given by someone else, they may inject in the upper arm. A new SDP will be used for each injection. If tirzepatide is to always be injected in the same body region, participants should be advised to use a different injection site each week.

Intensified conventional care

Investigators will determine the appropriate treatment and dose according to the local product label.

6.1.2. Devices

Tirzepatide single-dose pen

Tirzepatide will be provided in a pre-filled SDP.

Instructions for the pre-filled pen use are provided in the “Instructions for Use.”

Intensified conventional care

Devices may be used for dose delivery.

Instructions will be provided per the locally accepted guidelines and with approved local product label.

Product complaints

All PCs, including malfunction, use error and inadequate labeling, shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3) and appropriately managed by the sponsor.

6.1.3. Rescue Therapy

If a participant develops severe, persistent hyperglycemia after randomization, an additional antihyperglycemic medication may be medically indicated after investigator assessment.

Investigators will be trained on the application of criteria for deciding when and how to intervene with participants who do not reach glycemic targets.

First, investigators should confirm participant compliance with the assigned intervention and that they do not have an acute condition causing severe, persistent hyperglycemia.

Conditions for rescue therapy

The criteria for rescue therapy will be based on either FBG or HbA1c as below.

FBG conditions

This table describes FBG conditions for rescue therapy.

If any of the FBG values within 1 week for 2 consecutive weeks exceed the limits outlined below and no intercurrent cause of the hyperglycemia could be identified, rescue medication will be prescribed as an add-on to randomized treatment.

If a participant has persistently elevated FBG defined as…	**during this time…**	**then...**
FBG >270 mg/dL (>15.0 mmol/L)	from baseline to Week 8	rescue medication will be prescribed as an add-on to randomized treatment.
FBG >240 mg/dL (>13.3 mmol/L)	from Week 9 to Week 16	
FBG >200 mg/dL (>11.1 mmol/L)	Any time after Week 16	

Abbreviation: FBG = fasting blood glucose.

HbA1c conditions

This table describes HbA1c conditions for rescue therapy.

If a participant has an…	**during this time…**	**then...**
HbA1c ≥8.0% (≥64 mmol/mol)	on 2 consecutive measurements at least 12 weeks apart after Week 24.	rescue medication will be prescribed as an add-on to randomized treatment.

Abbreviation: HbA1c = hemoglobin A1c.

Allowed rescue treatments

The choice of rescue treatment for severe, persistent hyperglycemia will be at the discretion of the investigator. The investigators should follow current published standards of care from the

American Diabetes Association and/or a consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (ADA 2023, Davies et al. 2022).

Rescue therapy will be continued and adjusted per the investigator's discretion.

Participants randomly assigned to tirzepatide who receive rescue therapy are not allowed to modify their tirzepatide dose.

Prohibited rescue treatments

Tirzepatide treatment arm

Glucagon-like peptide-1 receptor agonists, DPP-4 inhibitors, and pramlintide are not allowed as rescue therapy.

Intensified conventional care treatment arm

Tirzepatide is not allowed as rescue therapy.

6.1.4. Background Therapy with Metformin

All participants in this study will receive metformin as background therapy.

Visit 1 through Visit 3

The prescreening dose and formulation of metformin, immediate or extended release, should be maintained from Visit 1 through randomization at Visit 3.

After Visit 3

After randomization, discontinuation of metformin or change in dosage and formulation are only permitted in the situations described in this table.

If…	then…
a hypoglycemic episode occurs, defined as clinical symptoms of hypoglycemia or blood glucose (BG)-confirmed symptomatic hypoglycemia of glucose concentration <54 mg/dL (<3.0 mmol/L)	participants may reduce the dose or discontinue metformin.
a participant develops contraindications to metformin	if dose or formulation change is not appropriate, discontinue metformin.
a participant experiences a situation that requires short-term discontinuation of metformin ≤14 days according to the local product label, for example, severe dehydration or elective surgery	metformin may be temporarily discontinued and restarted at the same dose prior to discontinuation at investigator discretion.
a participant experiences severe, persistent hyperglycemia	the dose may be increased.
a participant discontinues study intervention other than metformin	the metformin dose may be increased if it is not the only intervention assigned.

If a participant changes the dose or discontinues metformin for reasons other than those described here, it will be considered a protocol deviation.

Dose reduction or discontinuation of metformin during the study should be properly documented and recorded on the appropriate CRF.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization

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

Participants will be randomly assigned in a 1:1 ratio to tirzepatide or intensified conventional care, based on these stratification factors at screening:

- region: North America (NA), Latin America (LATAM), and Europe + Israel (EU + Israel)
- age (≤40 and ≥41 years), and
- HbA1c (≤8.0% or >8.0%)

Blinding

This is an open-label study.

6.4. Study Intervention Compliance

Participants will enter the intervention dose information in their eDiary.

The investigator or trained designee will assess treatment compliance at each visit based on review of the participant glycemic control, eDiary completion, and adherence to prescribed dose and study procedures.

If a participant is considered poorly compliant with their study procedures, for example, missed visits or specific diagnostic tests, they will be retrained as needed by designated study personnel.

6.5. Dose Modification

6.5.1. Tirzepatide Dose Escalation during the First 24 Weeks

The investigator is responsible for escalating the tirzepatide dose to 15 mg or the MTD.

This section outlines the

- general dose escalation process
- management of GI symptoms during the escalation process, and
- dose reduction guidance to manage GI tolerability issues.

Dose escalation

The initial dose escalation period occurs over 24 weeks, which allows 20 weeks to escalate to 15 mg and an additional 4 weeks to reach steady state.

Dose escalations will occur every 4 weeks.

At Visit 3, the starting dose will be 2.5 mg.

Beginning at Visit 4, the dose will increase by 2.5 mg every 4 weeks, that is 2.5 mg to 5 mg to 7.5 mg to 10 mg to 12.5 mg to 15 mg, until the 15 mg dose or MTD is reached.

6.5.1.1. Management of Participants with Gastrointestinal Symptoms

The dose escalation scheme is designed to minimize the development of intolerable GI symptoms. Every effort should be made by the investigator to escalate participants to tirzepatide 15 mg or MTD.

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

STEP 1	Advise participants to eat smaller meals, for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full.
STEP 2	Continue STEP 1 + Prescribe symptomatic medication, for example, anti-emetic or anti-diarrheal medication, per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the CRF.
STEP 3	Continue STEP 1 + STEP 2 + Temporarily interrupt tirzepatide; omit 1 dose, the participant will take 3 of 4 doses at that dose level. After the interruption, the investigator should restart the dose as required, with the participant taking medication to alleviate their GI symptoms. The data related to temporary interruption of study treatment should be documented in source documents.
STEP 4	If intolerable GI symptoms or events persist despite the above measures, the investigator may reduce the dose to the previous MTD. See Sections 6.5.2 and 6.5.3

Abbreviations: CRF = case report form; GI = gastrointestinal; MTD = maximum tolerated dose.

6.5.2. Tirzepatide Dose Reductions during the First 24 Weeks

If a participant experiences GI tolerability issues despite the measures listed in Section 6.5.1.1, then the investigator should follow the guidance in this table.

If a participant is currently taking…	then…
2.5 mg or 5 mg	permanently stop study intervention and have the participant remain in the study.
Any other dose	reduce the dose to the previous maximum tolerated dose.

If a participant's dose is reduced, the investigator may re-escalate the dose when considered appropriate. See Section 6.5.4 for guidance.

6.5.3. Tirzepatide Dose Reductions after Week 24

After the participants tirzepatide 15 mg or MTD is established, the investigator may modify the tirzepatide dose due to a safety-related concern in consultation with the Lilly medical monitor, such as recurrent intolerable GI AEs, excessive weight loss, or other chronic adverse conditions.

If BMI $\leq$22 kg/m^2 is reached at any time during the study and weight loss continues, or there are concerns related to the degree of weight loss that may lead to discontinuation from tirzepatide, the investigator should contact the Lilly medical monitor to consider a tirzepatide dose reduction.

Reaching an optimal glycemic target on study intervention is not a reason for dose reduction.

This table shows the allowable dose modifications.

If a participant is currently taking…	then…
5 mg	permanently stop study intervention and have the participant remain in the study.
Any other dose	reduce the dose to the previous maximum tolerated dose.

If a participant's dose is reduced, the investigator may re-escalate the dose when considered appropriate. See Section 6.5.4 for guidance.

6.5.4. Tirzepatide Dose Re-Escalation

To optimize the number of participants who achieve tirzepatide 15 mg or MTD, dose re-escalations are allowed through the entire length of the study treatment period when considered appropriate by the investigator.

