Protocol 18F-MC-GPGN(f)

The Effect of Tirzepatide versus Dulaglutide on Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes (SURPASS-CVOT)

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EudraCT number: 2019-002735-28

EU trial number: 2023-507846-96-00

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Tirzepatide (LY3298176)

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Protocol Amendment (f) Electronically Signed and Approved by Lilly on date provided below.

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment e	*04-Sep-2023*
Amendment d	*14-Dec-2021*
Amendment c	*12-Nov-2020*
Amendment b	*01-May-2020*
Amendment a	*10-Dec-2019*
Original Protocol	*07-Nov-2019*

Amendment [f]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The rationale for this amendment is to align with new EU Clinical Trial Regulation requirements.

Section # and Name	Description of Change	Brief Rationale
12. Appendices Appendix 8. Country-Specific Requirements	Added a new appendix applicable to EU-only sites by including the content from Protocol Addendum 9 "Appendix 8.4. Changes Applicable to Countries Allowing the Shipment of Study Drug Directly from Site to a Patient that Cannot Attend Clinic Visits"	For harmonization of the protocol and to avoid country- and region-specific protocol versions in the EU

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1. Synopsis

Title of Study:
The Effect of Tirzepatide versus Dulaglutide on Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes (SURPASS-CVOT)

Regulatory Agency Identifier Numbers:

IND: 128801
EudraCT number: 2019-002735-28
EU trial number: 2023-507846-96-00

Rationale:
Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist (RA). Both incretin pathways are apparent in the glucose lowering by tirzepatide. A Phase 2b study established a wide dose range of tirzepatide, which showed clinically meaningful and superior hemoglobin A1c (HbA1c) control with greater weight loss and an acceptable tolerability profile compared with a selective GLP-1 RA, dulaglutide. In addition, tirzepatide treatment resulted in marked reduction of serum triglyceride concentration, a cardiovascular (CV) risk factor in type 2 diabetes mellitus (T2DM).

Preclinical and early clinical studies have provided evidence that tirzepatide has characteristics similar to potent GLP-1 RAs, such as: glucose-dependent stimulation of beta cell insulin secretion, decreased glucagon secretion, weight reduction, and blood pressure reduction.

These attributes are considered to play a role in the CV protective efficacy of numerous GLP-1 RAs, such as liraglutide, albiglutide, and dulaglutide.

The magnitude of glycemic control and weight reduction appears to be more pronounced with tirzepatide than with most GLP-1 RAs. Moreover, the reduction in serum triglyceride is greater when compared with GLP-1 selective RAs. These clinically relevant additional benefits are probably the result of the simultaneous activation of both GIP and GLP-1 pathways by tirzepatide. When the additional benefits are prolonged during a longer treatment period, they could contribute to CV protection in patients with T2DM as observed by GLP-1 RAs.

Dulaglutide is 1 of the GLP-1 RAs that has demonstrated CV protection. In the REWIND study, dulaglutide 1.5 mg once weekly (QW) significantly reduced the incidence of major adverse cardiovascular events (MACE) composite outcomes, which comprised nonfatal myocardial infarction (MI), nonfatal stroke, and death from CV causes, in patients with T2DM and with increased risk for CV events when compared with placebo.

While changes in the surrogate markers for tirzepatide, as listed above, suggest potential for CV protection, the present study is also important to exclude CV harm by tirzepatide as required by the US Food and Drug Administration (FDA) for new antidiabetic agents. Similarly, since 2012, the European Medicines Agency (EMA)'s guidance for the development of diabetes products has outlined the expectation for development programs to provide sufficient information to support a lack of drug-induced excess CV risk for new products.

Objectives/Endpoints:

Objectives	Endpoints
Primary • To assess efficacy of maximally tolerated tirzepatide dose up to 15 mg QW compared to QW dulaglutide 1.5 mg on time to first occurrence of the composite endpoint of death from CV causes, MI, or stroke (MACE-3) when both are added to standard of care in patients with T2DM and high CV risk. • Primary analysis will be an assessment of NI of tirzepatide to dulaglutide for MACE-3. After establishing NI, superiority of tirzepatide compared to dulaglutide for MACE-3 will be evaluated.	• Time to first occurrence of any component event of MACE-3
Key Secondary **<u>Efficacy</u>** To assess the superiority of tirzepatide up to 15 mg QW compared to dulaglutide 1.5 mg QW.	• Time to death due to any cause • Time to CV death • Time to first occurrence of MI • Time to first occurrence of stroke • Time to first occurrence of the expanded composite CV outcome, defined as either CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina • Cumulative number of CV deaths and total (first and recurrent) HF events requiring hospitalization and/or urgent HF visits

Objectives	Endpoints
Additional Secondary To assess the superiority of tirzepatide up to 15 mg QW compared to dulaglutide 1.5 mg QW.	• Proportion of patients with more than 10% weight loss from screening after 36 months • Change from baseline in: o weight, BMI, and waist circumference o HbA1c o urinary albumin to creatinine ratio o blood lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides • Time to first occurrence of: o coronary, carotid, or peripheral revascularizations, individually and as composite o hospitalization due to unstable angina o composite endpoint of new or worsening nephropathy • Cumulative number of primary composite events of CV death and total (first and recurrent) MI and/or stroke
Safety • To rule out >30% increase in CV risk with tirzepatide in an indirect comparison to placebo by a direct comparison between tirzepatide and dulaglutide. • To assess the effects of maximally tolerated tirzepatide dose up to 15 mg QW compared to dulaglutide 1.5 mg QW.	• Time to first occurrence of any component event of MACE-3 • Incidence of TEAEs and permanent discontinuation of study drug due to AEs • Incidence of: o pancreatitis o severe gastrointestinal events o any malignancy (including medullary and papillary thyroid cancers) o severe hypoglycemic events o immune-mediated reactions including serious allergic and hypersensitivity reactions o hepatobiliary events (eg, acute cholecystitis, acute cholelithiasis, and drug-induced liver injury) o acute renal failure or exacerbation of chronic renal failure o diabetic retinopathy complications o supraventricular arrhythmias and cardiac conduction disorders • mean change from baseline: o blood pressure o pulse rate

Objectives	Endpoints
	○ lipase ○ pancreatic amylase ○ calcitonin ○ eGFR

Abbreviations: AE = adverse event; BMI = body mass index; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HF = heart failure; LDL = low-density lipoprotein; MACE-3 = major adverse cardiovascular events composite of myocardial infarction, stroke, or death from cardiovascular causes; MI = myocardial infarction; NI = noninferiority; QW = once weekly; TEAE = treatment-emergent adverse event; T2DM = type 2 diabetes mellitus.

Summary of Study Design:

Study I8F-MC-GPGN (GPGN), also known as SURPASS-CVOT, is a Phase 3, event-driven, multicenter, international, randomized, double-blind, active comparator, parallel-group study. This study will assess the effect of QW tirzepatide (up to 15 mg) versus dulaglutide (1.5 mg) on CV outcomes when added to the standard of care in patients with T2DM with established cardiovascular disease (CVD) and elevated risk for MACE.

Following a screening visit, eligible patients will be randomized to either tirzepatide up to 15 mg or dulaglutide 1.5 mg injected subcutaneously (SC) QW.

After randomization, patients will follow a dose escalation schedule in a double-blinded manner over 24 weeks.

Cardiovascular outcomes will be assessed as they occur, and other measures will be followed every 4 weeks for the first 6 months and then followed approximately every 3 months thereafter.

Study Population:

- Men or women at least 40 years old with a diagnosis of T2DM
- Established CVD, including at least 1 of the following:
    - Coronary artery disease
    - Cerebrovascular disease
    - Peripheral arterial disease
- HbA1c ≥7% (≥53 mmol/mol) and ≤10.5% (≤91.3 mmol/mol) based on central laboratory assessment at screening
- Body mass index ≥25 kg/m^2

Number of Patients:

SURPASS-CVOT will continue until at least 1615 patients experience at least 1 component of the primary composite endpoint of MACE-3. The study provides 90% power to demonstrate superior MACE-3 risk reduction with tirzepatide compared to dulaglutide at a 2-sided .0472 significance level, provided tirzepatide is associated with a 15% reduction in hazard compared to dulaglutide. The significance level is adjusted to account for an efficacy assessment at an interim

analysis. This study also provides 90% power to demonstrate noninferiority (NI) of tirzepatide to dulaglutide relative to MACE-3 risk reduction (with NI boundary of 1.05), provided tirzepatide is associated with a 10.5% reduction in hazard compared to dulaglutide. Use of log-rank test for comparing the distribution of time to first occurrence of MACE-3 between tirzepatide and dulaglutide is assumed for sample size calculation.

A mean follow-up of approximately 4 years and about 12,500 patients are anticipated. This prediction is based on the assumptions of an approximate MACE-3 rate of 3.5 events per 100 years of follow-up in patients in the dulaglutide treatment group and an additional 15% reduction in MACE-3 risk for tirzepatide compared to dulaglutide.

Treatment Groups and Duration:

The study comparison is between tirzepatide and dulaglutide. Assignment to tirzepatide or dulaglutide will be randomly allocated in a 1:1 ratio. Randomization will be stratified by country of enrollment and sodium-glucose cotransporter-2 inhibitor (SGLT-2i) use (Yes/No) at baseline.

The starting dose of tirzepatide 2.5 mg QW is to be escalated to 15 mg QW or to the highest maintenance dose tolerated by the patient.

The dose of dulaglutide will be initiated and maintained at 1.5 mg QW. No escalation or de-escalation will occur in the dulaglutide treatment group. However, in order to maintain the double-blind study design, a tirzepatide-matched sham dose escalation or de-escalation schedule will be followed.

It is expected that patients who do not reach the maximum dose during the initial dose escalation for any reason, should be offered the opportunity to undergo up to 2 additional dose escalations to reach the maximum dose. Patients who participate in an additional dose escalation will be scheduled to attend additional visits at 4-week intervals to allow for dose escalation until the maximum tolerated dose is reached (See Section 2).

The maximum duration of the study for an individual patient is dependent both on the time taken for recruitment and the observed MI, stroke, or death from CV causes (MACE-3) rate and could be as long as 5 to 6 years.

Statistical Analysis:

Two key analysis populations are of interest:

- the modified intention-to-treat efficacy (mITTE) population consisting of all randomized patients excluding inadvertently randomized patients and
- the modified intention-to-treat safety (mITTS) population consisting of patients receiving at least 1 dose of study drug.

Patients will be analyzed according to their randomized treatment.

For patients with a final visit where primary endpoint status is ascertained, the patient's end-of-follow-up will be defined as the earliest of a) date of death, or b) date of the patient's final visit.

For patients with documented withdrawal of consent (Section 8.2), the patient's end-of-follow-up will be the date they confirm withdrawal of consent. For patients prematurely discontinuing study but without documented withdrawal of consent (Section 8.2), the patient's end-of-follow-up will be the latest of a) date of the patient's post-ETV, b) date of ETV, or c) date of last contact when the primary end point status is ascertained prior to date of discontinuation. For patients who have neither a final visit where primary endpoint status is ascertained nor have prematurely discontinued from study, the patient's end-of-follow-up will be the date of last contact when the primary end point status is ascertained.

All efficacy events from the mITTE population that occur from randomization through patient's end-of-follow-up will be included in the efficacy analyses, regardless of patient compliance with study drug and adherence to study visits and procedures. All safety events from the mITTS population that occur from first dose of study drug through patient's end-of-follow-up will be included in the safety analyses, regardless of patient adherence to study drug or procedures.

The primary efficacy analysis will be based on time-to-first event analysis via a Cox proportional hazards regression model. The primary efficacy measure is the time from randomization to the first occurrence of any component of MACE-3. The estimate of the hazard ratio (HR) and 95.3% confidence intervals (CIs) (to account for alpha spent at the interim analysis) will be calculated. The estimate of the cumulative event rate function will be obtained using the Kaplan-Meier method.

The present study will be used to demonstrate that tirzepatide is not associated with increased CV risk. Traditionally, such studies are designed with placebo as the comparator arm to provide 90% power to exclude a 30% increase in CV risk compared to placebo (i.e., upper bound of 95% CI of the HR [active therapy versus placebo] <1.3) under the assumption of no harm. The sponsor proposes to discharge this requirement by a direct comparison of the primary endpoint between tirzepatide and dulaglutide.

Tirzepatide will be considered NI to dulaglutide if the upper bound of the 95.3% CI of the HR (tirzepatide versus dulaglutide) for the primary endpoint is <1.05 and superior to dulaglutide if the upper bound is <1.00.

Additional information regarding analysis of secondary endpoints, including details regarding type 1 error rate control strategy, will be provided in the statistical analysis plan (SAP).

An IDMC consisting of academic experts who are external to the sponsor will have access to unblinded data to allow monitoring of safety and efficacy. The first scheduled IDMC review will occur approximately 6 months after first patient visit. Thereafter, IDMC reviews will be planned approximately every 6 months throughout the study.

Tabular summaries of clinical endpoint events (reported and adjudicated) including deaths, MIs, strokes, selected clinically significant laboratory values, adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, and other relevant safety information by treatment group will be sent to the IDMC by an unblinded statistician external to and independent from the sponsor.

A single planned interim efficacy analysis will be performed once approximately 1075 CEC-confirmed MACE-3 endpoints have been accrued to consider early termination of the study if tirzepatide has demonstrated superiority over dulaglutide relative to the MACE-3 endpoint at a 2-sided .01 significance level. Details of membership, operations, and the communication plan are documented in the IDMC Charter.

Ethical Considerations of Benefit/Risk:

Participation in SURPASS-CVOT is expected to provide a positive benefit-to-risk impact to its participants. The potential benefits from participation in this study include improved glycemic control, frequent expert medical care for an approximately 54-month period, and potential CV protection.

Results from Phase 1 and Phase 2 studies also indicate that the potential risks/AEs with tirzepatide are consistent with the GLP-1 RAs. The risks also include the development of potential compound-specific antidrug antibodies, similar to other protein-based therapies. Results from toxicology studies suggest that the safety profile of tirzepatide is consistent with GLP-1 pharmacology. No apparent GIP RA effects have been identified that would suggest additional or differential safety risks.

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

Data Monitoring Committee: Yes

An Independent Data Monitoring Committee (IDMC) with membership external to the sponsor will monitor patient safety and scientific integrity of the data. A Clinical Endpoint Committee (CEC) with membership external to the sponsor will be responsible for event adjudication in a blinded fashion. Furthermore, the Executive Committee consisting of endocrinology and CV clinical experts will be responsible for providing academic oversight for the study.