If a re-escalation occurs, then additional visits at 4-week intervals will be scheduled to allow for the dose escalation until tirzepatide 15 mg or MTD is reached.

It is recommended that the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate tirzepatide supply at the site.

6.5.5. Intensified Conventional Care Dose Modifications

All participants will be on metformin background therapy.

Dosing will be individualized to achieve optimal glycemic control that is within a non-diabetic range, without compromising participant safety, primarily without increasing the risk of hypoglycemia.

If a participant has extremely high blood glucose levels at any point during the study, rescue therapy may be prescribed (see Section 6.1.3).

General guidance for treatment modifications

Investigators will evaluate glycemic control and assess the participant's treatment plan at every study visit.

This table describes general guidance for treatment modifications.

If…	Then…
glycemic control is not reached with metformin alone	add a new treatment based on the participant profile.
glycemic control is not reached with metformin + second line of treatment	change dose levels or add a new drug class treatment. When combining multiple treatments, a new drug class should be added rather than changing to another treatment within the same drug class.

A similar individualized approach should guide choice of the third- and fourth-line glucose-lowering therapy when additional glycemic control is still needed.

The choice of treatment should be consistent with the current published standards of care from the American Diabetes Association and/or a consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (ADA 2023, Davies et al. 2022).

Combination of DPP-4 inhibitors and GLP1-RA will not be allowed. Tirzepatide will not be allowed.

Treatment modification considerations

Cardiovascular disease

Participants with preexisting CVD or at high-risk for CVD will be excluded prior to randomization. Participants enrolled in both treatment groups will be early in the natural history of diabetes; therefore, it is anticipated that overall CV risk will be low and that a glucose-lowering treatment targeting CV risk specifically will not be indicated.

Weight

For participants who are overweight or obese, the investigator should consider a glucose-lowering treatment with added weight loss benefit, which may include but is not limited to GLP1-RA or SGLT2-inhibitor.

Renal disease or impairment

If a participant develops CKD (GFR < 60 ml/min/1.73 m^2) with albuminuria, the investigator should consider a glucose-lowering treatment with renal protection, which may include but is not limited to SGLT2-inhibitors.

Hypoglycemia

In order to minimize hypoglycemia, the investigator should consider a treatment with no or low risk of hypoglycemia, which may include, but is not limited to

- GLP1-RA
- SGLT2-inhibitor
- DPP-4 inhibitor, and
- Thiazolidinedione.

Insulin use

If a participant's HbA1c >10% mmol/mol or blood glucose ≥ 300 mg/dL (16.7 mmol/L) or there is evidence of ongoing catabolic weight loss or diabetic ketoacidosis, then the investigator should consider insulin use. As glucose toxicity resolves, investigators could consider simplifying the regimen or changing to noninsulin treatments as deemed appropriate.

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

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

6.7. Treatment of Overdose

6.7.1. Tirzepatide Overdose

Tirzepatide overdose is defined as administration of tirzepatide more than intended dose (more than 1 injection) in less than 72 hours.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention no longer has a clinical effect, and report the overdose event as an AE and document, and
- Appropriate supportive treatment should be initiated according to the participant's clinical signs and symptoms.

6.7.2. Intensified Conventional Care Overdose

Follow the instructions listed in the local product label for the assigned study intervention.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.

- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention no longer has a clinical effect, and
- Appropriate supportive treatment should be initiated according to the participant's clinical signs and symptoms.

6.8. Concomitant Therapy

6.8.1. Concomitant Therapy Regimens

All participants should maintain their usual medication regimens for concomitant conditions or diseases throughout the study, unless those medications are specifically excluded in the protocol (Section 5.2).

6.8.2. Changing Concomitant Therapy

Participants should consult with authorized study personnel before taking any new medications or supplements during the study. Authorized study personnel should consult the sponsor's medical monitor if there are any questions about concomitant therapies during the study.

The investigator is responsible for changes in diabetic medications.

6.8.3. Concomitant Therapy Data Collection

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study, authorized study personnel should collect

- Name of medication, vaccine, or therapy
- Reason for use
- Dates of administration including start and end dates, and
- Dosage information including dose and frequency for concomitant therapy of special interest.

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

6.8.4. Prohibited Concomitant Medications

The medications prohibited in the study are the medications intended to promote weight loss. This includes prescribed, over-the-counter, or alternative remedies. Examples include, but are not limited to

- Liraglutide 3.0 mg
- Semaglutide 2.4 mg
- Sibutramine
- Mazindol
- Lorcaserin
- Naltrexone/bupropion
- Zonisamide
- Topiramate
- Orlistat
- Phenylpropanolamine
- Phentermine
- Phentermine/topiramate combination, or
- Pramlintide.

SGLT-2 inhibitor therapy is only allowed for glycemic control and not allowed for any other indication unless it is used for concomitant glycemic control.

6.8.5. Allowed Antihyperglycemic Treatments other than Study Interventions

Antihyperglycemic medications other than study interventions are ONLY allowed during these circumstances

- for participants who require permanent discontinuation of tirzepatide but remain in the study
- for rescue therapy after randomization due to severe, persistent hyperglycemia or during the safety follow-up period
- for short-term insulin use up to 14 days for certain clinical situations, for example, elective surgery, during hospitalization, or hyperosmolar states. This insulin use must be differentiated from insulin use as rescue therapy when reported in the CRF.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9, Appendix 1.

7.1. Discontinuation of Study Intervention

Tirzepatide

When necessary, a participant may be permanently discontinued from tirzepatide. If so, the participant will remain in the study and follow procedures for remaining study visits, as shown in the SoA (Section 1.3).

A participant should be permanently discontinued from study intervention if:

- the participant becomes pregnant during the study
- the participant is diagnosed with T1D or LADA
- the participant requests to discontinue intervention
- the participant develops confirmed pancreatitis (if not confirmed, study intervention may be restarted)
- the participant is diagnosed with MTC, C-cell hyperplasia, or Multiple Endocrine Neoplasia Syndrome after randomization or has a calcitonin value ≥35 ng/L that has increased at least 50% over baseline after randomization
- the participant is diagnosed with an active malignancy or if a previously treated malignancy becomes known after randomization
- the participant experiences a significant study intervention-related hypersensitivity reaction after administration of study intervention
- any other AE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons, or
- the participant, for any reason, initiates treatment with a therapeutic agent that is prohibited by the protocol.

Participants who stop tirzepatide permanently will receive another locally approved antihyperglycemic medication, if needed per clinical judgment of investigator, and will continue participating in the study according to the protocol to collect all planned efficacy and safety measurements per SoA (Section 1.3), Adverse Events (Section 8.3), and Safety Assessments (Section 8.2) of this protocol.

The choice of antihyperglycemic medication will be at the discretion of the investigator. The investigators should follow current published standards of care from the American Diabetes

Association and/or a consensus report by the American Diabetes Association and the European Association for Study of Diabetes (ADA 2023, Davies et al. 2022).

Glucagon-like peptide-1 receptor agonists, DPP-4 inhibitors, and pramlintide are not allowed as an option for antihyperglycemic medication.

The new antihyperglycemic medication will be recorded on the CRF for antihyperglycemic medications.

Intensified conventional care

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will continue participating in the study according to the protocol to collect all planned efficacy and safety measurements per SoA (Section 1.3), Adverse Events (Section 8.3), and Safety Assessments (Section 8.2) of this protocol.

Additionally, a participant should also be permanently discontinued from study intervention under these conditions:

- the participant becomes pregnant during the study
- the participant is diagnosed with T1D or LADA
- the participant requests to discontinue intervention
- the participant is diagnosed with an active malignancy or if a previously treated malignancy becomes known after randomization
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons, or
- the participant, for any reason, initiates treatment with a therapeutic agent that is prohibited by the protocol.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation due to a hepatic event or liver test abnormality

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

The study intervention should be interrupted or discontinued if 1 or more of these conditions in the table occur.

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for study intervention interruption/ discontinuation decisions rather than TBL>2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

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

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

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

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified, including, but not limited to, changes from baseline in QT interval corrected using Fridericia's formula after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in 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.

7.1.3. Temporary Discontinuation of Study Intervention

7.1.3.1. Tirzepatide

The investigator may temporarily interrupt tirzepatide due to

- an AE
- clinically significant laboratory value
- hospital visits or medical procedures
- travel or shortage of study treatment supply, or
- any other event necessitating temporary discontinuation of tirzepatide.

If tirzepatide is temporarily interrupted for reasons other than tolerability, participants should be encouraged to restart tirzepatide as soon as it is safe to do so (Section 6.5.4).

During the escalation period, restarting tirzepatide can only occur at a scheduled study visit.

After dose escalation visit, restarting tirzepatide can occur at a scheduled study visit or at an unscheduled dosing visit.

For tirzepatide restart, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate intervention supply at the site.

Every effort should be made by the investigator to maintain participants on tirzepatide and to restart after any temporary interruption, as soon as it is safe to do so.

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

If the number of missed consecutive tirzepatide doses is...	Then...
2 or less	the study treatment can be restarted at the last administered dose, if it was well-tolerated prior to interruption.
3 or more	the IWRS will dispense 5 mg tirzepatide irrespective of the dose the participant was receiving before the interruption and subsequently escalate as required by the protocol until the 15 mg dose, or maximum tolerated dose is reached.

Abbreviation: IWRS = interactive web-response system.

If the tirzepatide interruption is due to intolerable persistent GI AE, such as nausea, vomiting, or diarrhea, the participant should be treated as suggested in Section 6.5.1.1.

Recording temporary discontinuation of tirzepatide

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

Participant noncompliance should not be recorded as interruption of study intervention on the CRF.

7.1.3.2. Intensified Conventional Care

The investigator may temporarily interrupt study intervention due to

- an AE
- clinically significant laboratory value
- hospital visits or medical procedures
- travel or shortage of study treatment supply, or
- any other event necessitating temporary discontinuation of study intervention.

If study intervention is temporarily interrupted for reasons other than tolerability, participants should be encouraged to restart study intervention as soon as it is safe to do so (Section 6.5.4).

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant will be discontinued from the study:

- at any time at the participant's own request
- if the participant is diagnosed with T1D or LADA
- if the participant is diagnosed with a malignancy after randomization
    - **Exceptions**:
        - 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.
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons

- if a female participant becomes pregnant, see Section 8.3.2
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

At the time of discontinuing from the study, if possible, the participant will complete procedures for an ED visit and safety follow-up, if applicable, as shown in the SoA (Section 1.3).

If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

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

Immediate safety concerns 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 (Section 1.3), is essential and required for study conduct.

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

8.1. Efficacy Assessments

Primary efficacy assessment

The primary efficacy measurement in this study is change in HbA1c values from baseline to Week 104, as determined from the central laboratory values. Blood samples for HbA1c measurements will be collected at specific clinic visits as summarized in the SoA (Section 1.3).

Other efficacy assessments

Other efficacy assessments include change in HbA1c, weight, waist circumference, fasting serum glucose, fasting lipids, BMI, urinary albumin to creatinine ratio, eGFR, number of antihyperglycemic medications, time to treatment failure, 7-point SMBG, β-cell function assessed by OGTT, and patient-reported outcomes.

8.1.1. Self-Monitoring of Blood Glucose (SMBG)

Participants must use only the study-provided monitors, provided per local guidelines, during the study.

Glucometer for participant use during the study

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

Glucometer training

Site personnel will train the participant on correct use of the glucometer for self-monitoring blood glucose and reporting of hypoglycemia data.

When to measure FBG during the study

Site personnel will train the participant to measure FBG daily when possible, and a minimum of 2 times per week using the study-provided glucometer.

The FBG should be measured upon waking in the morning, prior to food or caloric beverage intake.

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

Glucometer data transfer

The study-provided glucometer will wirelessly transmit blood glucose measurements to the participant's eDiary. Site personnel will be able to view SMBG data that have been transmitted to the eDiary through a web-based portal as well as any reported events of hypoglycemia.

SMBG for hypoglycemia or hyperglycemia

Participants should perform SMBG with the study-provided BG meter whenever hypoglycemia is experienced or suspected (with or without symptoms), when there is perceived, increased risk related to changes in dietary intake, physical activity, or inadvertent or atypical insulin dosing.

The participant's FBG and events of hypoglycemia will be used to determine the insulin dose and titration based on the dosing and titration algorithm (Section 6.1).

Participants may perform SMBG more frequently to check for instances of hyperglycemia, or as directed by the investigator. Investigators may also instruct participants to collect SMBG, at time points other than at fasting, to evaluate glycemic control.

8.1.2. β-cell Functions and Insulin Sensitivity Assessed by Oral Glucose Tolerance Test (OGTT)

Oral glucose tolerance tests of 180 minutes will be performed according to the SoA.

Results from the OGTT will provide these β-cell function results

- glucose sensitivity
- fasting and postmeal glucose (total and incremental $AUC_{0\text{-}240min}$), and
- fasting and postmeal insulin (total and incremental $AUC_{0\text{-}240min}$).

Section 10.8, Appendix 8 describes methods for OGTT test.

8.1.3. Patient-Reported Outcomes

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

The IWQOL Lite-CT (Kolotkin et al. 2017, 2019) is a 20-item, obesity-specific PRO instrument developed for use in weight management clinical studies.

The IWQOL-Lite-CT assesses 2 primary domains of obesity-related health-related quality of life

- Physical (7 items) and
- Psychosocial (13 items).

A 5-item subset of the Physical domain – the Physical Function composite – is also reported. Items in the Physical Function composite describe physical impacts related to general and specific physical activities.

All items are rated on either

- a 5-point frequency ("never" to "always") scale or
- a 5-point truth ("not at all true" to "completely true") scale.

The IWQOL-Lite-CT has a total score, which includes all 20 items. The IWQOL-Lite-CT scores range from 0 to 100, where raw and transformed scores are calculated, with higher composite scores indicating higher levels of functioning.

8.1.3.2. Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36v2, Acute)

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

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

The Physical-Functioning domain assesses limitations due to health "now" while the remaining domains assess functioning "in the past week."

Each domain is scored individually, and information from these 8 domains is further aggregated into 2 health-component summary scores: Physical-Component Summary and Mental-Component Summary. 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 (Maruish 2011).

8.1.3.3. Impact of Weight on Self Perception (IW-SP)

The IW-SP (Hayes and DeLozier 2015) is a PRO instrument that assesses the current impact of weight on the self-perception of people with type 2 diabetes mellitus and obesity.

The IW-SP contains 3 items that assess how often a participants' body weight affects how happy they are with their appearance and how often they feel self-conscious when out in public.

Each item is rated on a 5-point scale ranging from 1 = "always" to 5 = "never."

Total scores for the IW-SP are derived by summing the item scores and dividing by the number of items. The score is typically transformed to a range from 0 to 100, where higher IW-SP scores correspond to better self-perception.

8.1.3.4. Ability to Perform Physical Activities of Daily Living (APPADL)

The APPADL (Hayes et al. 2012) is a PRO instrument that assesses the current ability of people living with type 2 diabetes mellitus and obesity to perform physical activities of daily living.

The APPADL contains 7 items that assess how difficult it is for participants to engage in certain activities considered to be integral to normal daily life, such as walking, standing, and climbing stairs (Hayes et al. 2012).

Items are scored on a 5-point numeric rating scale, where 5 = "not at all difficult" and 1 = "unable to do."

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

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

- skin
- CV
- respiratory
- GI
- neurological systems
- thyroid examination, and
- foot examination, including evaluation for diabetic neuropathy.

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

Physical examinations during in-clinic visits will be performed by a physician or other qualified healthcare professional.

Height, weight, and waist circumference will be measured and recorded, per Appendix 9, Section 10.9. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Symptom-directed physical assessment after screening

These examinations are performed based on participant status and standard of care by a physician or other qualified healthcare professional.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3) and following the study-specific recommendations mentioned in Appendix 9, Section 10.9.

Vital signs including pulse rate (beats per minute) and blood pressure (mm Hg) will be measured after participant has been sitting for at least 5 minutes and before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required.

8.2.3. Electrocardiograms

A 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that preferably automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc stopping criteria.

The ECGs must be interpreted by the investigator or qualified designee at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, for

immediate participant management, if needed. The investigator or designee must document their review of the ECG. If a clinically relevant abnormality is observed on the participant's ECG, then the investigator should assess the participant for symptoms, such as palpitations, near syncope, syncope, or chest pain.

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

8.2.4. Dilated Fundoscopic Examination

A dilated fundoscopic examination will be performed by an ophthalmologist or optometrist for all participants between Visits 2 and 3.

A previous examination ≤90 days meeting study requirements from Visit 1 is acceptable to confirm eligibility. Additional dilated fundoscopic examinations should be performed when clinically indicated by any suspicion of worsening retinopathy and as outlined in the SoA (see Section 1.3).

8.2.5. Clinical Safety Laboratory Tests

See Section 10.2, Appendix 2 for the list of Clinical Laboratory Tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE.

The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator 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, Appendix 2, must be conducted in accordance with the SoA (Section 1.3), standard collection requirements, and laboratory manual.

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

8.2.6. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA (Section 1.3).