2. Schedule of Activities

Table GPGN.1. Schedule of Activities

Schedule of Activities: Screening through to 24 Weeks (Visit 14)

	Screening	Dose Escalation Period												
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week of Treatment	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Allowable Window (days)		**+7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Fasting (>8 hours)		**X**												
Optional Telephone Visit[a]			**X**		**X**		**X**		**X**		**X**		**X**	
Informed consent	X													
Entry criteria reviewed	X	X												
Randomization		X												
Dispense and Return Study Drug														
Dispense study drug		X		X		X		X		X		X		X
Collect and record unused study drug				X		X		X		X		X		X
Additional dose escalations (optional and not more than 2)														X
Clinical Assessments														
Medical history	X													
Physical examination[b]	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse rate and blood pressure[c]	X	X		X		X		X		X		X		X
ECG[d]		X												
Height	X[c]													
Weight	X[c]	X						X						X
Waist circumference[c]	X	X						X						X
Endpoint events[e]		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundoscopic examination[f]	X													X[f]
Laboratory Tests (Performed at a Central Laboratory except Urine Pregnancy)														
Serum pregnancy [g]	X													

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	Screening	Dose Escalation Period												
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week of Treatment	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Allowable Window (days)		**+7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Fasting (>8 hours)		**X**												
Optional Telephone Visit[a]			**X**		**X**		**X**		**X**		**X**		**X**	
Urine pregnancy [h]		X												
FSH[i]	X													
Chemistry panel	X							X						X
Fasting Serum Glucose		X												
Lipid panel		X												
Hematology	X													
Pancreatic amylase, lipase	X							X						
Calcitonin	X													
HbA1c	X							X						X
eGFR (CKD-EPI)[j]	X													
Urine ACR		X												
Cystatin-C		X												
Stored Samples														
Nonpharmacogenetic samples		X												
Pharmacogenetic samples[k]		X												
Patient Education														
Diabetes management education		X												
Adherence/lifestyle reinforcement										X		X		X
Instruct/review injection as required[l]		X												
Patient-Reported-Outcomes—patient to complete at site[m]														
APPADL		X												X
EQ-5D-5L		X												X
IW-SP		X												X

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Schedule of Activities: 9 Months to Final Visit

	Maintenance Period																Extended Maintenance Period[n]				Early Termination[o]		Unscheduled Visit (UV)[p]			Final Visit
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**EVa (31, 35, etc.)**	**EVb (32, 36, etc.)**	**EVc (33, 37, etc.)**	**EVd (34, 38, etc.)**	**ETV**	**Post-ETV (60)**	**UV**	**Dosing UV**	**Phone Follow-Up Dosing UV**	**99**
Study Month	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**51**	**54**	**(+3)**	**(+6)**	**(+9)**	**(+12)**		**(+1)**				**-**
Allowable Window (days)	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**		**±7**				
Fasting (>8 hours)		**X**				**X**								**X**							**X**		**X[r]**			**X**
Dispense and Return Study Drug																										
Dispense study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X		
Collect and record unused study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X
Additional dose escalations (optional and not more than 2)[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X		
Clinical Assessments																										
Physical examination																					X					X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Pulse rate and blood pressure[c]		X		X		X		X		X		X		X		X		X		X	X		X	X		X
ECG[d]																							X[d]			
Height																					X					X
Weight		X				X				X				X				X			X			X[c]		X
Waist circumference[c]		X				X				X				X				X			X			X[c]		X
Endpoint events[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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	Maintenance Period																Extended Maintenance Period[n]				Early Termination[o]		Unscheduled Visit (UV)[p]			Final Visit
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**EVa (31, 35, etc.)**	**EVb (32, 36, etc.)**	**EVc (33, 37, etc.)**	**EVd (34, 38, etc.)**	**ETV**	**Post-ETV (60)**	**UV**	**Dosing UV**	**Phone Follow-Up Dosing UV**	**99**
Study Month	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**51**	**54**	**(+3)**	**(+6)**	**(+9)**	**(+12)**		**(+1)**				**-**
Allowable Window (days)	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**		**±7**				
Fasting (>8 hours)		**X**				**X**								**X**							**X**		**X[r]**			**X**
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundoscopic examination[f]		X[f]																								
Laboratory Tests (Performed at a Central Laboratory except Urine Pregnancy)																										
Chemistry panel		X				X				X				X				X			X		X[r]			X
Lipid panel		X				X								X							X		X[r]			X
Hematology																					X		X[r]			X
Pancreatic amylase, lipase		X				X				X				X				X			X		X[r]			X
Calcitonin		X				X				X				X				X			X		X[r]			X
HbA1c		X				X				X				X				X			X		X[r]			X
eGFR (CKD-EPI)[j]		X				X				X				X				X			X		X[r]			X
Urine ACR		X				X				X				X				X			X		X[r]			X
Urine Pregnancy																					X[s]		X[r]			X[s]
Cystatin-C		X				X				X				X				X			X		X[r]			X
Stored Samples																										
Nonpharmacogenetic samples						X															X					X

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	Maintenance Period																Extended Maintenance Period[n]				Early Termination[o]		Unscheduled Visit (UV)[p]			Final Visit
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**EVa (31, 35, etc.)**	**EVb (32, 36, etc.)**	**EVc (33, 37, etc.)**	**EVd (34, 38, etc.)**	**ETV**	**Post-ETV (60)**	**UV**	**Dosing UV**	**Phone Follow-Up Dosing UV**	**99**
Study Month	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**51**	**54**	**(+3)**	**(+6)**	**(+9)**	**(+12)**		**(+1)**				**-**
Allowable Window (days)	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**	**±15**		**±7**				
Fasting (>8 hours)		**X**				**X**								**X**							**X**		**X[r]**			**X**
Patient Education																										
Adherence/ lifestyle reinforcement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Patient-Reported Outcomes—patient to complete at site[m]																										
APPADL						X															X					X
EQ-5D-5L						X															X					X
IW-SP						X															X					X

Abbreviations: ACR = albumin/creatinine ratio; APPADL = Ability to Perform Physical Activities of Daily Living; CKD-EPI = Chronic Kidney Disease-Epidemiology; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EQ-5D-5L = 5-level EQ-5D; ETV = Early Termination Visit; EVa = Extended Maintenance Visit a; EVb = Extended Maintenance Visit b; EVc = Extended Maintenance Visit c; EVd = Extended Maintenance Visit d; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; ICF = informed consent form; IW-SP = Impact of Weight on Self-Perception; WOCBP = women of childbearing potential.

a If a telephone visit is deemed necessary to support patient compliance, this is allowable at the discretion of the investigator site.

b A physical examination will be performed at Visit 1 and the final visit (or ETV, if applicable) according to local procedure. In the case of patient transfers, the investigator may perform a physical exam at the first visit for the transfer patient.

c Vital Signs: The patient should sit quietly for 5 minutes before vital sign measurements are taken. For each parameter, 2 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart. Blood pressure must be taken with an automated blood pressure machine.
Height and weight measurements will be used to calculate BMI. BMI = weight (kg) / [height (m)]^2
Waist circumference: The waist circumference should be measured twice, rounded to the nearest 0.5 cm. The measuring tape should be removed between the 2 measurements. For unscheduled visits, weight and waist circumference are optional.

d The order of conducting the local ECG, vital sign measurements, and blood samples for laboratory testing is determined at the investigator site. At unscheduled visits, ECG is per investigator discretion.

e Solicitation of new adverse events and potential endpoint events will be collected and recorded for all visits from randomization, regardless of whether the patient is on study drug.

f Dilated fundoscopic exam will be evaluated by an eye care professional (ophthalmologist or optometrist) for all patients (after signed informed consent and prior to randomization). This diagnostic procedure can be either a direct fundus examination or a review of fundus photographs. Either of the 2 procedures must be finalized prior to randomization. The results from this exam will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy. If based on a recent (performed ≤ 90 days prior to randomization) fundus examination, the eCRF could be completed, there is no need for repeated procedure during screening period (after signed informed consent and prior to randomization). A follow-up dilated fundoscopic exam should be performed when clinically indicated by any adverse event suspected of worsening retinopathy, and the findings should be recorded on the retinopathy eCRF. For participants with severe non-proliferative retinopathy or proliferative retinopathy and/or macular edema at baseline, a follow up fundoscopic exam at Visit 14 ±30 days and Visit 16 ±30 days is required and should be recorded in the eCRF.

g A serum pregnancy test must be performed at Visit 1 in WOCBP.

h A local urine pregnancy test must be performed at Visit 2 with the result available prior to randomization and first injection of study drug(s) for WOCBP only. Additional local urine pregnancy tests may be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period.

i Follicle-stimulating hormone test performed at Visit 1 for women at least 40 years of age in whom confirmation of menopause is necessary (Section 6.1).

j The CKD-EPI equation will be used by the central laboratory to estimate and report eGFR.

k Pharmacogenetic sample will be collected 1 time only, at randomization (Visit 2).

l At Visit 2, patients should be observed injecting the first dose of study medication (the entire solution in the single dose pen) under the supervision of the investigator site. After Visit 2, injection instructions will be reviewed as needed.

m Patient-reported outcomes should be completed before any other visit procedures if the patient is not adversely affected by the fasting condition resulting in hypoglycemia. In this case, the patient can complete the PROs after recovery of the event.

n Approximately 54 months (Visit 30) of treatment are planned. If required, additional visits will occur beyond 54 months. Additional visits after Visit 30 will occur every 3 months. The visits occurring after Visit 30 will follow the Extended Maintenance Visit schedule in sequence (EVa, EVb, EVc, EVd) then repeat.

o Patients discontinuing from the study prematurely per criteria outlined in Section 8.2 should complete an early termination visit (ETV), followed by a post-ETV 1 month later, and follow up for annual vital status should be entered into the eCRF (see Section 8.2).

p There are 3 types of Unscheduled Visits (UV):

- Unscheduled Visits (UV) – Unscheduled Visit per investigator discretion. The study site will determine if fasting status is needed prior to the visit. Concomitant medications, adverse events, and endpoint events are required and should be recorded in the eCRF.
- Dosing Unscheduled Visit (UV) (required use of IWRS unscheduled A / B visit starting at Visit 14) – these visits will include dose re-escalation and dose restart (reinitiation). The study drug must be restarted when it is safe to do so and only on a clinic visit. This visit must include collection of concomitant medications, pulse rate and blood pressure, endpoint events, and adverse events in the eCRF. The subsequent dosing visits will be scheduled every 4 weeks (±7 days) until maximum tolerated dose is achieved.
- Phone Follow-up Dosing Unscheduled Visit (UV) – these visits are optional phone visits.

NOTE: If an Unscheduled Visit (UV) visit falls on a regularly scheduled visit, the additional procedures in the Unscheduled Visit (UV) will be included.

q It is expected that patients who do not reach the maximum dose during the initial dose escalation for any reason, should be offered the opportunity to undergo up to 2 additional dose escalations to reach the maximum dose. Patients who participate in an additional dose escalation will be scheduled to attend additional visits at 4-week intervals (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B visit starting at Visit 14] and subsequent dosing visits) to allow for dose escalation until the maximum tolerated dose is reached. Optional telephone dosing unscheduled (UV) visits can be performed approximately 2 weeks after each dose escalation.

r Unscheduled Visit: laboratory tests may be drawn according to investigator discretion or to repeat laboratory tests as needed.

s A local urine pregnancy test will be performed at the time of permanent study drug discontinuation (i.e., at the end of relevant systemic exposure).

3. Introduction

3.1. Study Rationale

Study I8F-MC-GPGN (GPGN), also known as SURPASS-CVOT, is designed to examine the cardiovascular (CV) safety of tirzepatide. SURPASS-CVOT is a Phase 3, event-driven, multicenter, international, randomized, double-blind, active comparator, parallel-group study. This study will assess the effect of once weekly (QW) tirzepatide (up to 15 mg) versus QW dulaglutide (1.5 mg) on CV outcomes when added to standard of care in type 2 diabetes mellitus (T2DM) patients with established cardiovascular disease (CVD) and elevated risk for major adverse cardiovascular events (MACE).

The target dose for all patients in the tirzepatide arm is 15 mg following gradual dose escalation schedule.

Dulaglutide was selected as the active comparator for the current study. In the REWIND study, dulaglutide reduced MACE composite outcomes, which comprised nonfatal myocardial infarction (MI), nonfatal stroke, and death from CV causes, in patients with T2DM with elevated CV risk (Gerstein et al. 2019).

The population of the study includes T2DM patients with established CVD only. Patients with higher CV risk are likely to benefit most from tirzepatide due to the experiences with other incretins, as well in terms of absolute risk reduction.

Myocardial infarction, stroke, or death from CV causes (MACE-3) have been selected as the primary outcome. The components of MACE-3 represent the most devastating CV complications of T2DM and are the primary target of prevention. Secondary outcomes include various glycemic, body weight/composition, renal, biochemical, and health outcome endpoints relevant to the study population.

SURPASS-CVOT fulfills the present requirement of regulatory agencies. The present CV outcome study is to confirm the CV safety of tirzepatide and to generate data to assess the cardioprotective effect of tirzepatide in patients with T2DM.

3.2. Background

Type 2 diabetes mellitus is a metabolic condition characterized by impaired glycemic control caused by increased insulin resistance, progressive beta cell failure, and consequently, inadequate insulin secretion. Type 2 diabetes mellitus is associated with comorbidities such as increased weight or obesity, hypertension, dyslipidemia, and a higher risk for macro and microvascular complications.

Two incretin hormones play an important role in the pathophysiology and potentially in the therapy of T2DM: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Glucagon-like peptide-1 is a hormone that is synthesized in the L cells, mainly in the distal ileum, and released in response to a meal. It acts to increase pancreatic insulin secretion in response to glucose, suppress glucagon secretion, and suppress appetite through a central effect. Patients with T2DM have reduced secretion of GLP-1 in response to

meals, and this defect contributes to reduced insulin secretion, increased glucagon secretion, and hyperglycemia (Verspohl 2009).

Glucose-dependent insulinotropic polypeptide is secreted from enteroendocrine K cells and, like GLP-1, is a potent stimulator of glucose-dependent insulin secretion. The reduced insulin-secreting incretin effect in T2DM could also be due to the markedly reduced insulinotropic response of beta cells to GIP. While GLP-1 secretion and activity are preserved in T2DM, it appears that this endogenous GIP exposure is insufficient to trigger a physiological GIP response (Nauck 2011; Asmar et al. 2016; Nauck et al. 2017).