Serum pregnancy test must be performed only for WOCBP and females with a history of tubal ligation.

A local urine pregnancy test must be performed for WOCBP only, prior to administering study intervention, or must be performed with the result available prior to first dose or injection of study intervention (s).

Additional pregnancy tests, beyond those required per the SoA, should be performed at any time during the study if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation. If the participant is pregnant, she must be permanently discontinued from study intervention and the study (Section 7).

8.2.7. Hepatic Monitoring

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

Laboratory tests (Appendix 5, Section 10.5), including ALT, AST, ALP, TBL, direct bilirubin, 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 of these conditions occur:

If a participant with baseline Visit 1 results of ...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline at Visit 1
ALP ≥1.5x ULN	ALP ≥2x baseline at Visit 1

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

Note: All ULN values should be age adjusted.

What to do if the abnormal condition persists or worsens

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including

- symptoms
- recent illnesses, for example, heart failure, systemic infection, hypotension, or seizures
- recent travel
- history of concomitant medications, including over-the-counter, herbal and dietary supplements, and
- history of alcohol drinking and other substance abuse.

Frequency of monitoring

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

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

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

Special care should be taken to minimize the volume of blood taken during hepatic monitoring.

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

If a participant with baseline Visit 1 results of...	**develops the following elevations:**
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms[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 at Visit 1 with hepatic signs/symptoms [a], or ALT or AST ≥3x baseline at Visit 1
ALP ≥1.5x ULN	ALP ≥2x baseline at Visit 1

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

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

Note: All ULN values should be age and gender adjusted.

What a comprehensive evaluation should include

At a minimum, this evaluation should include

- physical examination and a thorough medical history, as outlined above, and
- tests for PT-INR and direct bilirubin, if total bilirubin was elevated.

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

- viral hepatitis A, B, C, and E
- autoimmune hepatitis, or
- an abdominal imaging study, for example, ultrasound, MRI, or CT scan.

Consider additional tests, based on the medical history and clinical picture, including tests for

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

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

Special care should be taken to prioritize more pertinent blood tests and minimize the volume of blood taken during hepatic evaluation. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a 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 Visit 1 ALT <1.5x ULN
   - In participants with baseline Visit 1 ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevated TBL to ≥ 2x ULN, except for cases of known Gilbert's syndrome
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests, if baseline at Visit 1 ALP <1.5x ULN
   - In participants with baseline Visit 1 ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study intervention due to a hepatic event

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

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

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

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

- AEs
- SAEs, and
- PCs.

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and safety topics of special interest, as defined in Section 8.3.3, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.3, Appendix 3.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Adverse Event					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

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

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; PC = product complaint; SAE = serious adverse event.

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

After learning of a pregnancy in the female partner of a study participant, the investigator will

- obtain a consent to release information from the pregnant female partner directly, and
- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

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

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

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

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Safety Topics of Special Interest

8.3.3.1. Gastrointestinal Adverse Event

Tirzepatide may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as anti-emetic/anti-diarrheal use will be collected in the CRF/AE form.

For detailed information concerning the management of GI AEs, refer to Section 6.5.1.1.

8.3.3.2. Dehydration

Severe gastrointestinal events may lead to dehydration and volume depletion, which can cause a deterioration in renal function including acute renal failure. Many of the reported adverse renal events occurred in participants who had experienced nausea, vomiting, diarrhea, or dehydration. Participants should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal adverse reactions or other AEs, and take precautions to avoid fluid depletion.

8.3.3.3. Renal Safety

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute or worsening of chronic renal disease.

8.3.3.4. Exocrine Pancreas Safety

Diagnosis of acute pancreatitis

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

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

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase 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, MRI, 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 (Koizumi 2006; Steinberg et al. 2017a, 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia, lipase 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 CRF page. The adjudication committee representative will enter the results of adjudication into a corresponding CRF page.

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

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

The assessment of thyroid safety during the study will include reporting of any case of thyroid malignancy including MTC and papillary carcinoma and measurements of calcitonin. Calcitonin measurements will assess the potential of tirzepatide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms. These data will be captured in specific CRFs.

If an increased calcitonin value (≥35 ng/L AND an increase by ≥50% compared with baseline) is observed in a participant who has administered a medication that is known to increase serum calcitonin, this medication must be stopped and calcitonin levels must be measured after an appropriate washout period. A consultation with a thyroid specialist or an endocrinologist should be obtained. See Section 7.1 for thyroid-related discontinuation criteria.

If the confirmed calcitonin value is <35 ng/L, tirzepatide should be restarted when it is safe to do so.

8.3.3.6. Hypoglycemia

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia in the study according to the SoA (Section 1.3). Participants will enter all hypoglycemic episodes in eCOA device.

To avoid duplicate reporting, all consecutive BG values ≤70 mg/dL (3.9 mmol/L) occurring within 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

Hypoglycemia classification and definitions

Level 1

Glucose <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L)

Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

Level 2

Glucose <54 mg/dL (<3.0 mmol/L)

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

Level 3 Severe

A severe hypoglycemic event is characterized by altered mental or physical status requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions for the treatment of hypoglycemia.

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

Examples of severe hypoglycemia in adults are

- altered mental status and the inability to assist in their own care
- semiconscious or unconscious, or
- coma with or without seizures.

Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

Nocturnal hypoglycemia

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

Reporting of severe hypoglycemic events

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

The investigator should also determine if repeated or prolonged episodes of hypoglycemia occurred prior to the severe event.

8.3.3.7. Severe, Persistent Hyperglycemia

Severe, persistent hyperglycemia will be assessed during the study to determine the risk of extreme imbalance in glycemic control.

Investigators will be trained on the application of criteria for deciding when and how to intervene with participants who do not reach glycemic targets. An additional therapeutic intervention should be considered in participants who develop severe, persistent hyperglycemia after randomization. Rescue medication will be prescribed as an add-on to randomized treatment, and participants will continue to follow the protocol-specified visit schedule as described in Section 6.1.3.

8.3.3.8. 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 the following:

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

8.3.3.9. Arrhythmias and Cardiac Conduction Disorder

Participants who develop any event from these groups of disorders should undergo an ECG. Additional diagnostic tests to determine exact diagnosis should be performed, as needed.

The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Appendix 3, Section 10.3, must be reported as SAEs.

After enrollment, if a clinically significant finding is identified by ECG including, but not limited to, changes from baseline in QT/QTc interval, the investigator or qualified designee will determine if any change in study participant management is needed. See Section 7.1.2. for QTc stopping criteria. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding must be reported as an AE or SAE (if applicable).

8.3.3.10. Hypersensitivity Reactions

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

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

In the case of generalized urticaria or anaphylaxis, additional blood samples should be collected as described in Appendix 2, Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

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

8.3.3.11. Injection-Site Reactions

Symptoms and signs of a local ISR may include erythema, induration, pain, pruritus, and edema.

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

At the time of AE occurrence in the tirzepatide group, samples will be collected for measurement of tirzepatide anti-drug bodies and tirzepatide concentration.

8.3.3.12. Diabetic Retinopathy Complications

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

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

A follow-up dilated fundoscopic examination occurs for all randomized participants at Visit 16 (Week 104) and Visit 25 (Week 208).

8.3.3.13. Hepatobiliary Disorders

All events of treatment-emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In

cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.2.7.

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study. In the case of hypersensitivity or ISR, samples will be collected if needed as described in Section 10.2.1.

8.5. Pharmacodynamics

Samples to assess the PD properties of tirzepatide are included in the efficacy measures and not applicable in this section.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Serum and plasma samples will be used for exploratory biomarker research, where local regulations allow. See Clinical Laboratory Tests, and the SoA for sample collection information.

Samples will be used for research on the drug target, disease process, variable response to tirzepatide, pathways associated with diabetes, mechanism of action of tirzepatide, and/or research method or in validating diagnostic tools or assay(s) related to diabetes. Sample retention is described in Section 10.1.12.

8.8. Immunogenicity Assessments

Immunogenicity parameters are not evaluated in this study. In the case of hypersensitivity or ISR, samples will be collected if needed as described in Section 10.2.1.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

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

9.1. Statistical Hypotheses

The null hypothesis corresponding to the primary objective of this study is as follows:

- **$H_{1,0}$**: tirzepatide 15 mg or MTD is inferior to intensified conventional care with respect to HbA1c mean change from baseline at Week 104 by 0.3% or more.

The null hypotheses corresponding to the key secondary objectives are as follows:

- **$H_{2,0}$**: tirzepatide 15 or MTD is not superior to intensified conventional care with respect to HbA1c mean change from baseline at Week 104.
- **$H_{3,0}$**: tirzepatide 15 or MTD is not superior to intensified conventional care with respect to mean weight change from baseline at Week 104.
- **$H_{4,0}$**: tirzepatide 15 or MTD is not superior to intensified conventional care with respect to mean waist circumference change from baseline at Week 104.
- **$H_{5,0}$**: tirzepatide 15 mg or MTD is inferior to intensified conventional care with respect to HbA1c mean change from baseline at Week 208 by 0.3% or more.
- **$H_{6,0}$**: tirzepatide 15 mg or MTD is not superior to intensified conventional care with respect to HbA1c mean change from baseline at Week 208.
- **$H_{7,0}$**: tirzepatide is not superior to intensified conventional care with respect to weight mean change from baseline at Week 208.
- **$H_{8,0}$**: tirzepatide is not superior to intensified conventional care with respect to waist circumference mean change from baseline at Week 208.

Operationally the hypotheses will be evaluated by 2-sided tests.

9.1.1. Multiplicity Adjustment

The primary and the key secondary objectives will be evaluated using both the treatment-regimen and the efficacy estimands. Since the purpose for each estimand is different, multiplicity adjustment will be conducted for each estimand separately.

A prespecified graphical scheme (Bretz et al. 2009, 2011) will be implemented to control the family-wise error rate at a 2-sided alpha level of 0.05. More specifically, multiple testing adjusted p-values described by Bretz et al. (2009) will be calculated, and any hypothesis tests with a multiple testing adjusted p-value of less than 0.05 will be considered statistically significant. This graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all endpoints (Bretz et al. 2009, 2011; Alosh et al. 2014).

The testing scheme will be fully detailed in the statistical analysis plan. Unless otherwise specified, there will be no adjustment for multiple comparisons for any other analyses outside the

primary and key secondary endpoints. The testing scheme will be finalized before the first participant visit.

9.2. Analyses Sets

This table defines the analysis population and datasets for the purposes of analysis based on the estimands defined in Section 3.

Population/Analysis Set	Description
Screened population	All participants who signed informed consent.
Randomized population	All participants who are randomly assigned to a treatment group.
Modified intent-to-treat population (mITT)	All randomly assigned participants who are exposed to at least 1 dose of study intervention. Participants will be analyzed according to the treatment they were randomly assigned to regardless of the treatment actually received.
Efficacy Analysis Set: This analysis set will be used to estimate the efficacy estimand for the primary and key secondary objectives	Data obtained during the Treatment Period from the mITT population, excluding participants inadvertently enrolled, excluding data after permanent discontinuation of treatment or initiation of antihyperglycemic rescue or prohibited medication.
Full Analysis Set: This analysis set will be used to estimate the treatment-regimen estimand for the primary and key secondary objectives	Data obtained during the treatment period from the mITT population, excluding participants inadvertently enrolled regardless of adherence to treatment or initiation of antihyperglycemic rescue or prohibited medication (excluding non-study tirzepatide). Data after taking non-study tirzepatide will be excluded.
Safety Analysis Set (SS): This analysis will be used to assess the safety of study treatment	Data obtained during the Treatment Period plus Safety Follow-up from the mITT population, regardless of adherence to treatment or initiation of antihyperglycemic rescue antihyperglycemic medication.

9.3. Statistical Analyses

9.3.1. 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 statistical analysis plan or clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05/1-sided alpha level of .025, unless otherwise stated, and all confidence intervals will be given at a 2-sided [95%] level. In statistical summaries and analyses, all data will be analyzed by randomized treatment assignment. Participants will be analyzed according to the treatment they were randomly assigned to, regardless of the treatment actually received.

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

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

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

- treatment
- visit
- treatment-by-visit interaction
- region (LATAM, NA, EU+Israel)
- age
- baseline HbA1c category (≤8.0% or >8.0%), and
- baseline measurement as a covariate.

For analyses of HbA1c, the baseline HbA1c category will not be included in the model. An unstructured covariance structure 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. The negative binomial regression model will be used for the treatment comparison of discrete count measures if deemed appropriate.

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

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final clinical study report.

9.3.2. Primary Endpoint Analysis

The primary endpoint for this study is change from baseline in HbA1c to the 104-week visit (Visit 16). This endpoint will be used to evaluate the primary objective of the study for both the treatment-regimen and the efficacy estimands (Section 3).

The null hypothesis corresponding to the primary objective is as follows: tirzepatide 15 mg or MTD is inferior to intensified conventional care with respect to HbA1c mean change from baseline at Week 104 by 0.3% or more (Section 9.1).

The primary objective based on the treatment-regimen estimand defined in Section 3 will be evaluated using the full analysis set dataset (Section 9.2) using an analysis of covariance with terms for

- treatment
- region
- age, and
- baseline HbA1c.

For the purpose of the treatment-regimen estimand, missing HbA1c values at the 104-week visit will be imputed based on observed data in the same treatment arm from participants who had their efficacy assessed after early discontinuation of study intervention. This analysis will be conducted with multiple imputations, and statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

The primary objective based on the efficacy estimand defined in Section 3 will be evaluated using the EAS dataset (Section 9.2). The primary analysis model for HbA1c measurements over time will be an MMRM. The response variable of MMRM will be change in HbA1c values from baseline obtained at each scheduled postbaseline visit. The independent variables of the MMRM model are treatment, visit, treatment-by-visit interaction, and region as fixed effects, and age and baseline HbA1c as covariates. Missing data will be addressed by the MMRM model. No explicit imputation methods for missing data will be employed.

For both estimands, non-inferiority will be based on the 2-sided 95% CI for the difference in mean change in HbA1c from baseline to the 104-week visit between tirzepatide 15 or MTD treatment arm and the intensified conventional care group. If the upper limit of the CI is below 0.3%, the tirzepatide 15 mg or MTD arm will be declared non-inferior to intensified conventional care.

9.3.3. Secondary Endpoints Analysis

The endpoints corresponding to secondary study objectives subject to type 1 error rate control are specified in Section 3 under “Key Secondary (Controlled for Type 1 error) endpoints.”

The null hypotheses corresponding to the key secondary objectives can be found in Section 9.1.

Key secondary objectives will be evaluated based on the treatment-regiment and the efficacy estimands (Section 3), similar to the primary objective.

Change from baseline in HbA1c, body weight, and waist circumference at the 104- and 208-week visits (Visits 16 and 25, respectively) will be conducted in a manner similar to the primary efficacy analyses (Section 9.3.2).

Baseline HbA1c category (≤8.0% or >8.0%) and baseline of the corresponding variable will be added in the model for body weight and waist circumference.

Endpoints for additional secondary objectives are described in Section 3 and will be evaluated based on the efficacy estimand.

Additional details will be provided in the SAP.

9.3.4. Exploratory Endpoints Analysis

Endpoints for exploratory objectives are described in Section 3 and will be evaluated based on the efficacy estimand. Additional details will be provided in the SAP.

9.3.5. Safety Analyses

Safety assessments will be done using the Safety Analysis Set (see Section 9.1) irrespective of adherence to study intervention or initiation of rescue antihyperglycemic therapy, unless indicated otherwise.

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

Summary statistics will be provided for incidence of TEAEs, SAEs, and study discontinuation due to AEs, study intervention discontinuation due to AEs, or deaths from the time of first dose through end of safety follow-up. Counts and proportions of participants experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

9.3.5.1. Hypoglycemic Events

Incidence of documented symptomatic hypoglycemia events and severe hypoglycemia will be summarized and compared between the tirzepatide 15 mg or MTD and the intensified conventional care group. Rate of hypoglycemic episodes will be analyzed using a generalized linear mixed-effects model assuming negative binomial distribution for hypoglycemic episodes if data warrant. Some analyses may be conducted excluding data after introducing another antihyperglycemic therapy.

9.3.5.2. Gastrointestinal Events

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

9.3.5.3. Adjudicated Cardiovascular Events

Listing of deaths, myocardial infarctions, strokes, and hospitalization for unstable angina confirmed by an independent clinical endpoint committee will be provided. The dates of randomization, event, first dose and last dose of study intervention, and time from randomization to event will be listed.

9.3.5.4. 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 between treatment groups relative to continuous change from baseline values assessed over time will be an MMRM, with terms: treatment, visit, and treatment-by-visit interaction, region, and age and baseline measurement as covariates.

An unstructured covariance structure will model relationship of within-participant errors.

The percentages of participants with treatment-emergent abnormal, high, or low laboratory measures at any time will be summarized and compared between treatment groups by using Fisher's exact test.

A treatment-emergent abnormal value is defined as a change from normal value at baseline to an abnormal value at any time during the follow-up.

A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time during the Treatment and Follow-up periods.