Recently, GLP-1 receptor agonists (RAs) have been used for the treatment of T2DM. The metabolic effects of GLP-1 RAs can be enhanced by combining them with the actions of other enteropancreatic hormones. Glucose-dependent insulinotropic polypeptide stimulates insulin secretion in a glucose-dependent manner and may exert actions beyond its role as an incretin that may improve therapeutic efficacy when combined with GLP-1 RAs (eg, improved lipid homeostasis and whole-body energy metabolism) (Asmar et al. 2016; Nauck and Meier 2018).

In general, glycemic control through appropriate lifestyle modifications, such as diet, exercise, weight loss, and glucose-lowering medications, is the mainstay of treatment for T2DM. In addition to glycemic control, several agents in the GLP-1 RA and sodium-glucose cotransporter-2 inhibitor (SGLT-2i) classes have shown macrovascular protection with a reduction in MACE or hospitalization for heart failure (HF) (Zinman et al. 2015; Marso et al. 2016a, 2016b; Hernandez et al. 2018; Gerstein et al. 2019). In the recently completed REWIND study, the GLP-1 RA dulaglutide reduced the occurrence of a composite of CV death, MI, or stroke compared to placebo (Gerstein et al. 2019).

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the GIP receptor and the glucagon-like peptide-1 receptor (GLP-1R). Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety (Coskun et al. 2018). It is administered QW by subcutaneous (SC) injection. As a dual GIP/GLP-1 RA, tirzepatide could exceed the efficacy of currently available selective GLP-1R analogs by recruiting metabolically active tissues not targeted by selective GLP-1R analogs (eg, adipose tissue as indicated by the observation of increased energy utilization) (Baggio and Drucker 2007). In addition, tirzepatide may be also superior in regulation of energy balance through greater effect on appetite/food control and energy utilization versus selective GLP-1 RAs (Coskun et al. 2018). Moreover, tirzepatide has the potential to reach higher glucose-lowering efficacy in target tissues, such as insulin-producing pancreatic beta cells that express both GIP receptor and GLP-1R, before reaching its therapeutic limitation.

Three tirzepatide clinical studies have completed dosing and analysis: 1 Phase 1 study, Study I8F-MC-GPGA (GPGA), and 2 Phase 2 studies, Study I8F-MC-GPGB (GPGB) and Study I8F-MC-GPGF (GPGF).

Phase 1 Study GPGA was a combination of a single-ascending and multiple-ascending dose study in healthy patients and a multiple dose study in patients with T2DM. Study GPGA investigated safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of

tirzepatide administered as SC injections. A total of 142 patients (89 healthy patients and 53 patients with T2DM) received at least 1 dose of treatment. Doses of tirzepatide ranged from 0.25 mg to 8 mg in the single-ascending dose (with maximum tolerated dose achieved at 5 mg); multiple doses from 0.5 mg to 4.5 mg QW; titrated doses up to 10 mg QW for 4 weeks in healthy patients; and multiples doses at 0.5 mg and 5 mg QW and titrated to 15 mg QW for 4 weeks in patients with T2DM have been investigated in the multiple-ascending dose study.

The safety, tolerability, and PK/PD profiles of tirzepatide at doses and escalation regimens administered in this Phase 1 study supported further development of tirzepatide for QW dosing in patients with T2DM.

A 26-week Phase 2 study (GPGB) assessed the efficacy, tolerability, and safety of 4 doses (1 mg, 5 mg, 10 mg, and 15 mg) of tirzepatide QW versus placebo and an active comparator (dulaglutide 1.5 mg) in 318 patients with T2DM with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy. The doses of 10 mg and 15 mg were attained by titration (Frias et al. 2018). Additionally, a 12-week, placebo-controlled study (GPGF) assessed the efficacy of 3 different dose escalation schemes to attain doses as high as 15 mg in patients with T2DM.

Study GPGB demonstrated that 5 mg, 10 mg, and 15 mg tirzepatide doses significantly lowered hemoglobin A1c (HbA1c) and body weight in a dose-dependent manner in patients with T2DM in comparison to placebo. In addition, reductions in HbA1c in the tirzepatide 5 mg, 10 mg, and 15 mg doses were greater than with dulaglutide 1.5 mg QW. Relative to placebo, the reduction in HbA1c from baseline to 26 weeks was greater with tirzepatide, across all 3 doses, in a dose-dependent manner. Mean HbA1c changes with tirzepatide versus placebo were -1.67% (-1.88 to -1.46) for 5 mg, -1.83% (-2.04 to -1.61) for 10 mg, and -1.89% (-2.11 to -1.67) for 15 mg. Compared with dulaglutide (-1.21% versus placebo), the mean differences were -0.52% (-0.72 to -0.31) for 5 mg, -0.67% (-0.89 to -0.46) for 10 mg, and -0.73% (-0.95 to -0.52) for 15 mg tirzepatide, respectively. In this study population of patients with T2DM, tirzepatide reduced body weight by 4.8 kg, 8.7 kg, and 11.3 kg at dose levels of 5 mg, 10 mg, and 15 mg, respectively, while the weight loss observed in patients on dulaglutide or on placebo was 2.7 kg and 0.4 kg, respectively. Changes in triglyceride concentration ranged from -0.5 mmol/L to -0.8 mmol/L for tirzepatide 5 to 15 mg (versus 0.3 mmol/L for placebo and -0.3 mmol/L for dulaglutide). Similar to the GLP-1 RA class and the Phase 1 study, most of the tirzepatide adverse events (AEs) were gastrointestinal (GI)-related, consisting mainly of nausea, vomiting, and diarrhea, and were dose-dependent. The GI AEs were usually mild to moderate in intensity. Serious adverse events (SAEs) were balanced across the treatment groups and none of the groups in the study reported severe hypoglycemia (Frias et al. 2018).

As it was recognized that the dose escalation scheme employed in Study GPGB was unlikely to be optimal for the reduction of GI-related AEs expected with tirzepatide, Study GPGF was designed to explore alternative dose escalation schemes (longer time intervals between dose escalations and different dose escalations) to support evaluation of optimized dosing regimen(s) in Phase 3. The results suggest that slower, stepwise escalation of tirzepatide at initiation can improve its tolerability and enable evaluation of the 5 mg, 10 mg, and 15 mg doses of tirzepatide.

The Phase 2 data have demonstrated clinically significant improvements in glucose homeostasis and beta cell function accompanied with marked weight reduction, improvements in lipoprotein profile, and small incremental blood pressure (BP) reduction with an acceptable safety profile. These data support continued development of tirzepatide as a therapy for patients with T2DM and for assessment of CV protection.

Dulaglutide 1.5 mg QW has been chosen as active comparator to tirzepatide. In the REWIND study, the addition of dulaglutide 1.5 mg QW versus placebo to the medical regimen of patients with T2DM, various levels of glycemia, and increased CV risk, improved glycemic control and reduced weight, BP, and MACE incidences over a 5-year period (Gerstein et al. 2019).

The planned premarketing application for tirzepatide consists of a meta-analysis of Phase 3 studies to satisfy the Food and Drug Administration (FDA) requirement to discharge excess CV risk by demonstrating the upper bound of the 95% confidence interval (CI) for MACE for tirzepatide versus comparators is less than 1.8. For this assessment, the primary endpoint is the composite of CV death, MI, stroke, or hospitalization for unstable angina (MACE-4). Provided that the upper bound of the 95% CI for MACE-4 in the meta-analysis is between 1.3 and 1.8, according to FDA guidance, a post-marketing trial may be necessary to definitively show that the upper bound of the 2-sided 95% CI for the estimated risk ratio is less than 1.3 when compared to placebo. Additionally, in the present study (SURPASS-CVOT), the sponsor plans to assess both noninferiority (NI) and superiority of tirzepatide to the active comparator dulaglutide to evaluate CV safety and CV protection of tirzepatide in patients with T2DM.

3.3. Benefit/Risk Assessment

Participation in SURPASS-CVOT is expected to provide a positive benefit-to-risk impact to its participants. The potential benefits from participation in this study include improved glycemic control, frequent expert medical care for an approximately 54-month period, and potential CV protection.

The safety characteristics of tirzepatide in the Phase 2 study were similar to that of dulaglutide. The most common AEs were nausea, vomiting, and diarrhea (Frias et al. 2018). In general, these events were mild or moderate, with few severe events, and transient. Differences between the 5 mg and 10 mg tirzepatide doses and dulaglutide were not clinically meaningful in terms of the frequency of GI AEs or treatment discontinuations, despite their superior glycemic and body weight efficacy. Tirzepatide 15 mg was associated with more GI AEs and an increased frequency of patients discontinuing study treatment early after a relatively short dose escalation period: 5 mg QW for 2 weeks and 10 mg QW for another 4 weeks prior to starting administration of 15 mg QW. Additional Phase 2 data, as well as PK/PD modelling, suggest that slower dose escalation and smaller dose increments might improve tolerability.

Results from Phase 1 and Phase 2 studies also indicate that the potential risks/AEs with tirzepatide are consistent with the GLP-1 RAs. The risks also include the development of potential compound-specific antidrug antibodies, similar to other protein-based therapies. Results from toxicology studies suggest that the safety profile of tirzepatide is consistent with GLP-1

pharmacology. No apparent GIP RA effects have been identified that would suggest additional or differential safety risks.

In clinical trials completed to date, dulaglutide has exhibited the expected GLP-1 RA pharmacological effect on insulin secretion resulting in significant reductions in HbA1c. Dulaglutide administration in patients with T2DM has been associated with reductions in body weight. The most common AEs reported in patients administered dulaglutide are those related to the GI organ class, including nausea and vomiting. Detailed information about the known and expected benefits and risks of dulaglutide may be found in the Trulicity US package insert (Trulicity USPI 2021) and Summary of Product Characteristics (Trulicity SmPC 2021).

Various antihyperglycemic background medications will be used throughout the study. Some agents, like sulfonylureas (SUs) and insulins, may be associated with occurrence of hypoglycemia. This potential risk will be monitored throughout the study and measures will be implemented to reduce the risk of hypoglycemia, including initial dose reduction and/or discontinuation of these agents and frequent dose adjustment at the investigator's discretion.

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

4. Objectives and Endpoints

Table GPGN.2 shows the objectives and endpoints of the study.

Table GPGN.2. Objectives and Endpoints

Objectives	Endpoints
Primary • To assess efficacy of maximally tolerated tirzepatide dose up to 15 mg QW compared to QW dulaglutide 1.5 mg on time to first occurrence of the composite endpoint of death from CV causes, MI, or stroke (MACE-3) when both are added to standard of care in patients with T2DM and high CV risk. • Primary analysis will be an assessment of NI of tirzepatide to dulaglutide for MACE-3. After establishing NI, superiority of tirzepatide compared to dulaglutide for MACE-3 will be evaluated.	• Time to first occurrence of any component event of MACE-3
Key Secondary **<u>Efficacy</u>** • To assess the superiority of tirzepatide up to 15 mg QW compared to dulaglutide 1.5 mg QW.	• Time to death due to any cause • Time to CV death • Time to first occurrence of MI • Time to first occurrence of stroke • Time to first occurrence of the expanded composite CV outcome, defined as either CV death, MI, stroke, coronary revascularization, hospitalization for unstable angina • Cumulative number of CV deaths and total (first and recurrent) HF events requiring hospitalization and/or urgent HF visits

Objectives	Endpoints
Additional Secondary • To assess the superiority of tirzepatide up to 15 mg QW compared to dulaglutide 1.5 mg QW.	• Proportion of patients with more than 10% weight loss from screening after 36 months • Change from baseline in: o weight, BMI, and waist circumference o HbA1c o urinary albumin to creatinine ratio o blood lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides • Time to first occurrence of: o coronary, carotid, or peripheral revascularizations, individually and as composite o hospitalization due to unstable angina o composite endpoint of new or worsening nephropathy • Cumulative number of primary composite events of CV death and total (first and recurrent) MI and/or stroke
Safety • To rule out >30% increase in CV risk with tirzepatide in an indirect comparison to placebo by a direct comparison between tirzepatide and dulaglutide. • To assess the effects of maximally tolerated tirzepatide dose up to 15 mg QW compared to dulaglutide 1.5 mg QW.	• Time to first occurrence of any component event of MACE-3 • Incidence of TEAEs and permanent discontinuation of study drug due to AEs • Incidence of: o pancreatitis o severe gastrointestinal events o any malignancy (including medullary and papillary thyroid cancers) o severe hypoglycemic events o immune-mediated reactions including serious allergic and hypersensitivity reactions o hepatobiliary events (eg, acute cholecystitis, acute cholelithiasis, and drug-induced liver injury) o acute renal failure or exacerbation of chronic renal failure o diabetic retinopathy complications o supraventricular arrhythmias and cardiac conduction disorders • Mean change from baseline: o blood pressure o pulse rate

Objectives	Endpoints
	○ lipase ○ pancreatic amylase ○ calcitonin ○ eGFR
Exploratory The exploratory objectives are to assess the effects of add-on therapy with up to 15 mg tirzepatide compared to dulaglutide 1.5 mg on the following.	• Change of antihyperglycemic drugs • Patient-reported outcome ○ APPADL ○ IW-SP ○ EQ-5D-5L • Time to initiation of insulin of more than 3 months duration for those patients not treated with insulin at study start • eGFR from Cystatin-C.

Abbreviations: AE = adverse event; APPADL = Ability to Perform Physical Activities of Daily Living; BMI = body mass index; CV = cardiovascular; eGFR=estimated glomerular filtration rate; EQ-5D-5L = 5-level EQ-5D; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HF = heart failure; IW-SP= Impact of Weight on Self-Perception; LDL = low-density lipoprotein; MACE-3 = major adverse cardiovascular events composite of myocardial infarction, stroke, or death from cardiovascular causes; MI = myocardial infarction; NI = noninferiority; QW=once weekly; TEAE = treatment-emergent adverse event; T2DM = type 2 diabetes mellitus.

5. Study Design

5.1. Overall Design

SURPASS-CVOT is a Phase 3, event-driven, multicenter, international, randomized, double-blind, active comparator, parallel-group study. This study will assess the effect of QW tirzepatide, up to 15 mg, on MACE-3, compared to QW dulaglutide 1.5 mg, when added to the standard of care in patients with T2DM with established CVD and elevated risk for MACE.