A treatment-emergent 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 the Treatment and Follow-up periods.

High and low limits will be provided in SAP.

9.3.6. Subgroup Analyses

Subgroup analyses of the primary endpoint, change from baseline in HbA1c, will be made to assess consistency of the intervention effect across the following subgroups:

- Age group: ≤40 years vs ≥41 years
- Sex: female vs male
- Race: white vs black vs other
- Ethnicity: Hispanic vs not Hispanic
- Duration of diabetes (≤2 years, >2 year)
- Baseline HbA1c (≤8.0%, >8.0%), and
- Region: NA, LATAM, EU+Israel.

9.4. Interim Analysis

An interim analysis for primary outcome will be performed when all participants complete 104 weeks of treatment or discontinue. Final analysis will be performed when all participants complete the study.

No additional interim analyses are planned for this study.

The SAP will describe the planned interim analyses in greater detail.

The timing of dissemination of data summaries based on interim analyses is addressed in Section 10.1.6.

9.5. Sample Size Determination

Although the primary objective of the trial is to demonstrate that tirzepatide 15 mg or MTD is non-inferior to intensified conventional care for the primary endpoint (change in HbA1c from baseline to Week 104) with a 0.3% non-inferiority margin, sample size selection is guided by establishing superiority of tirzepatide 15 mg or MTD compared to intensified conventional care for change in HbA1c from baseline to Week 104 and to Week 208 (key secondary objectives),

irrespective of adherence to treatment or introduction of antihyperglycemic rescue medication (treatment-regimen estimand).

A sample size of 780 participants (390 per group) will provide at least 90% power to detect a difference between treatment groups at both Week 104 and Week 208 irrespectively of adherence to treatment, changes in background metformin medication, or introduction of antihyperglycemic rescue medication.

This sample size is based on a treatment difference of 0.33% at Week 104 and 0.38% at Week 208 with a common standard deviation of 1.3% and 1.4%, respectively, using a two-group t-test and a 0.05 two-sided significance level. The treatment differences are based on the following assumptions:

- Efficacy observed for intensified conventional care at Weeks 104 and 208 will be similar to that of semaglutide 1.0 (50% of the participants) and semaglutide 2.0 (50% of the participants)
- Tirzepatide 15 mg or MTD will be comprised of these tirzepatide doses
    - 15 mg dose: 80% of the participants
    - 10 mg dose: 15% of the participants, and
    - 5 mg dose: 5% of the participants
- Increases of HbA1c over time
    - intensified conventional care will show a 0.25% increase in HbA1c at Week 104 and 0.4% at Week 208, and
    - Tirzepatide will show a 0.2% increase in HbA1c at Week 104 and 0.3% at Week 208.

In addition, the planned sample size provides at least 90% power to detect a difference between treatment groups at both Week 104 and Week 208 after randomization regardless of changes in background metformin medication, assuming that participants had stayed on treatment and not taken antihyperglycemic rescue medication.

This sample size is based on a treatment difference of 0.33% at Week 104 and 0.38% at Week 208 with a common standard deviation of 1.1%, using a two-group t-test and a 0.05 two-sided significance level. The treatment differences are based on the same assumptions stated above for the treatment-regimen estimand with the following discontinuation rates

- 25% of the participants discontinue study intervention by Week 104, and
- 35% of the participants discontinue study intervention by Week 208.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH Good Clinical Practice Guidelines
- International Organization for Standardization (ISO) 14155, and
- applicable laws and regulations.

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
- Reporting significant issues related to participant safety, participant rights, or data integrity.

Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. 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 the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

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

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

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

A copy of the ICF(s) must be provided to the participant and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Internal Assessment Committee

Not applicable.

10.1.5.2. External Clinical Endpoint Committee

An independent clinical endpoint committee, external to Lilly, will be formed to adjudicate major adverse cardiovascular events and acute pancreatitis. This committee will be blinded to treatment assignment.

10.1.6. Dissemination of Clinical Study Data

Reports

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

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, study not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

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

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

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

Data and documents, including the study protocol, statistical analysis plan, clinical study report, and 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.

10.1.7. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically, for example, laboratory data.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

Quality tolerance limits

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

Data monitoring and management

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

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

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

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

Records retention and audits

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

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

Data capture system

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

Electronic data capture system

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.

Clinical outcome assessments

Additionally, eCOA data (participant-focused outcome instrument) will be directly recorded by the participant, into an instrument, for example, handheld smart phone or tablet. The eCOA data will serve as the source documentation, and the investigator does not maintain a separate written or electronic record of these data.

Data storage and access

Data collected via the sponsor-provided data capture system(s) will be stored at third parties.

The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system, and reports 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.

10.1.8. Source Documents

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

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

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

10.1.9. Study and Site Start and Closure

First act of recruitment

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

The first act of recruitment is the first site's first participant visit (Visit 1) and will be the study start date.

Study or site termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.10. Publication Policy

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

10.1.11. Investigator Information

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

10.1.12. Sample Retention

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

Sample Type	Custodian	Retention Period after Last Patient Visit[a]
Exploratory Biomarker Samples	Sponsor or Designee	15 years
Tirzepatide anti-drug antibodies[b]	Sponsor or Designee	15 years

[a] Retention periods may differ locally.

[b] Sample collection only for hypersensitivity and ISRs.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the Lilly-designated laboratory or by the local laboratory as specified in the table below.

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

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

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

Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Differential	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Lipid Panel	Assayed by Lilly-designated laboratory.
Total cholesterol	
Triglycerides	
High-density lipoprotein (HDL-C)	
Low-density lipoprotein (LDL-C)	Generated by Lilly-designated laboratory. If Triglycerides are >400, direct LDL will be measured.
Very low-density lipoprotein (VLDL-C)	Generated by Lilly-designated laboratory.

Hormones (female)	
Serum pregnancy	Assayed by Lilly-designated laboratory.
Urine pregnancy	Assayed and evaluated locally.
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory.
Urine Chemistry	Assayed by Lilly-designated laboratory.
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI) calculated using creatinine	Results will not be provided to the investigative sites.
eGFR (CKD-EPI) calculated using cystatin-C	Results will not be provided to the investigative sites.
eGFR (CKD-EPI) calculated using creatinine and cystatin-C	
Urinary albumin/creatinine ratio (UACR)	
Additional Testing	Assayed by Lilly-designated laboratory.
Glucose	
HbA1c	
Cystatin-c	
Calcitonin	
Pancreatic amylase	
Lipase	
Anti-glutamic acid decarboxylase antibody	
Microalbumin	
C-reactive protein, high-sensitivity (hsCRP)	
Stored Samples	
Exploratory biomarker samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
Plasma (EDTA)	
Plasma (P800)	
Oral glucose tolerance test (OGTT)	Assayed by Lilly-designated laboratory.
Glucose	
Glucagon	Results will not be provided to the investigative sites.
C-peptide	Results will not be provided to the investigative sites.
Insulin	Results will not be provided to the investigative sites.
Intact proinsulin	Results will not be provided to the investigative sites.

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

Purpose of collecting samples after a systemic hypersensitivity event

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

When to collect samples after a systemic hypersensitivity event occurs

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

Obtain follow-up pre-dose samples at the next regularly scheduled laboratory sample collection, ideally prior to the next dose after the event, to assess post-event return-to-baseline values.

Timing	Laboratory Test[a]
Collect from 30 min to 4 hr after the start of the event. ● Note: The optimal collection time is from 1 to 2 hr after the start of event.	Total tryptase
	Complements (C3, C3a, and C5a)
	Cytokine panel (IL-6, IL-1β, IL-10, or any cytokine panel that includes these 3 cytokines)
Collect only if not already collected on the same day as the event. ● Note: If collecting, collect up to 12 hr after the start of the event.	Tirzepatide anti-drug antibodies
	Tirzepatide concentration

Abbreviation: IL = interleukin.

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease or 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 and 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication

prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect • Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.
f. Other situations • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
g. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product Complaint
• A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs: o deficiencies in labeling information, and

- use errors for device or drug-device combination products due to ergonomic design elements of the product.

- Product Complaints related to study interventions used in clinical studies are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation, for example, hospital progress notes, laboratory reports, and diagnostics reports, related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page, and product complaint information is reported on the Product Complaint Form.

  Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or 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: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with 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 pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send 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 AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

10.3.5. Reporting of SAEs

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

SAE Reporting via Paper Form
• Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor or designee. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in site training materials.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting
Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. ● The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. ● An investigator who receives an investigator safety report describing 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.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

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

Examples of different forms of contraception

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

[a] Advise participants using oral hormonal contraceptives to switch to a non-oral contraceptive method listed in the highly effective contraception list or add a barrier method of contraception (i.e., effective contraception list above) for 4 weeks after initiation and for 4 weeks after each dose escalation with tirzepatide.