In addition to study drug, all patients should receive standard of care for their diabetes and CV disease.

The study comparison is between tirzepatide and dulaglutide. Assignment to tirzepatide or dulaglutide will be randomly allocated in a 1:1 ratio. Randomization will be stratified by country of enrollment and SGLT-2i use (Yes/No) at baseline.

The starting dose of tirzepatide is 2.5 mg QW, which is to be escalated at 4-weekly intervals to a maximum of 15 mg QW or to the highest maintenance dose tolerated by the patient (see Section 7). The dose of dulaglutide will be initiated and maintained at 1.5 mg QW. To maintain blinding, a sham escalation of dulaglutide will be employed.

In order to reduce risk of hypoglycemia, specific, individually tailored adjustments of the respective antihyperglycemic medications should be considered during the entire study. At Visit 2, with the initiation of study drug, the dose adjustments to the following concomitant glucose lowering medications are recommended.

Sulfonylureas: Sulfonylurea dose is recommended to be reduced at least 50% or discontinued, especially if the patient is receiving a low dose at randomization.

Insulins: For patients on basal-only or premixed insulin regimens and with screening HbA1c of ≤8.5%, the daily dose is recommended to be reduced by at least 20%. It is also recommended to convert premixed-insulin treatment to basal-only insulin treatment. The number and the timing of the daily injection(s) should be individually determined at the investigator's discretion.

Irrespective of the screening HbA1c concentration, it is recommended that patients on basal-bolus regimens reduce or discontinue the regular use of pre-meal insulin per investigator discretion at randomization. The investigator may make adjustments to the patient's insulin any time after randomization to maintain appropriate glycemic control.

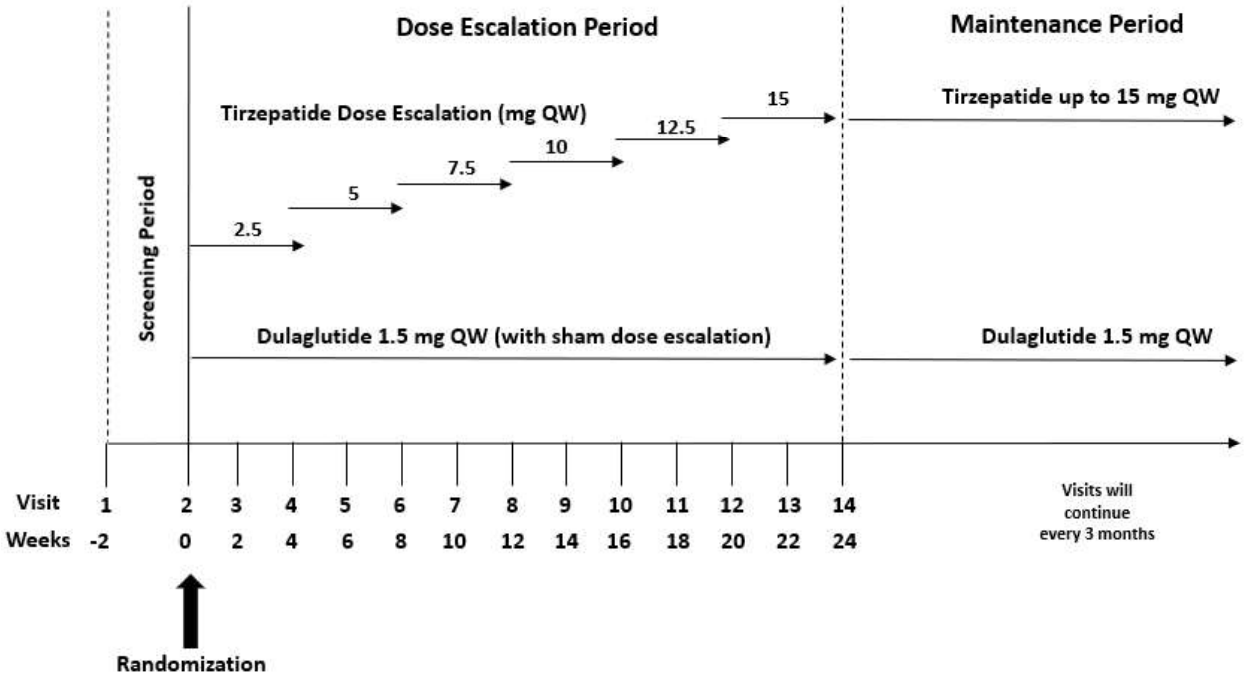
Any time the patient is within a dose escalation, it is not recommended to increase (up-titrate) the total daily dose of insulin, unless required for controlling worsening hyperglycemia and its acute complications.

Once the patient has completed dose escalation and is maintained on a dose of study drug, further insulin dose reduction for the prevention of hypoglycemia is to be considered at the investigator's discretion. In general, insulin doses should be adjusted according to the routine practice of the investigator for optimal glycemic control.

Standard of Care: The standard of care for diabetes and CV disease may be adjusted at the discretion of the investigator as clinically indicated in accordance with local standard of care and professional society guidelines. In order to achieve/maintain glycemic control, antihyperglycemic medications can be used with the exception of GLP-1 RAs and pramlintide. The new introduction of dipeptidyl peptidase-4 (DPP-4) inhibitors is discouraged (Davies et al. 2018).

Study governance considerations are described in detail in Appendix 3.

Figure GPGN.1 illustrates the study design.



Abbreviation: QW= once weekly.

Figure GPGN.1. Illustration of study design for Study I8F-MC-GPGN (SURPASS-CVOT).

Patients 40 years of age or older who have T2DM treated either with lifestyle or with various antihyperglycemic regimens, have an HbA1c value ≥7.0 (≥53 mmol/mol) and ≤10.5 (≤91.3 mmol/mol) at screening, and have established CVD, will be eligible to participate in this trial. Postscreening, patients who are deemed eligible, as assessed by inclusion and exclusion criteria, will be randomized in a 1:1 ratio to either tirzepatide or dulaglutide 1.5 mg injected SC QW (Figure GPGN.1). At Visit 2, the patient will inject the first dose of study drug at the study site.

For patients randomized to tirzepatide, the starting dose will be 2.5 mg QW with dose escalation every 4 weeks at 2.5 mg increments (2.5 mg to 5 mg to 7.5 mg to 10 mg to 12.5 mg to 15 mg) until the 15 mg dose is reached, or to the highest maintenance dose tolerated by the patient (5 mg or 10 mg).

For patients randomized to dulaglutide, the 1.5 mg QW dose is started at Visit 2 (randomization) and maintained throughout the study. However, in order to maintain blinding, patients in the dulaglutide treatment group will also be dispensed study drug every 4 weeks during the dose escalation period, following a sham dose escalation schedule to match the tirzepatide treatment group.

During a dose escalation, if a telephone visit is deemed necessary to support patient compliance, this is allowable at the discretion of the investigator site personnel. Optional telephone visits can be performed approximately 2 weeks after starting study drug and after each dose increase.

To optimize the number of patients who achieve the maximum dose, both tirzepatide and dulaglutide, it is expected that patients who do not reach the maximum dose during the initial dose escalation for any reason and/or have de-escalated their dose after the initial dose escalation, should be offered the opportunity to undergo up to 2 additional attempts for dose escalations. Patients who participate in an additional dose escalation will be scheduled to attend additional visits at 4-week intervals (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B visit starting at Visit 14] and subsequent dosing visits) to allow for dose escalation until the maximum tolerated dose is reached. Optional Phone Follow-up Dosing unscheduled visits (UV) can be performed approximately 2 weeks after each dose escalation. For study drug restart or additional dose escalation at or after V14, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate drug supply at the site. Dosing visits at or after V14 can be performed at scheduled or unscheduled visits.

Patients will be followed for CV outcomes and other measures every 4 weeks for the first 24 weeks and then followed approximately every 3 months thereafter. In order to prevent hypoglycemia risk at study drug initiation, management of glycemic control is recommended based on the guidance as previously described for the first 24 weeks postrandomization (dose escalation period) and thereafter at the discretion of the study investigator and informed by current guidelines and routine patient management. Either the study investigator or the patient's usual physician(s) will manage other CV risk factors and comorbid conditions (depending on local arrangements). The primary analysis of this study is an intention-to-treat (ITT) analysis using modified intention-to-treat efficacy (mITTE) population; therefore, every patient in mITTE population will be followed until the patient's "end-of-follow-up," regardless of compliance with study drug and adherence to study visit schedule.

Approximately 12,500 patients will be enrolled at approximately 650 sites globally and randomized to 1 of 2 treatment groups: tirzepatide or dulaglutide 1.5 mg. Patients will be randomized in a 1:1 ratio to tirzepatide or dulaglutide using country of enrollment and SGLT-2i use (Yes/No) at baseline as stratification factors. Patients will be followed until at least 1615 patients experience a primary endpoint event, centrally adjudicated as such. This is projected to occur after an average of approximately 48 months of follow-up. The trial may be stopped earlier on the basis of an Independent Data Monitoring Committee (IDMC) safety review or for efficacy at the interim analysis.

Patient compliance with study drug and adherence to study visits and procedures will be vitally important to meet the study objectives. This will be emphasized through comprehensive site training and consistently monitoring patient retention throughout the duration of the study.

Details regarding the study procedures at each visit are presented in the Schedule of Activities (Section 2). A study duration of approximately 54 months is planned, but duration depends on accrual of the requisite number of patients experiencing at least 1 component of the primary endpoint. Consequently, additional visits may be required beyond the planned duration. These additional visits, similar to visits during the maintenance period, will occur every 3 months. Study drug dispensing will occur at Visit 2 (randomization), Visit 4, Visit 6, Visit 8, Visit 10, Visit 12, Visit 14, and every scheduled visit thereafter (Section 2) except for the early termination visit (ETV), post-ETV, and final visit.

Please refer to the Schedule of Activities (Section 2) for procedures associated with screening, randomization, dose escalation, and maintenance periods.

Remote visits may be considered at the discretion of the investigator if a patient is unable to come to their scheduled on-site visit. If a remote visit occurs, this should be entered in the patient's eCRF. Alternative options to visit procedures must be considered with prior consultation and written approval of the sponsor.

The progress toward the goal of 1615 patients with at least 1 component of the primary endpoint will be monitored during the study based on blinded data. Approximately 3 months prior to the anticipated date of attaining 1615 events, a study close-out period will be declared. During the study close-out period, a final visit will be planned for each patient with exception of patients who have died or prematurely discontinued from the study (Section 8.2). Study procedures for the final visit will be performed as outlined in the Schedule of Activities (Section 2) whenever possible.

If an on-site clinic or remote final visit with the patient is not possible, contact with the patient's family or the patient's primary physician or medical record review during the close out period of the study to ascertain vital status and record safety and efficacy endpoints is required. National registries/databases, medical records, voter records, third-party patient locator services, or other means may be used to ascertain this information. At a minimum, vital status (alive or dead) should be ascertained for all randomized study participants, including participants who are considered high risk of being lost to follow-up or participants who have withdrawn consent.

Note: If the investigator site personnel are unable to contact the patient, they may give the patient's name and last known contact information to a patient locator service to try to find current information, if not prohibited by local laws and regulations. The patient locator service will **not** contact the patient directly and any new information they find will be shared with investigator site personnel.

All unused study drug (unused single dose pens) must be returned for compliance and final drug accountability to be recorded in the eCRF. The sharp items container should also be returned to site or disposed of per local regulations.

5.2. Number of Participants

This is an event-driven study. As such, approximately 12,500 participants will be followed for a mean duration of approximately 4 years until at least approximately 1615 patients experience at least 1 component of the primary composite endpoint of MACE-3.

5.3. End of Study Definition

The end of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last active patient.

5.4. Scientific Rationale for Study Design

SURPASS-CVOT is designed to examine the CV safety of tirzepatide. SURPASS-CVOT is a Phase 3, event-driven, multicenter, international, randomized, double-blind, active comparator, parallel-group study. This study will assess the effect of QW tirzepatide (up to 15 mg) versus dulaglutide (1.5 mg) on CV outcomes when added to standard of care in patients with T2DM with established CVD and elevated risk for MACE.

The target dose for all patients in the tirzepatide arm is 15 mg, as this dose has demonstrated the most benefits for patients in the Phase 2 program. Due to the GI intolerance observed at initiation and escalation to higher doses of tirzepatide in the Phase 2 program (Frias et al. 2018), similar to the ongoing Phase 3 program, the current study applies a longer, more gradual dose escalation and reinitiation algorithm than the Phase 2 studies. Consequently, due to the evaluation of GI tolerability and the dispensing of different strengths of tirzepatide, 4-week visits are scheduled during the first 24 weeks of the study. Optional phone visits further assure the proper escalation of the study drug. Similarly, a 4-week visit schedule will support the reintroduction of the study drug after temporary interruption for any reason and during an additional dose escalation.

In the rest of the study, 3-month visit intervals are scheduled for drug dispensing and clinic visits. Patients are allowed to be on lower maintenance doses of tirzepatide (5 mg or 10 mg) due to GI intolerance. To optimize the number of patients who achieve the maximum dose, both tirzepatide and dulaglutide, it is expected that patients who do not reach the maximum dose during the initial dose escalation for any reason and/or have de-escalated their dose after the initial dose escalation, should be offered the opportunity to undergo up to 2 additional attempts for dose escalations. Patients who participate in an additional dose escalation will be scheduled to attend additional visits at 4-week intervals (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B visit starting at Visit 14] and subsequent dosing visits) to allow for dose escalation until the maximum tolerated dose is reached. Optional Phone Follow-up Dosing unscheduled visits (UV) can be performed approximately 2 weeks after each dose escalation. For study drug restart or additional dose escalation at or after V14, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate drug supply at the site. Dosing visits at or after V14 can be performed at a scheduled or unscheduled visit.

Dulaglutide was selected as the active comparator for the current study. In the REWIND study, dulaglutide reduced MACE-3 in patients with T2DM with elevated CV risk (Gerstein et al. 2019). Recently, several previous cardiovascular outcomes trials (CVOTs) investigating GLP-1

RAs have demonstrated CV protection versus placebo (see below). These results create opportunities to compare tirzepatide to dulaglutide as a licensed GLP-1 RA with CV benefit, and thus ensure that all study participants in the control group will have access to state of the art cardioprotective diabetes care. Dulaglutide is produced by the same manufacturer and is available in an identical proprietary injection device and optic as tirzepatide, allowing the double-blind design of the current study.

To date, all GLP-1 RAs and SGLT-2i investigational drugs in CVOTs in patients with T2DM have been compared with placebo in addition to standard of care in all patients and in the respective populations (Zinman et al. 2015; Marso et al. 2016a, 2016b; Hernandez et al. 2018; Gerstein et al. 2019). The standard of care for patients with T2DM and increased CV risk consists, among others, of an optimal combination of antihyperglycemic medications and drugs for CV prevention. In CVOTs investigating GLP-1 agonists, the use of GLP-1 agonists was not allowed in the placebo arm. This study design has been widely accepted, as the placebo group could also be treated optimally, according to local practice and international guidelines.

Recent results of several CVOTs, including trials with SGLT-2 inhibitors and GLP-1 RAs, have demonstrated risk reduction of MACE in patients with T2DM and high CV risk (Zinman et al. 2015; Marso et al. 2016a, 2016b; Hernandez et al. 2018; Gerstein et al. 2019). In part, due to these studies, the American Diabetes Association (ADA 2017) and European Association for the Study of Diabetes working groups suggest that GLP-1 RAs should be considered for treatment of patients with T2DM and atherosclerotic CVD (Davies et al. 2018). On the other hand, SGLT-2 inhibitors are suggested as treatment for those at high risk of HF or with progressive decline in estimated glomerular filtration rate (eGFR) (Davies et al. 2018; Home 2019). These drug classes are being considered as part of a future standard of care for patients with T2DM and prompt rethinking of future CVOT designs for this population. Thus, long-term studies of patients with T2DM and high CV risk that include control groups without access to GLP-1 RAs and/or SGLT-2 inhibitors raise potential ethical considerations. Studies of new incretin-based drugs or SGLT-2 inhibitors that prohibit the use of 1 of these 2 antihyperglycemic therapies in a placebo group can be challenged since these treatments have demonstrated benefit on CV outcomes. An alternative design that addresses these potential ethical challenges and risk-benefit considerations is a head-to-head comparison of the investigational product with a drug of the same or comparable class that has demonstrated CV benefit.

Dulaglutide is a QW GLP-1 RA for the treatment of T2DM. By contrast with native GLP-1, dulaglutide is resistant to DPP-4 degradation and has a large molecular weight that slows absorption and minimizes renal clearance. This results in a soluble molecule with a prolonged half-life of about 5 days, suitable for QW SC administration. Findings from Phase 3 trials showed that QW dulaglutide 1.5 mg treatment added to various baseline and concomitant use of antihyperglycemic medications resulted in the reduction of HbA1c with weight loss and a safety and tolerability profile that is consistent with the GLP-1 RA class. Dulaglutide has also been shown to have significant, sustained effects on both fasting and postprandial glucose concentrations (Umpierrez et al. 2014; Zhang et al. 2016). In a recently completed CVOT

(REWIND), QW dulaglutide 1.5 mg significantly reduced the incidence of MACE-3 when compared with placebo in patients with T2DM on standard of care (Gerstein et al. 2019).

Both dulaglutide and tirzepatide can be administered QW in a double-blinded manner. The tolerability of both drugs is similar to other agents in the GLP-1 RA class: the treatment initiation can frequently be associated with GI side effects such as nausea, vomiting, and diarrhea. Moreover, both tirzepatide and dulaglutide are highly effective in improving glycemic control.

Patients can be assured that they receive either tirzepatide (potential CV benefit) or dulaglutide (proven CV benefit) during the entire study duration, which can help to maintain high study compliance. In addition, the effective glycemic control as well as potential appearance of GI side effects, unlike in a placebo comparator design, do not unmask the blinded medications for patients or study personnel. Importantly, the portfolio of antihyperglycemic treatments during the study course includes a broad range of drugs: any regimen of insulins, metformin, SUs, SGLT-2 inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, or others. Sodium glucose cotransporter 2 inhibitors particularly, with proven benefit for preventing congestive heart failure (CHF) and deterioration of renal function, can also be used. The use of DPP-4 inhibitors in combination with GLP-1 RAs is discouraged (Davies et al. 2018). The use of GLP-1 RAs and pramlintide is not allowed.

The population of the study includes patients with T2DM with established CVD only. The active comparator design will reduce the occurrence of MACE. Thus, patients with higher risk for MACE are necessary to achieve the event-driven endpoints. In addition, patients with higher CV risk are likely to benefit from tirzepatide due to the experiences with other incretins.

MACE-3 has been selected as the primary outcome. MACE-3 represents the most devastating CV complications of T2DM and is the primary target of prevention. Secondary outcomes include various glycemic, body weight/composition, renal, biochemical, and health outcome endpoints relevant to the study population.

The SURPASS-CVOT trial fulfills the present requirement of regulatory agencies. The FDA has issued guidance on evaluating CV risk in new antidiabetic therapies to treat patients with T2DM (FDA 2008). Additionally, since 2012, the European Medicines Agency (EMA)’s guidance for the development of diabetes products has outlined the expectation for development programs to provide sufficient information to support a lack of drug-induced excess CV risk for new products (EMA 2012). For a premarketing application that contains a meta-analysis of MACE, for which the upper bound of the 95% CI for the relative risk comparing investigational drug and placebo is between 1.3 and 1.8, a postmarketing trial is necessary to definitively show that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the investigational drug and placebo is less than 1.3. This CV outcome study is to confirm the CV safety of tirzepatide and to generate data to assess the cardioprotective effect of tirzepatide in patients with T2DM.

Based on the assumptions gleaned from differences in mechanism of action and clinical and biochemical surrogate markers, tirzepatide may be more effective in CV prevention than dulaglutide. In order to evaluate any clinically meaningful differences between the 2 drugs, a large number (at least 1615) of patients with MACE-3 need to be observed in the study. This is

possible if the study population includes vulnerable patients with uncontrolled T2DM. Despite the recent introduction of better treatment options, this population still has high incidence of morbidity and mortality, has significant unmet need, and could benefit from new treatment options for improved glycemic control without increased risk of severe hypoglycemia and prevention of MACE.

This study is designed to determine the comparative CV benefits and risks of QW tirzepatide up to 15 mg versus QW dulaglutide 1.5 mg in patients with T2DM with established CVD. An active comparator of the incretin drug, dulaglutide, rather than placebo was selected for this trial because it includes patients with uncontrolled T2DM despite oral antihyperglycemic therapies and increased risk for CVDs who will be studied for a longer period, approximately 4 years. Tirzepatide, as a dual GIP and GLP-1 RA, represents a new class in the incretin family, which also includes the selective GLP-1 RAs. The numerous clinical effects of tirzepatide are similar to GLP-1 RAs, although the effects on glycemic control, weight reduction, and triglyceride concentrations may be greater. Similar to GLP-1 RAs, tirzepatide treatment also resulted in a small decrease in diastolic and systolic BP despite baseline values in the normotensive range (Frias et al. 2018).

5.5. Justification for Dose

Tirzepatide doses of up to 15 mg administered SC QW will be evaluated in this study.

Patients may be treated with lower maintenance doses of 5 mg or 10 mg if they do not achieve full dose escalation to 15 mg and/or do not tolerate 15 mg.

These doses and associated escalation schemes were selected based on assessment of safety, efficacy (glycemic and weight loss benefit), and GI tolerability data followed by exposure response modeling of data in patients with T2DM in Phase 1 and Phase 2 studies. Dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5 mg increments every 4 weeks should permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns.

The dose selection of tirzepatide is based on the findings of the Phase 2 study results. Tirzepatide doses of 5 mg, 10 mg, and 15 mg QW have been tested and compared with dulaglutide 1.5 mg QW or placebo in a Phase 2 study (Frias et al. 2018). While all 3 doses of tirzepatide significantly improved the glycemic control versus dulaglutide, the largest difference was observed in the 15-mg tirzepatide treatment group. Moreover, the reduction in body weight on tirzepatide was also dose-dependent and greatest in the 15-mg QW treatment group.

6. Study Population

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria at screening:

[1] Men or women at least 40 years old with a diagnosis of T2DM (WHO 2019)

[2] Established CVD, including at least 1 of the following (a through c):

a. Coronary artery disease (CAD) with ANY of the following:
- Documented history of spontaneous MI
- ≥50% stenosis in 1 or more major coronary arteries, determined by invasive angiography
- ≥50% stenosis in 2 or more major coronary arteries, determined by computed tomography coronary angiography (CTCA)
- History of surgical or percutaneous coronary revascularization procedure

b. Cerebrovascular disease – ANY of the following:
- Documented history of ischemic stroke
- Carotid arterial disease with ≥50% stenosis, documented by carotid ultrasound, magnetic resonance imaging (MRI), or angiography
- Carotid stenting or surgical revascularization

c. Peripheral arterial disease with EITHER of the following:
- Intermittent claudication and ankle-brachial index <0.9
- Prior nontraumatic amputation or peripheral vascular procedure (eg, stenting or surgical revascularization), due to peripheral arterial ischemia

Note: Supporting medical documentation is required in all instances (a, b, and c above)

[3] HbA1c ≥7% (≥53 mmol/mol) and ≤10.5% (≤91.3 mmol/mol) based on central laboratory assessment at screening

[4] Body mass index (BMI) ≥25 kg/m^2

[5] At the time of signing the informed consent:

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

Male patients:

Men, regardless of their fertility status, with nonpregnant women of childbearing potential (WOCBP) partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms, as well as 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral

contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days following the last dose of study drug.

a) Men and their partners may choose to use a double–barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined).
b) Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of the estimated relevant potential exposure in WOCBP (90 days).

Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days following the last dose of study drug.

Men who are in exclusively same-sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

Female patients:

Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Otherwise, WOCBP participating must agree to use 2 forms of effective contraception, where at least 1 form is highly effective (less than 1% failure rate), for the entirety of the study. Contraception must continue following completion of study drug administration for the entirety of the study and for 30 days thereafter.

a) WOCBP participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.
b) Two forms of effective contraception, where at least 1 form is highly effective, (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) will be used. Effective contraception (such as male or

female condoms with spermicide, diaphragms with spermicide, or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (ie, condom with spermicide, diaphragm with spermicide, or female condom with spermicide). It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Women not of childbearing potential may participate and include those who are:

c) infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis, or
d) postmenopausal – defined as either
   i. A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL; or
   ii. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
   iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

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

- learn how to self-inject treatment (tirzepatide or dulaglutide), as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug),
- inject study drug QW,
- have a sufficient understanding of 1 of the provided languages of the country such that they will be able to complete the patient questionnaires, and
- make themselves available for the duration of the study, and who will comply with the required study visits.

Informed Consent

[7] Capable of giving signed informed consent as described in Appendix 3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

Medical Conditions

[8] Have type 1 diabetes mellitus

[9] Have uncontrolled diabetes requiring immediate therapy (such as diabetic ketoacidosis) at screening or randomization, in the judgment of the physician

[10] Have had 1 or more events of severe hypoglycemia and/or 1 or more events of hypoglycemia unawareness within 6 months prior to screening

[11] Are currently planning treatment for diabetic retinopathy and/or macular edema.

[12] Have been hospitalized for CHF within 2 months prior to screening

[13] Have chronic New York Heart Association Functional Classification IV CHF

[14] Are currently planning a coronary, carotid, or peripheral artery revascularization

[15] Had chronic or acute pancreatitis any time prior to screening, irrespective of etiology

[16] Have a known clinically significant gastric emptying abnormality such as severe gastroparesis or gastric outlet obstruction, or have undergone or currently planning any gastric bypass (bariatric) surgery or restrictive bariatric surgery

[17] Have acute or chronic hepatitis, signs or symptoms of any other liver disease, an alanine aminotransferase (ALT) level ≥3X the upper limit of normal (ULN) for the reference range, as determined by the central laboratory

Note: Patients with nonalcoholic fatty liver disease are eligible to participate if their ALT level is <3X the ULN for the reference range

[18] Have known chronic severe renal failure (defined as a known eGFR <15 mL/minute/1.73 m^2) or are on chronic dialysis

[19] Have evidence of a significant, uncontrolled endocrine abnormality (eg, thyrotoxicosis or adrenal crises)

[20] Have a family or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (MTC) or personal history of nonfamilial MTC

[21] Have a serum calcitonin level at screening of: (based on central laboratory results)

- ≥20 ng/L at Visit 1, if eGFR ≥60 mL/min/1.73 m^2, or
- ≥35 ng/L at Visit 1, if eGFR <60 mL/min/1.73 m^2

[22] Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy for less than 5 years. An exception for this criterion is basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer

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

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

[25] Have any other condition (eg, hypersensitivity) that is a contraindication to any incretin or GLP-1 RAs

[26] Have had an MI, percutaneous coronary revascularization procedure, ischemic stroke, carotid stenting or surgical revascularization, nontraumatic amputation, or peripheral vascular procedure (eg, stenting or surgical revascularization) less than 60 days prior to screening

[27] Have had coronary artery bypass graft surgery less than 5 years prior to screening

[37] Have had a blood transfusion or severe blood loss within 90 days prior to screening or have known hematological conditions that may interfere with HbA1c measurement.

Prior/Concomitant Therapy

[28] Treatment with GLP-1 RA or pramlintide, in a period of 3 months prior to Visit 1

[29] Discontinuation of GLP-1 RA or pramlintide, due to intolerability any time prior to Visit 1

[30] Exclusion Criterion [30] has been deleted.

Prior/Concurrent Clinical Trial 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 trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed

[33] Have previously completed or withdrawn from this study or randomized into any other study investigating tirzepatide

Other Exclusions

[34] 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

[35] Are Lilly employees

[36] Are women who are pregnant or breastfeeding

6.3. Lifestyle Restrictions

Per the Schedule of Activities (Section 2), qualified medical staff will provide diabetes management counseling, which will include instructions on diet and exercise and education about the signs, symptoms, and treatment of hypoglycemia, should it occur.

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

Study participants should be instructed not to donate blood or blood products during the study and for 8 weeks following the study.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to an investigational product. 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.

If a patient is not eligible for the trial after the initial screening and is willing to participate, the patient may be rescreened on 2 occasions. All other patients who do not meet eligibility criteria, and do not wish to undergo rescreening, will not participate further. If rescreening is performed, the individual will sign a new consent form and be assigned a new identification number.