10.4.2. Contraception Guidance

Guidance for women of childbearing potential

This table provides guidance for WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle.

WOCBP Must…	Must not…

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

This table provides guidance for WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle.

Topic	Condition
Pregnancy testing	Negative serum result at screening followed by a negative urine result prior to first dose of intervention. Perform additional pregnancy tests as per SoA
Contraception	Agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception. These forms of contraception must be used during the study and for at least 1 month after the last dose of the study intervention.

Guidance for males

The table below describes contraception guidance for all men.

Topic	Guidance
All male participants	should refrain from sperm donation for the duration of the study and for 120 days (4 months) after the last tirzepatide injection
Contraception for men with female partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), OR • must use condoms during intercourse for the duration of the study and for 120 days (4 months) after the last tirzepatide injection
Contraception for men in exclusively same-sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

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

Hepatic evaluation testing

See protocol Section 8.2.7 or guidance on appropriate test selection.

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

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

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

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

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

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

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

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

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

10.6. Appendix 6: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

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

10.7. Appendix 7: Country-Specific Requirements

10.7.1. Germany

This section describes protocol changes applicable to adult participants in study sites in Germany.

This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name	Description of the Change	Brief Rationale
8.3. Adverse Events, Serious Adverse Events, and Product Complaints 10.11. Appendix 11: Abbreviations and Definitions	Deleted references to "legally authorized representative"	The German Drug Law (Arzneimittelgesetz – AMG) requires per Paragraph 40 (1-3) and Paragraph 41 (3) that adult participants act on their own behalf and provide their own written informed consent. If written consent is not possible, verbal consent with a witness is acceptable. No legal representative consent is accepted.
10.10. Appendix 10: Provisions for Changes in Study Conduct During Exceptional Circumstances	Replaced references to "exceptional circumstances" with the "COVID-19 pandemic"	Temporary measures may only be used in response to the COVID-19 pandemic.

The revised text in the following sections shows the changes applicable to adult participants at study sites in Germany. Deletions are identified by ~~strikethrough format~~ and additions by underlined text.

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

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

- AEs
- SAEs, and
- PCs.

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

Section 10.10. Appendix 10: Provisions for Changes in Study Conduct ~~During Exceptional Circumstances~~ due to the COVID-19 Pandemic

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~~ Study disruptions due to the COVID-19 pandemic

Individual, site, or regional restrictions due to the COVID-19 pandemic ~~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~~ during the COVID-19 pandemic

~~In an exceptional circumstance, a~~ 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~~ the COVID-19 pandemic

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.

To ensure the quality of data and the well-being of participants, it will be ensured that the investigator sites and their staff are following GCP principles and are meeting the sponsor responsibilities of Section 5 of ICH GCP. Throughout these activities the participant remains under the care of the primary investigator.

Remote visits

Types of remote visits

Telemedicine:

Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. The study site should capture the visit location and method with a specific

explanation for any data missing because of missed in-person site visits in source document and CRF. Examples of assessments to be completed in this manner include AEs and PCs, concomitant medications, review study participant eDiary, including study intervention compliance, review diet and exercise goals.

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~~ the COVID-19 pandemic if written approval is provided by the sponsor and permitted by local regulations. Procedures performed at such visits may include, but are not limited to, weight measurement, blood sampling, vital signs, conducting physical assessments, administering PROs, and collecting health information.

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

Additional consent from the participant will be obtained for participants if needed per local regulations.

Other alternative locations:

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: hsCRP, insulin, and lipid samples. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken:

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

Screening period guidance

Visit 1 to Visit 2

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening are valid for a maximum of 30 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to ~~exceptional circumstances~~ the COVID-19 pandemic:

- If screening is paused for less than 30 days from screening to Visit 2: the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 14 days from first screening.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.

- If screening is paused for more than 30 days from screening: The participant must be discontinued because of screening interruption due to ~~an exceptional circumstance~~ the COVID-19 pandemic. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at the screening visit to ensure participant eligibility by Visit 2.

Visit 2 to Visit 3

To ensure safety of study participants, laboratory values and other eligibility assessments taken at Visit 2 are valid for a maximum of 30 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to ~~exceptional circumstances~~the COVID-19 pandemic:

- If screening is paused for less than 30 days from Visit 2 to Visit 3: the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 30 days from randomization.

  - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
  - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.

- If screening is paused for more than 30 days from Visit 2: The participant must be discontinued because of screening interruption due to ~~an exceptional circumstance~~ the COVID-19 pandemic. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at Visit 2 to ensure participant eligibility by Visit 3.

Adjustments to visit windows

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

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.

The primary endpoint visit and end of treatment visit, Visit 16 (Week 104) and Visit 25 (Week 208), should be completed per original schedule whenever possible and safe to do so. The visit window should be within ±7 days relative to the target visit date.

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~~ the COVID-19 pandemic. 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.

Section 10.11. Appendix 11: Abbreviations and Definitions

enter	Participants entered into a study are those who sign the informed consent form directly ~~or through their legally acceptable representatives.~~

10.8. Appendix 8: OGTT Test

Oral glucose tolerance test will be performed at as outlined in the SoA. The key objectives of the OGTT are to assess α and β cell function and insulin sensitivity.

Each 3-hour OGTT will be performed in the morning after an overnight fast. If participant arrives in non-fasting state, the OGTT test must be rescheduled within the allowable visit windows.

Participants are required to take all antihyperglycemic medications the day before OGTT according to their routine dosing schedule. On the day of OGTT, participants will be required to come fasting and not to take their antihyperglycemic medications until the OGTT is complete. During each OGTT, venous blood samples will be collected for measurement of glucose, C-peptide, intact proinsulin, insulin, and glucagon. Two baseline blood samples will be drawn at approximately −15 and 0 minutes. Immediately after collection of the Time 0 sample, a 75-g glucose dose will be given orally. The participant should consume the glucose load within approximately 5 minutes. Blood samples will be collected at approximately 15, 30, 60, 90, 120, and 180 minutes post glucose solution consumption. The participant should remain minimally active for the duration of the test.

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

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

Measuring height

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

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

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

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

Measuring weight

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

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

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

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

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

Measuring waist circumference

- Use non-stretchy tape
- Waist circumference should be measured at midpoint, between lower margin of last palpable rib and top of iliac crest (~1 inch [2.54 cm] above the navel)
- Participants should be lightly clothed, and
- Measure to the nearest 0.5 cm.

Step 1. Ask the participant to stand with their feet close together, and arms at their side with their body weight evenly distributed.

Step 2. Ask participant to relax.

Step 3. Measurements should be recorded at the end of a normal expiration.

Calculation of BMI

Height and weight measurements will be used to calculate BMI.

- BMI = weight (kg) / [height (m)]^2.

Calculation of BMI with amputation or limb loss

In participants with limb amputation or limb loss, use the formula given in the following link: Amputee Coalition – https://www.amputee-coalition.org/limb-loss-resource-center/resources-filtered/resources-by-topic/healthy-living/about-bmi/.

Vital sign measurements (blood pressure and heart rate)

- Vital sign measurements, measured by pulse, should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing.
- An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of BP measurements.
- Blood pressure should be taken with an automated blood pressure instrument.
- If blood pressure and pulse measurements are taken separately, pulse should be taken prior to blood pressure.

Step 1. The participant should sit quietly for approximately 5 minutes before vital signs measurements are taken.

Step 2. For each parameter, 3 measurements will be taken using the same arm, preferably the nondominant arm.

Step 3. The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and blood pressure needs to be recorded in the CRF.

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.

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

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

After approval by local Ethical Review Boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required, for example, upon 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.

Remote visits

Types of remote visits

Telemedicine:

Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. The study site should capture the visit location and method with a specific explanation for any data missing because of missed in-person site visits in source document and CRF. Examples of assessments to be completed in this manner include AEs and PCs, concomitant medications, review study participant eDiary, including study intervention compliance, review diet and exercise goals.

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 and permitted by local regulations. Procedures performed at such visits may include, but are not limited to, weight measurement, blood sampling, vital signs, conducting physical assessments, administering PROs, and collecting health information.
Every effort should be made for the participant to return to on-site visits as soon as reasonably possible, while ensuring the safety of the participant and investigational site staff.
Additional consent from the participant will be obtained for participants if needed per local regulations.

Other alternative locations:

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for calcitonin. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken:

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

Screening period guidance

Visit 1 to Visit 2

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening are valid for a maximum of 30 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 30 days from screening to Visit 2: the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 14 days from first screening.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 30 days from screening: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the

one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at the screening visit to ensure participant eligibility by Visit 2.