7. Treatments

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

7.1. Treatments Administered

Patients who have T2DM treated either with lifestyle or with 1 or more oral antihyperglycemic medication(s) in combination with or without insulin will participate in Visit 1 to assess eligibility in line with the inclusion and exclusion criteria. Patients who are willing and deemed eligible to continue with the regimen of study treatment throughout the duration of the trial will be randomized (Visit 2) to tirzepatide or dulaglutide, while stratified for country of enrollment and SGLT-2i use at baseline.

This table lists the interventions used in this clinical study.

Intervention Name	Tirzepatide	Dulaglutide
Dosage Level(s)	Up to 15 mg QW	1.5 mg QW
Route of Administration	SC injection	SC injection
Authorized as defined by EU Clinical Trial Regulation	Authorized and used according to EU authorization	Authorized and used according to EU authorization

Abbreviations: QW = once weekly; SC = subcutaneous.

At randomization (Visit 2):

- antihyperglycemic medications (SUs and insulins) are recommended to be adjusted as described in Section 5.1,
- self-monitoring of blood glucose (BG) testing supplies will be dispensed,
- BG measurement technique will be reviewed,
- patients will be advised regarding the frequency of self-monitoring of BG testing according to their other medications and the investigator's clinical judgment,
- patients will be instructed on SC administration of study drug, and
- patients will inject the first dose of study drug at the study site.

Tirzepatide and matching dulaglutide 1.5 mg will be provided as a single dose pen for delivery of the investigational product. The single dose pen is intended for single use by the patient. Tirzepatide or dulaglutide 1.5 mg is intended for self-administration as an SC injection in the abdomen or thigh. Assisted injection may also be administered in the upper arm region. Rotation of injection sites is recommended. Tirzepatide or dulaglutide and insulin may be injected in the same body region, but the injections should not be adjacent to each other.

There are no restrictions on the time of day each weekly dose of study drug is given, but it is advisable to administer the SC injections on the same day and same time each week. If

1 injection of study drug is inadvertently missed, the patient should take it as soon as possible unless it is within 72 hours of the next dose, in which case, that injection should be skipped and the next injection should be taken at the appropriate time. The contents of the label will be in accordance with all applicable regulatory requirements.

After randomization, patients will follow a dose escalation schedule in a double-blinded manner over 24 weeks. The starting dose of tirzepatide is 2.5 mg QW, which is to be escalated to a maximum of 15 mg QW, or to the maximum dose tolerated by the patient. To optimize the number of patients who achieve the maximum dose, both tirzepatide and dulaglutide, it is expected that patients who do not reach the maximum dose during the initial dose escalation for any reason and/or have de-escalated their dose after the initial dose escalation, should be offered the opportunity to undergo up to 2 additional attempts for dose escalations. Patients who participate in an additional dose escalation will be scheduled to attend additional visits at 4-week intervals (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B visit starting at Visit 14] and subsequent dosing visits) to allow for dose escalation until the maximum tolerated dose is reached. Optional Phone Follow-up Dosing unscheduled visits (UV) can be performed approximately 2 weeks after each dose escalation. For study drug restart or additional dose escalation at or after V14, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate drug supply at the site. Dosing visits at or after V14 can be performed at a scheduled or unscheduled visit. (see Section 7.4.2).

Dulaglutide 1.5 mg will be injected subcutaneously QW from the start through to the end of the study. No escalation or dose adjustment will occur in the dulaglutide treatment group. However, in order to maintain the double-blind study design, a tirzepatide-matched sham dose escalation schedule will be followed.

Every effort should be made by the investigator to maintain patients on study drug and to restart study drug promptly after any temporary interruption, as soon as it is safe to do so (see Section 8.1.2). The patient will remain in the study to be evaluated for efficacy and safety endpoints and monitored for all visits and testing regardless of whether the patient is taking study drug. The dates of temporary study drug interruption and restart or permanent study drug discontinuation will be documented in the electronic case report form (eCRF).

The investigator or his/her designee is responsible for the following:

- to consider adjusting the dose of antihyperglycemic medications (see Section 5.1) at Visit 2 from first administration of study drug,
- explaining the correct use of the investigational product(s) to the patient,
- verifying that instructions are followed properly,
- maintaining accurate records of investigational product dispensing and collection,
- at the end of the study, returning all unused medication to Lilly or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law,
- record the date of the first dose at Visit 2, and

- record the date of the most recent dose of IP at each study visit on the eCRF.

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

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

7.1.1. Dose Escalation Scheme

For patients randomized to tirzepatide, the starting dose at Visit 2 (randomization) will be 2.5 mg QW for 4 weeks. The dose will then be increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg to 12.5 mg to 15 mg) until the 15 mg dose, or maximum tolerated dose, is reached. The initial dose escalation schedule is considered to be 24 weeks, which allows 20 weeks to escalate to 15 mg tirzepatide and an additional 4 weeks to reach steady-state.

To optimize the number of patients who achieve the maximum dose, both tirzepatide and dulaglutide, it is expected that patients who do not reach the maximum dose during the initial dose escalation for any reason and/or have de-escalated their dose after the initial dose escalation, should be offered the opportunity to undergo up to 2 additional attempts for dose escalations. Patients who participate in an additional dose escalation will be scheduled to attend additional visits at 4-week intervals (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B visit starting at Visit 14] and subsequent dosing visits) to allow for dose escalation until the maximum tolerated dose is reached. Optional Phone Follow-up Dosing unscheduled visits (UV) can be performed approximately 2 weeks after each dose escalation. For study drug restart or additional dose escalation at or after V14, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate drug supply at the site. Dosing visits at or after V14 can be performed at a scheduled or unscheduled visit (see Section 7.4.2).

The objective of the additional dose escalations is to maximize treatment benefits in patients who are not on the 15 mg maintenance dose. A portion of these patients may adapt and better tolerate tirzepatide after approximately 1 year of exposure and could tolerate a higher dose than the originally maximum tolerated dose of 5 mg or 10 mg reached during the first dose escalation period.

For patients randomized to dulaglutide, the 1.5 mg QW dose is started at Visit 2 (randomization) and maintained throughout the study. However, in order to maintain blinding, patients in the dulaglutide treatment group will be dispensed study drug every 4 weeks during the dose escalation period, following a sham dose escalation schedule to match the tirzepatide dose escalation. During additional dose escalations, dulaglutide will also be dispensed following a sham dose escalation schedule to match the tirzepatide dose escalation.

After completing the dose escalation schedule, study drug will be dispensed every 3 months (Schedule of Activities [Section 2]).

The dose escalation scheme has been designed to minimize the development of intolerable GI symptoms. During the 24-week dose escalation period, a telephone visit can be performed approximately 2 weeks after starting study drug and after each dose escalation, if deemed necessary to support patient compliance and safety. Every effort should be made by the investigator to escalate patients to the maximum tolerated dose.

To mitigate GI symptoms and manage patients with intolerable GI AEs, the investigator should:

- Advise patients to eat smaller meals, for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full.
- Consider prescribing symptomatic medication antiemetic or antidiarrheal medication per local country availability and individual patient needs. Use of symptomatic medication should be captured as concomitant medication in the eCRF.
- Omit 1 injection; the patient will take 3 of 4 injections at that dose level.
- Encourage the patient to continue taking medication to alleviate their GI symptoms, as required.

During a dose escalation:

- If the number of consecutive missed injections is 2 or less, the dose escalation will continue as planned.
- If the number of consecutive missed injections is 3 or more, the dose escalation scheme will be restarted at 5 mg and escalation will continue until a maximum tolerated dose is achieved. Patients on dulaglutide will follow sham dose escalation. During the Escalation Period (V2-V14), restarting study drug can only occur at a scheduled study visit. After V14, restarting study drug can occur at a scheduled study visit or at an unscheduled dosing visit (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B visit starting at Visit 14]) (See Section 7.1.1). The data related to temporary interruption of study treatment should be documented in source documents and entered in the eCRF.
- For study drug restart at or after V14, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate drug supply at the site.

7.1.1.1. De-Escalation during Dose Escalation

During any dose escalation, if intolerable GI symptoms or events persist despite the above measures (Section 7.1.1), the investigator may decide to lower or continue study drug on the participant's maximum tolerated dose . For any study drug de-escalation before V14, this can only be done at a scheduled visit. For study drug de-escalation during any visit after V14, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate drug supply at the site. For dosing visits after V14, this can be performed at a scheduled or unscheduled visit.

In the tirzepatide treatment group:

- Patients at 2.5 mg will have study drug temporarily interrupted (Section 8.1.2).
- Patients at 5 mg will have study drug temporarily interrupted or will maintain their current dose (Section 8.1.2).
- Patients at 7.5 mg will have their dose de-escalated to 5 mg.

- Patients at 10 mg will have their dose de-escalated to 5 mg or will maintain their current dose.
- Patients at 12.5 mg will have their dose de-escalated to 10 mg.
- Patients at 15 mg will have their dose de-escalated to 10 mg or will maintain their current dose.

Note: Intermediate doses of 2.5 mg, 7.5 mg, and 12.5 mg will only be used during dose escalations and not be used during a de-escalation, as described in the examples above.

In the dulaglutide treatment group:

- When dose de-escalation is requested due to tolerability issues, the site will follow the same process for a dose de-escalation, but the 1.5 mg dulaglutide dose will be maintained, as this represents the sham dose de-escalation to maintain the blinding.

For both treatment groups:

If de-escalation or maintenance of study drug dose is necessary, the investigator site personnel will use the interactive web-response system (IWRS) to receive the appropriate study drug dispensing information. Patients who have their dose de-escalated or maintained will be offered an opportunity to re-escalate when the investigator deems it appropriate (see Section 7.4.2).

If the GI tolerability issues persist, and if study drug discontinuation is requested, study drug will be temporarily discontinued (see Section 8.1).

Every effort should be made by the investigator to maintain patients on study drug and to restart study drug promptly after any temporary interruption, as soon as it is safe to do so (include procedures in dosing unscheduled visits [UV] in the SoA, Section 2). The dose escalation scheme will be restarted at 5 mg and escalation will continue until a maximum tolerated dose is achieved. Patients on dulaglutide will follow sham dose escalation. During the Escalation Period (V2-V14), restarting study drug can only occur at a scheduled study visit. After V14, restarting study drug can occur at a scheduled study visit or at an unscheduled dosing visit (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B visit starting at Visit 14]). For study drug restart after V14, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate drug supply at the site.

Regardless of whether the patient is taking study drug, the patient will remain in the study to be evaluated for efficacy and safety endpoints and monitored for all visits and tests. The dates of study drug discontinuation, reason for temporary interruption, and dates of restart will be documented in the eCRF.

7.1.2. Packaging and Labeling

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

- Tirzepatide and dulaglutide will be provided in single dose pens.
- Study drug must be stored per label instructions.
- Temperature logs must be maintained to verify correct storage conditions at the investigator site throughout the study.
- Access to and administration of the study drug will be limited to the investigator and authorized site staff (investigator or designee).
- Study drug must be dispensed or administered only to patients enrolled in the study and in accordance with the protocol.
- Patients should be instructed to store the study drug in their refrigerator but are not required to maintain temperature logs.

7.1.3. Materials and Supplies

The sponsor will provide the study drug, sharp items containers, and BG monitoring supplies. Clinical trial materials in each participating country will be labeled according to the country's regulatory requirements. Patients will be provided a commercially available BG meter and test strips for use during the study. An adequate supply of BG testing materials will be dispensed at each visit. Study personnel will review that the patient is correctly administering the assigned study drug and storing the study drug according to the provided instructions.

7.1.4. Medical Devices

The investigational products provided for use in the study include a tirzepatide investigational single fixed dose pen and a matched dulaglutide single dose pen with identical volume and appearance.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to 1 of 2 study treatment groups at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. Patients will be randomized in a 1:1 ratio to receive tirzepatide up to 15 mg or dulaglutide 1.5 mg with randomization stratified for country of enrollment and baseline SGLT-2i use (Yes/No).

7.3. Blinding

This is a double-blind study.

Participants who meet all criteria for enrollment will be randomized to 1 of the 2 study treatment groups at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS.

Investigators, site staff, clinical monitors, and participants will remain blinded to the treatment assignments until the study is complete. If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be permanently discontinued from study drug, but should be continued in the study to be evaluated for efficacy and safety endpoints and monitored for all visits and testing (see Section 8.1.1).

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

Emergency unblinding may be performed through the IWRS. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

7.4. Dosage Modification

7.4.1. Dosage Modification After Initial Dose Escalation

After the initial dose escalation and at the investigator's discretion, due to a patient's safety related concern, such as weight loss or other chronic adverse conditions (eg, chronic or recurrent GI AEs), the dose of the study drug can be de-escalated. Patients on 10 mg of tirzepatide will be de-escalated to 5 mg. Patients on 15 mg of tirzepatide will be de-escalated to 10 mg, or if deemed necessary, to 5 mg. Continuation of the safety related concern could result in temporary study drug interruption. Patients on 5 mg will have study drug temporarily interrupted (Section 8.1.2). This can be performed through IWRS at a scheduled visit prior to V14 and at scheduled or unscheduled visits (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B visit starting at Visit 14]) after V14.

Patients in the dulaglutide treatment group will follow a sham dose de-escalation schedule to match the tirzepatide treatment group's dose de-escalation.

Reaching optimal glycemic target on study medication is not a reason for dose de-escalation.

Patients who have de-escalated their dose will be offered an opportunity to re-escalate when the investigator deems it appropriate to re-initiate dose escalation (see Section 7.4.2).

7.4.2. Additional Dose Escalations

To optimize the number of patients who achieve the maximum dose, both tirzepatide and dulaglutide, it is expected that patients who do not reach the maximum dose during the initial dose escalation for any reason and/or have de-escalated their dose after the initial dose escalation, should be offered the opportunity to undergo up to 2 additional attempts for dose escalations. Patients who participate in an additional dose escalation will be scheduled to attend additional visits at 4-week intervals (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B

visit starting at Visit 14] and subsequent dosing visits) to allow for dose escalation until the maximum tolerated dose is reached. Optional Phone Follow-up Dosing unscheduled visits (UV) can be performed approximately 2 weeks after each dose escalation. For study drug restart or additional dose escalation at or after V14, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate drug supply at the site. Dosing visits at or after V14 can be performed at a scheduled or unscheduled visit.

For patients randomized to the dulaglutide treatment group, they will maintain a 1.5 mg dose of dulaglutide and continue to escalate on a sham dose escalation to match tirzepatide dose escalation.

IWRS will dispense the appropriate dose for the re-escalation of study drug at the dispensing visit. For example:

- Patients on a temporary interruption who are ready to reinitiate study drug will receive a 4-week supply of 5 mg tirzepatide.
- Patients on 5 mg tirzepatide will receive a 4-week supply of 7.5 mg tirzepatide.
- Patients on 10 mg tirzepatide will receive a 4-week supply of 12.5 mg tirzepatide.

Subsequently, these patients will be scheduled to attend additional visits at 4-week intervals (IWRS A / B visits / dosing unscheduled visits [UV] in the SoA, see Section 2) to allow for dose escalation in 2.5 mg increments until the 15 mg tirzepatide dose is reached. Optional telephone visits can be performed approximately 2 weeks after each dose increase (phone follow-up dosing unscheduled visits [UV] in the SoA, see Section 2). If patients develop intolerable GI symptoms any time during this period despite the recommended measures in Section 7.1.1, they may de-escalate to the nearest maintenance dose of 5 mg or 10 mg accordingly.

7.4.3. Reinitiating Study Drug After Interruptions Not Related to Tolerability

If study drug is temporarily interrupted for reasons other than tolerability, patients should be encouraged to restart study drug as soon as it is safe to do so.

During the Escalation Period (V2-V14), restarting study drug can only occur at a scheduled study visit. After V14, restarting study drug can occur at a scheduled study visit or at an unscheduled dosing visit (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B visit starting at Visit 14]) (See Section 7.1.1). The data related to temporary interruption of study treatment should be documented in source documents and entered in the eCRF. For study drug restart at or after V14, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate drug supply at the site.

For patients randomized to the tirzepatide treatment group:

- If the number of consecutive missed injections is 2 or less, the treatment will resume at the same dose.
- If the number of consecutive missed injections is 3 or more, the treatment will be restarted at 5 mg irrespective of the dose the patient was receiving before the interruption.

- Patients will be scheduled to attend additional visits at 4-week intervals to allow for dose escalation in 2.5 mg increments until reaching the maintenance dose the patient was on immediately prior to the temporary interruption (IWRS visits A / B / dosing unscheduled visit [UV] in the SoA, see Section 2). If the patient's maintenance dose is less than the maximum dose, the patient may be offered the opportunity to escalate to the maximum dose at the discretion of the investigator (Section 7.4.2).
- If patients develop intolerable GI symptoms any time during this dose escalation despite the recommended measures in Section 7.1.1, they may de-escalate to the nearest maintenance dose of 5 mg or 10 mg accordingly (see Section 7.1.1.1).
- If a telephone visit is deemed necessary to support patient compliance, this is allowable at the discretion of the investigator site personnel. Optional telephone visits can be performed approximately 2 weeks after restarting study drug and after each dose increase (optional phone follow-up dosing unscheduled visit [UV] in the SoA, see Section 2).

For patients randomized to the dulaglutide treatment group, they will resume with 1.5 mg QW treatment. To keep the study double-blinded integrity, when the number of the consecutive missed injections is 3 or more, a sham re-initiation identical to the tirzepatide procedure described above will also be performed in the dulaglutide treatment group.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee is responsible for the following:

- Confirming appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Ensuring that only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

The study site must store the study drug in a locked and secure environment. The study drug should be refrigerated (not frozen) until use. Dry ice should not be used for cooling. Patients will receive insulated bags with cooling gel packs for use in transporting the study drug carton from the site to their home.

Patients will be instructed to return any unused study drug at the next study visit. Used single dose pens should be disposed of in the sharp items container and the container should be returned to the site (or disposed of per local regulations) when full or sooner, unless the pen is damaged.

In the case of a damaged pen, the patient is to report the product complaint to the site (per Section 9.2.3) and return the damaged pen in the original box provided to the site. Study site staff must regularly assess whether the patient is correctly administering the assigned study drug and storing the study drug according to the provided instructions.

7.6. Treatment Compliance

The investigator site personnel will assess study drug compliance at each visit by reviewing the amount of unused study medication returned in addition to study drug injection information provided by the patient. Study drug accountability will be recorded on the eCRF for each visit interval after randomization when study drug is dispensed.

Any instances of overdose will be documented and summarized. Study drug overdose is defined as injection of study drug more than 1 time in any 3 calendar days. Documented overdose will be reported as a treatment-emergent adverse event (TEAE) and will be summarized (Section 9.3).

Patients considered poorly compliant with study drug and/or poorly adherent to the study procedures should receive additional training and instructions.

7.7. Concomitant Therapy

Patients will be permitted to use concomitant medications that they require during the study, with the exceptions of GLP-1 RAs and pramlintide, which may interfere with the assessment of efficacy and safety characteristics of the study treatments. Discontinuation of DPP-4 inhibitors at randomization is recommended in line with guidelines. Similarly, the initiation of DPP-4 inhibitor therapies during the study is also discouraged (Davies et al. 2018). Medications for optimal glycemic control (with the exception of GLP-1 RAs and pramlintide) may be adjusted any time after randomization during the study as determined by the investigator.

Investigative site staff will inform patients that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the study. This may not be possible when initiated for treatment of medical emergencies, in which case the patient will inform the investigator or a designated site staff member as soon as possible. Any additional medication initiated during the course of the study (including over-the-counter drugs such as paracetamol or aspirin) must be documented, and the name of the drug and the date(s) of administration must be recorded on the “Concomitant Medications” section of the eCRF.

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

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

7.8. Treatment after the End of the Study

Neither tirzepatide nor dulaglutide will be made available to patients after conclusion of the study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Drug

In rare instances, it may be necessary for a patient to permanently discontinue study drug.

To ensure study integrity, it is important that patients continue study follow up after permanent study drug discontinuation. Permanent discontinuation of study drug will not automatically lead to discontinuation from the study. When considering permanent discontinuation of study drug, the investigator should consult with the sponsor-designated medical resource.

The reason for permanent discontinuation of study drug should be documented in the eCRF. If the discontinuation of study drug is due to an AE, the event should be documented in the eCRF. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained.

Possible reasons leading to permanent discontinuation of study drug:

- **Patient decision**
  - The patient requests to discontinue study drug.
- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are permanently discontinued from study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via the eCRF.

  Temporary interruption or discontinuation of the study drug for abnormal liver tests **should be** considered by the investigator when a patient meets 1 of the following conditions after consultation with the sponsor-designated medical resource:

  - ALT or aspartate aminotransferase (AST) >8X ULN,
  - ALT or AST >5X ULN for more than 2 weeks,
  - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio >1.5. In patients with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/discontinuation decisions rather than TBL >2X,
  - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%),
  - Alkaline phosphatase (ALP) >3X ULN, when the source of the increased ALP is the liver,
  - ALP >2.5X ULN and TBL >2X ULN. In patients with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/discontinuation decisions rather than TBL >2X, or
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Patients that meet 1 of these hepatic discontinuation criteria should be monitored as outlined in Section 9.4.5.1. Continuation of the study drug can be considered only in consultation with the

Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited non-drug etiology is identified.

- Patients will be permanently discontinued from the study drug in the following circumstances:
    - acute or chronic pancreatitis (see Section 9.2.2.2),
    - if a patient is diagnosed with thyroid C-cell hyperplasia or MTC after randomization,
    - if a patient is diagnosed with pancreatic cancer after randomization,
    - if any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken,
    - if a patient is diagnosed with type 1 diabetes mellitus,
    - if an investigator, site personnel performing assessments, or patient is unblinded, or
    - if the investigator, after consultation with the sponsor-designated medical resource, determines that a clinically significant systemic hypersensitivity reaction has occurred. A clinically significant systemic hypersensitivity reaction is one that occurs after administration of the investigational product (eg, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) and requires parenteral medication, does not respond to symptomatic medication, results in clinical sequelae, or is an anaphylactic reaction.

Patients who stop the study drug permanently will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements (Section 2, Schedule of Activities).

If the patient is unwilling or unable to return for all scheduled follow-up visits in person, the site will attempt to collect as much follow-up information as possible via telephone or other remote methods of direct patient contact with the patient. Sites are expected to conduct these alternative visit methods according to the visit interval outlined in the Schedule of Activities.

If patients refuse all means of completing study visits, contact with the patient's family or the patient's primary physician or medical record review during the study and at the end of the study to ascertain vital status and record safety and efficacy endpoints is required.

If a patient has withdrawn consent, defined as documented refusal of all methods of follow-up for the duration of the study, following discontinuation of study drug, there is still an expectation to attempt to ascertain vital status via a third-party patient locator service and/or national registries as applicable by local laws/regulations (See Section 5.1, Final Visit).

All attempts to communicate with the patient and/or other contacts should be documented. Any refusals to accept these attempts should also be documented.

8.1.2. Temporary Interruption of Study Drug

In certain situations during the dose escalation period or maintenance period, the investigator may need to temporarily interrupt study drug. Every effort should be made by the investigator to

maintain patients on study drug and to restart study drug after any temporary interruption, as soon as it is safe to do so (Section 7.1.1 and Section 7.4.2).

To optimize the number of patients who achieve the maximum dose, both tirzepatide and dulaglutide, it is expected that patients who do not reach the maximum dose during the initial dose escalation for any reason and/or have de-escalated their dose after the initial dose escalation, should be offered the opportunity to undergo up to 2 additional attempts for dose escalations. Patients who participate in an additional dose escalation will be scheduled to attend additional visits at 4-week intervals (Dosing Unscheduled Visit [UV] [IWRS unscheduled A / B visit starting at Visit 14] and subsequent dosing visits) to allow for dose escalation until the maximum tolerated dose is reached. Optional Phone Follow-up Dosing unscheduled visits (UV) can be performed approximately 2 weeks after each dose escalation. For study drug restart or additional dose escalation at or after V14, the study team should be notified at least 2 weeks prior to the dosing visit to ensure adequate drug supply at the site. Dosing visits at or after V14 can be performed at a scheduled or unscheduled visit.

If study drug interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 9.2 of this protocol. If the study drug interruption is due to an intolerable persistent GI AE (eg, nausea, vomiting, or diarrhea), the patients should be treated as suggested in Section 7.1.1.

Patients that become pregnant should be temporarily interrupted from study drug, however need to continue following study procedures as outlined in the SoA, see section 2. After giving birth and completion of lactation, the investigator may consider re-initiation of study drug.

In rare circumstances, study drug may need to be permanently discontinued (Section 8.1.1). Regardless of whether or not participants continue to take study drug, they will continue to be followed for AEs and endpoints. Thus, every attempt should be made to encourage all patients to come for their study visits, regardless of study drug adherence. Follow-up with the patient/designee by alternative visit methods should be established and maintained where 2 or more clinic visits are missed and patient is temporarily or permanently off study drug.

The data related to temporary interruption of study drug will be entered in the eCRF. In order to avoid having patients store expired study drug, patients should return all unused study drug and, if possible, empty packaging material at the next scheduled clinic or dispensing visit, whichever comes first. Temporary interruption of study drug will not automatically lead to participant discontinuation from the study.

In the event a patient has a temporary interruption during the initial dose escalation and requires extending the escalation beyond Visit 14, unscheduled visits are required in IWRS to facilitate a 4 week dispensing schedule to complete the escalation (dosing unscheduled visits [UV] in the SoA, see Section 2).

Patients who have a temporary interruption of the study drug will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements (Section 2, Schedule of Activities).

Patients temporarily interrupting study drug for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.2. Discontinuation from the Study

In order to minimize the amount of missing data and to enable assessment of study objectives as planned in the study protocol, every attempt will be made to keep patients in the study, irrespective of the following:

- compliance to study drug,
- adherence to visit schedule,
- missing assessments,
- study drug discontinuation due to AE (Section 8),
- development of comorbidities, and
- development of clinical outcomes.

Patients will be discontinued from study in the following circumstances:

- if the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled.

Patients discontinuing from the study should discontinue study drug and complete an early termination visit (ETV), and a post-ETV (Visit 60) 1 month later, as outlined in Section 2 (Schedule of Activities). If the ETV coincides with a scheduled visit, then the ETV should be completed instead of the scheduled visit. Attempts should be made to ascertain vital status (alive or dead) from 12 months post-ETV and each year thereafter, up to and including vital status ascertainment during the study closeout period. Annual vital status should be entered in the eCRF.

A study participant may withdraw consent from the trial:

- at any time at his/her own request, or
- at the request of his/her designee (eg, legal guardian).

Discontinuation from the study due to withdrawal of consent is expected to be rare and patients should be provided with options for alternative follow-up methods and/or end of study vital status/endpoint ascertainment. If the study 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 study participant withdraws consent, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

In the event of patient withdrawal of consent, every allowable effort should be made to ascertain vital status at the end of the study via public record search, national registries, and patient locator services in accordance with local laws and regulations.

8.3. Lost to Follow-Up

A patient will be considered high risk for lost to follow-up if he or she repeatedly fails to return for scheduled visits. A patient will be considered as lost to follow-up only if the patient is unable to be contacted by the study site during the study close-out period, and no data on vital status (alive or dead) is available through accepted methods for ascertainment, including query of public databases. Investigator site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

For endpoint/end of study purposes, investigator site personnel should make every effort to ascertain endpoints by contacting the patient's family or designee/personal contact (eg, friend), family doctor, or attempt to determine vital status and endpoints via other means (if not prohibited by local laws) (eg, national registries/databases, medical records, voter records, and third-party patient locator services). At a minimum, vital status should be ascertained for all randomized study participants, including participants who are considered high risk of being lost to follow-up or participants who have withdrawn consent.

Note: If the investigator site personnel are unable to contact the patient, they may give the patient's name and last known contact information to a patient locator service to try to find current information, if not prohibited by local laws and regulations. The patient locator service will **not** contact the patient directly and any new information they find will be shared with investigator site personnel.

If vital status is determined, this will be documented and the patient will not be considered lost to follow-up. If no final visit is available, and vital status is not determined during the study close-out period, this will be documented and the patient will be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities with the study procedures and their timing (including tolerance limits for timing). Appendix 2, lists the laboratory tests that will be performed for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The primary efficacy measure is the time to first occurrence (after randomization) of the composite of death from CV causes, MI, or stroke. An independent Clinical Endpoint Committee (CEC) will adjudicate all primary endpoint events. The CEC Charter will contain the final detailed event definitions.