Visit 2 to Visit 3

To ensure safety of study participants, laboratory values and other eligibility assessments taken at Visit 2 are valid for a maximum of 30 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 30 days from Visit 2 to Visit 3: the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 30 days from randomization.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 30 days from Visit 2: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at Visit 2 to ensure participant eligibility by Visit 3.

Adjustments to visit windows

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

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.

The primary endpoint visit and end of treatment visit, Visit 16 (Week 104) and Visit 25 (Week 208), should be completed per original schedule whenever possible and safe to do so. The visit window should be within ±7 days relative to the target visit date.

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.

10.11. Appendix 11: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence.
ADA	American Diabetes Association
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Anti-GAD	anti-glutamic acid decarboxylase
APPADL	Ability to Perform Physical Activities of Daily Living
AST	aspartate aminotransferase
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product.
BG	blood glucose
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidential interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CT	computed tomography
CV	cardiovascular
CVD	Cardiovascular disease

DPP-4	dipeptidyl peptidase
Device deficiencies	Equivalent to product complaint
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
ED	early discontinuation
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FBG	fasting blood glucose
FSG	fasting serum glucose
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ISR	injection-site reaction
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment-regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
IWRS	interactive web-response system
IW-SP	Impact of Weight on Self Perception
LADA	latent autoimmune diabetes in adults
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, pre-filled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription.
MEN2	multiple endocrine neoplasia syndrome type 2
mITT	modified intent-to-treat

MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
MTD	maximum tolerated dose
NAFLD	nonalcoholic fatty liver disease
OGTT	oral glucose tolerance test
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QTc	corrected QT interval
QW	once-weekly
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SDP	single-dose pen
SF-36	36-item short-form health survey
SGLT-2	sodium-glucose cotransporter-2
SMBG	self-monitoring of blood glucose
SoA	schedule of activities
T1D	type-1 diabetes
T2D	type-2 diabetes

TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.12. Appendix 12: Protocol Amendment History

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

Amendment (b): (02-Nov-2022)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The rationale for amending the protocol is to address Regulatory Agency requests for information and to perform minor clarifications, formatting, and editorial changes.

Section # and Name	Description of Change	Brief Rationale
Title page	Deleted the EudraCT number and retained only the EU trial number as the submission is through the new system	Correction
1.1. Synopsis	Updated the section to align with the changes in the main body of the protocol	For consistency
1.3.1. Screening Visits 1-2, and Treatment Visits 3-9	• Added urine pregnancy test at Weeks 4, 8, 12, 16, 20, and 24 • To Urine pregnancy (local) row, added "Monthly home urine pregnancy test is required in between visits after Visit 9" to comments	Updated in response to Regulatory Agency information request
1.3.2. Treatment Visits 10-25, Early Discontinuation, and the Post-treatment Follow-up Visit 801	• Added urine pregnancy test at Weeks 32, 44, 68, 92, 116, 140, 164, 188, and 208 • To Urine pregnancy (local) row, added "Monthly home urine pregnancy test is required in between visits" to comments	Updated in response to Regulatory Agency information request
	Added visit interval tolerance of "±7" days for Period III Safety Follow-up	To provide minor clarification to timing of safety follow-up period
2.3. Benefit/Risk Assessment	Updated the language to clearly provide additional information on benefit/risk assessment for participants with T2D	Updated in response to Regulatory Agency information request
3. Objectives, Endpoints, and Estimands	Used "insulin secretion rate" without abbreviation (ISR) to avoid confusion with "injection site reaction" which uses the ISR abbreviation	Correction
3. Objectives, Endpoints, and Estimands	Updated the definition of estimands by including prohibited medication	Updated in response to Regulatory Agency information request
	Removed "There are no remaining intercurrent events" and added "Initiation of non-study tirzepatide is	

Section # and Name	Description of Change	Brief Rationale
	addressed by the hypothetical strategy; that is, as if participants had not taken non-study tirzepatide"	
4.1.1. Design Outline	Added "if available" to Visit 2 details	Clarification
5.1. Inclusion Criteria	• Added "ADA classification" to Inclusion Criterion 1 • Added "and no other antihyperglycemic medication for" to Inclusion Criterion 3	Updated in response to Regulatory Agency information request
	Added "new intensive" to Inclusion Criterion 4 for diet	Clarification
	Updated the contraceptive language in Inclusion Criterion 6	To provide clarification and remove redundant wording
5.2. Exclusion Criteria	Split the Exclusion Criterion 14 into 2 parts, moved the second part as Exclusion Criterion 37	Correction
5.3. Lifestyle Considerations	Changed "Inclusion Criterion [5]" to "Inclusion Criterion [4]" in Paragraph 3	Correction
6.1.3. Rescue Therapy 6.5.5. Intensified Conventional Care Dose Modifications 7.1. Discontinuation of Study Intervention 11. References	Updated to 2022 consensus report and replaced the old citation and reference with the new citation and reference	Updated to the new ADA/EASD consensus report
6.3. Measures to Minimize Bias: Randomization and Blinding	Changed ">40" to "≥41" in age stratification factor	Clarification
6.5.4. Tirzepatide Dose Re-Escalation	Updated the number of attempts allowed for re-escalation of tirzepatide	Updated in response to Regulatory Agency information request
6.5.5. Intensified Conventional Care Dose Modifications	Added "Tirzepatide will not be allowed."	Updated in response to Regulatory Agency information request
7.1. Discontinuation of Study Intervention	Added "the participant, for any reason, initiates treatment with a therapeutic agent that is prohibited by the protocol" for both Tirzepatide and Intensified conventional care.	Updated in response to Regulatory Agency information request
7.2. Participant Discontinuation/Withdrawal from the Study	Removed "if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent"	Updated in response to Regulatory Agency information request
8.2.4. Dilated Fundoscopic Examination	Removed "of screening" and added "from Visit 1" in second paragraph	To provide clarification on the timing of examination that was done prior to Visit 1

Section # and Name	Description of Change	Brief Rationale
8.3. Adverse Events, Serious Adverse Events, and Product Complaints	Changed "Appendix 10" to "Appendix 3" in the last paragraph	Correction
8.3.3.10. Hypersensitivity Reactions	Changed "Appendix 3, Section 10.3" to "Appendix 2, Section 10.2.1."	Correction
8.4. Pharmacokinetics	Added "In the case of hypersensitivity or ISR, samples will be collected if needed as described in Section 10.2.1."	To provide clarification on when blood samples will be collected for hypersensitivity reaction and injection site reaction to be consistent with what were listed in the appendix
8.8. Immunogenicity Assessments	Added "In the case of hypersensitivity or ISR, samples will be collected if needed as described in Section 10.2.1."	To provide clarification on when blood samples will be collected for hypersensitivity reaction and injection site reaction to be consistent with what were listed in the appendix
9.2. Analyses Sets	Updated the table as per the SAP and addressed the updates to the estimands	For consistency with SAP and to address the updates to the estimands
9.3.2. Primary Endpoint Analysis	Removed "and/or initiation of rescue antihyperglycemic medication and/or changes to background metformin medication" from Paragraph 4.	Clarification
9.3.6. Subgroup Analyses	Changed "<40 years vs ≥40 years" to "≤40 years vs ≥41 years"	Clarification
10.1.12. Sample Retention	Added footnote b: "Sample collection only for hypersensitivity and ISRs" to "Tirzepatide anti-drug antibodies"	Clarification
10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event	Removed the second column	Updated as per the standard language
10.4.1. Definitions	Added footnote a: "Advise participants using oral hormonal contraceptives to switch to a non-oral contraceptive method listed in the highly effective contraception list or add a barrier method of contraception (i.e., effective contraception list above) for 4 weeks after initiation and for 4 weeks after each dose escalation with tirzepatide" to "combination oral contraceptive pill" and "progestin-only contraceptive pill (mini-pill)."	Updated in response to Regulatory Agency information request
10.4.2. Contraception Guidance	Updated the contraceptive language	Updated in response to Regulatory Agency information request
10.12. Appendix 12: Protocol Amendment History	Added this new section and included the protocol amendment summary of changes table from previous protocol amendment	As per Lilly's internal guidance

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore, not detailed

Amendment [a]: (20-June-2022)

Overall Rationale for the Amendment:

The rationale for amending the protocol is to update the EU trial number. The table below provides the details of the changes.

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated EU trial number.	EU CTIS required a new EU trial number to replace the previous number.
Title Page	Document ID was added.	To align with current formatting standard.
1.1. Synopsis	Updated EU trial number.	EU CTIS required a new EU trial number to replace the previous number.

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