Cardiovascular Death

Cardiovascular death includes death resulting from:

- acute MI,
- sudden cardiac death,
- death due to CHF,
- death due to stroke,
- death due to CV procedures,
- death due to CV hemorrhage, and
- death due to other CV causes.

Myocardial Infarction (Cardiac Ischemic Event)

The term acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

Stroke (Cerebral Ischemia)

Subdural hematomas are intracranial hemorrhagic events and not strokes. The distinction between a transient ischemic attack (TIA) and an ischemic stroke is the presence of infarction on imaging. Persistence of symptoms is an acceptable indicator of acute infarction. The duration of symptom persistence used to distinguish between transient ischemia and acute infarction is defined as greater than or equal to 24 hours.

9.1.2. Secondary Efficacy Assessments

Key secondary efficacy measures are as follows:

- time to death due to any cause,
- time to CV death,
- time to first occurrence of MI,
- time to first occurrence of stroke,
- time to first occurrence of expanded composite CV outcome, defined as either CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina, and
- cumulative number of CV deaths and total (first and recurrent) HF events requiring hospitalization and/or urgent HF visits.

Additional secondary efficacy measures are as follows:

- time to first occurrence of:
  - coronary, carotid, or peripheral revascularizations, individually and as composite
  - hospitalization due to unstable angina
  - diabetic nephropathy,
    - composite nephropathy endpoint including new or worsening nephropathy consisting of
      i) persistent macroalbuminuria,
      ii) persistent doubling of serum creatinine level and creatinine clearance (per eGFR <45 mL/min/1.73 m^2),
      iii) need for continuous renal-replacement therapy, or
      iv) death due to renal disease
- proportion of patients with more than 10% weight loss from screening after 36 months,
- change from baseline in:
  - weight, BMI, and waist circumference
  - HbA1c
  - urinary albumin to creatinine ratio
  - blood lipids: total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and triglycerides,
- cumulative number of primary composite events of CV death and total (first and recurrent) MI(s) and/or stroke(s).

The independent CEC will adjudicate vascular events resulting in death, MI, hospitalizations for HF, urgent HF visit, unstable angina, coronary revascularization, stroke, and TIA. The CEC Charter will contain the final detailed event definitions used for adjudication of secondary efficacy CV events.

9.1.2.1. Other Measures

A hospitalization will be defined as a hospital admission (including admission to a chest pain observation unit) or a visit to an emergency department that results in a stay >24 hours. Development of cholelithiasis will be defined as any new diagnosis of cholelithiasis after randomization, as evidenced on an imaging examination (eg, ultrasound or CT scan). Measurements of weight and waist circumference are discussed in Section 9.4.2.

9.1.3. Appropriateness of Assessments

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

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, investigator site personnel will record via the eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, investigator site personnel will record any worsening in the condition(s) and any new conditions as AEs as well as medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and investigational product via the eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study drug, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause-and-effect relationship between the investigational product, study device and/or study procedure, and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, investigator site personnel must report this to Lilly or its designee via the eCRF, clarifying, if possible, the circumstances leading to any dosage modifications or discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death (Note exception in Section 9.2.1.1.1),
- initial or prolonged inpatient hospitalization (Note exception in Section 9.2.1.1.1),
- a life-threatening experience (that is, immediate risk of dying),
- persistent or significant disability/incapacity,
- congenital anomaly/birth defect, or
- important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

When a condition related to the drug delivery system necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

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

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

In case of 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 in Veeva as an AE on the AE eCRF and should be reported via the paper

pregnancy form, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

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. 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.

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

Exceptions include primary and secondary efficacy events listed in Section 9.2.1.1.1 and will not be reported to Lilly or its designee using the SAE eCRF, unless the investigator believes the event may have been caused by the investigational product, study procedure, or investigational device (eg, drug delivery system).

SAE regulatory reporting

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 evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or study procedure. United States 21 CFR 312.32 and European Union-Clinical Trial Regulation 536/2014 and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.1.1.1. Primary, Secondary, and Additional Study Endpoint Reporting

The following investigator-reported events are considered potential endpoints and must be reported first as an AE on the AE eCRF (with the appropriate designation for seriousness) following the AE reporting eCRF guidelines. They must then be reported as an endpoint on the eCRF with all required source documents provided for adjudication to the CEC. The endpoint

reporting begins after randomization. These potential endpoints (even if they meet criteria for a serious event) are not to be reported on the SAE eCRF **unless** considered as possibly related to study drug, the drug delivery system, or study procedure. Potential endpoints that are serious **and** considered as possibly related to study drug, the drug delivery system, or study procedure must also be reported as an SAE using the SAE eCRF:

- death,
- MI,
- stroke or TIA,
- hospitalization for HF or an urgent HF visit,
- hospitalization for unstable angina, and
- coronary revascularizations.

In the case where 1 of the above endpoint events is reported but does not meet a prespecified event definition detailed in the CEC Charter, as reviewed by the independent CEC, no further action will be taken by the study site.

9.2.2. Adverse Events of Special Interest

9.2.2.1. Clinically Significant and Severe Hypoglycemia

Patients should report information on clinically significant or severe hypoglycemic events, including nocturnal hypoglycemia, starting from Visit 2 until the last study visit. For that purpose, patients will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to report appropriate information for each hypoglycemic event to the investigator site personnel.

Level 2 (clinically significant hypoglycemia), Level 3 (severe hypoglycemia) hypoglycemic events, and nocturnal hypoglycemia are to be reported in the eCRF. Investigators should use the following definitions and criteria when diagnosing and categorizing an event considered to be related to hypoglycemia (the BG values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips) in accordance with the 2017 American Diabetes Association position statement on glycemic targets (ADA 2017):

Clinically Significant Hypoglycemia (Level 2):

- Documented symptomatic hypoglycemia is defined as any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of <54 mg/dL (<3.0 mmol/L).
- Documented asymptomatic hypoglycemia is defined as any event not accompanied by typical symptoms of hypoglycemia but with a measured BG <54 mg/dL (<3.0 mmol/L).
- Documented unspecified hypoglycemia is defined as any event with no information about symptoms of hypoglycemia available but with a measured BG <54 mg/dL (<3.0 mmol/L).

Severe Hypoglycemia (Level 3):

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

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

Nocturnal Hypoglycemia:

Nocturnal hypoglycemia is defined as any hypoglycemic event that occurs between bedtime and waking. If a hypoglycemic event meets the criteria of severe, it should be recorded as serious on the AE eCRF and reported to Lilly as an SAE. To avoid duplicate reporting, all consecutive BG values ≤70 mg/dL (≤3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

9.2.2.2. Pancreatitis

Acute pancreatitis is defined as an AE of interest in all trials with tirzepatide, including this trial. Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks et al. 2013). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half the cases) (Banks et al. 2013; Koizumi et al. 2006); the pain is often associated with nausea and vomiting,
- serum amylase (total and/or pancreatic) and/or lipase ≥3X ULN, or
- characteristic findings of acute pancreatitis on CT scan or MRI.

If acute pancreatitis is suspected by the investigator,

- appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed).
- Imaging studies such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound should be performed.
- If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the patient must permanently discontinue study drug, but will continue in the study to be evaluated for efficacy endpoints and AEs until the final visit.
- The most appropriate diabetes therapeutic regimen will be decided by the investigator based on the patient's clinical status. A review of the patient's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.
- All cases of suspected pancreatitis must be submitted for adjudication, regardless of the outcome.

Each AE of pancreatitis must be reported.

- If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (total and/or pancreatic amylase) and imaging studies, the event must be reported as an AE.
- An event determined to meet SAE criteria (See Section 9.2.1) must be reported as an SAE.
- For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug(s).

Each patient will have measurements of pancreatic amylase and lipase (assessed at the central laboratory) as shown on the Schedule of Activities (Section 2) 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 patients (Nauck et al. 2017; Steinberg et al. 2017a, 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic amylase ≥3X ULN) is not mandated, but may be performed based on the investigator's clinical judgment and assessment of the patient's overall clinical condition.

- Cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis must be submitted for adjudication, regardless of the outcome.

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent CEC.

- In addition, AEs of **severe or serious** abdominal pain of **unknown etiology** will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease.

  Relevant data from patients with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically-designed eCRF page by study site. The adjudication committee representative will enter the results of adjudication in a corresponding electronic form.

9.2.2.3. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or multiple endocrine neoplasia-2 will be excluded from the study. The assessment of thyroid safety during the study will include reporting of any case of thyroid malignancy including MTC and papillary carcinoma and measurements of calcitonin. This data will be captured in specific eCRFs. The purpose of calcitonin measurements is to assess the potential of study drug to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms. When the possibility of thyroid diseases such as C-cell hyperplasia, MTC, and papillary carcinoma is excluded as background of an elevated calcitonin concentration and no further increase in calcitonin concentration occurs, study drug can be restarted at the discretion of the investigator.

Calcitonin Measurements in Participants with eGFR ≥60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR ≥60 mL/min/1.73 m^2 is defined below. If a participant's laboratory results meet these criteria, these clinically significant laboratory results should be recorded as an AE:

- Calcitonin value ≥20 ng/L and <35 ng/L AND ≥50% increase from the screening value. These participants will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), study drug should be temporarily interrupted, and the participant encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude any serious adverse effect on the thyroid.
- Calcitonin value ≥35 ng/L AND ≥50% over the screening value. In these participants, study drug should be temporarily interrupted, and the participant recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist.

Calcitonin Measurement in Participants with eGFR <60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR <60 mL/min/1.73 m^2 is defined as a calcitonin value ≥35 ng/L AND ≥50% over the screening value. If a participant's labs meet these criteria, these clinically significant labs should be recorded as an AE.

In these participants, study drug should be temporarily interrupted (after first confirming the value) and the participant recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist to exclude any serious adverse effect on the thyroid.

9.2.2.4. Treatment-Emergent Supraventricular Arrhythmias and Cardiac Conduction Disorders

Patients who develop any event from these groups of disorders should undergo an electrocardiogram (ECG). Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 9.2.1 must be reported as SAEs.

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

9.2.2.5. Hypersensitivity Events and Allergic/Hypersensitivity Reactions

All allergic or hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Additional data, such as type of reaction and treatment received, will be collected on any AEs or SAEs that the investigator deems related to study drug(s) via the eCRF created for this purpose.

In the case of generalized urticaria or anaphylaxis, additional samples should be collected as outlined in Appendix 6. Laboratory results are provided to the sponsor via the central laboratory.

Study drug(s) should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug(s). Study drug(s) may be restarted when/if it is safe to do so in the opinion of the investigator and only on a clinic visit. If study drug(s) is/are permanently discontinued, the patient will continue in the trial to collect all planned efficacy and safety measurements.

9.2.2.6. Diabetic Retinopathy Complications

All participants must have a dilated retinal fundoscopic exam evaluated by an eye care professional (ophthalmologist or optometrist) after signed informed consent and prior to randomization. This diagnostic procedure can be either a direct fundus examination or a review of fundus photographs taken after signing the ICF. The results from this exam will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy. If based on a recent (performed ≤ 90 days prior to randomization) fundus examination, the eCRF could be completed, there is no need for repeated procedure during screening period. Either of the 2 procedures must be finalized prior to randomization.

A follow-up dilated fundoscopic exam or other retinal diagnostic procedure is recommended to be performed by the study approved eye care specialist when clinically indicated by any AE suggestive of a change from baseline in retinopathy or macular edema, and the findings should be recorded on the Fundoscopic Exam - Follow Up eCRF. For participants with severe non-proliferative retinopathy or proliferative retinopathy, and/or macular edema at baseline, a follow up fundoscopic exam at Visit 14 ±30 days and Visit 16 ±30 days is required and should be recorded in the eCRF.

In addition, the first occurrence of the composite diabetic retinopathy endpoint consisting of i) retinal photocoagulation, ii) vitreous hemorrhage, iii) treatment with intravitreal agents, or iv) onset of diabetes-related significant visual loss will be also analyzed.

9.2.2.7. 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 Appendix 4.

Hepatobiliary disorders will specifically include: acute cholecystitis, acute cholelithiasis, and drug-induced liver injury.

9.2.2.8. Severe Gastrointestinal Adverse Events

Tirzepatide may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the eCRF/AE form. For detailed information concerning the management of GI AEs, see Section 7.1.1.

9.2.2.9. Acute Renal Failure or Exacerbation of Chronic Renal Failure

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute or worsening of chronic renal failure. GI AEs have been reported with tirzepatide, including nausea, diarrhea, and vomiting. This is consistent with other GLP-1 RAs (Aroda and Ratner 2011). The events may lead to dehydration, which could cause a

deterioration in renal function, including acute renal failure. Patients should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

9.2.2.10. Amputation/Peripheral Revascularization

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

9.2.3. Complaint Handling

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

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

The required Product Complaint Form should be completed and reported within 1 business day after awareness and within 24 hours if associated with an SAE.

9.3. Treatment of Overdose

Study drug overdose, defined as documented injection of study drug more than 1 time in any 3 calendar days, will be reported as a TEAE and will be summarized for each treatment group.

Considering the mechanism of action of both study drugs, potential overdose effects can be GI disorders and hypoglycemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

Patients considered poorly compliant with study drug or poorly adherent to the study procedures should receive additional training and instructions.

9.4. Safety

9.4.1. Vital Sign Measurements

Vital signs (pulse rate and BP) will be measured in the seated position according to instructions in this section and the Schedule of Activities (Section 2). At screening (Visit 1), the patient should sit quietly for 5 minutes before vital sign measurements are taken.

Pulse Rate and Blood Pressure

Pulse rate and BP should be measured 2 times in the same arm in the seated position. The measurements should be taken at least 1 minute apart.

Pulse rate should be measured after the patient has been seated for at least 5 minutes. Pulse rate measurements should be taken by palpation of the radial or brachial artery for 1 full minute.

Blood pressure must be taken with an automated BP machine. Blood pressure should be measured after the patient has been seated for at least 5 minutes and the patient should have emptied his/her bladder prior to the measurements. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of BP measurements. Position the middle of the cuff bladder directly over the brachial artery. The lower edge of the

cuff should be 2 to 3 cm above the midpoint of the brachial artery pulsation. The arm should be supported at the level of the heart. The same method used to assess BP should be used consistently throughout the trial.

9.4.2. Anthropomorphic Measurements

Anthropomorphic measurements will be taken according to the Schedule of Activities (Section 2). See Appendix 5 for more details.

Body Weight and Height

Body weight and height should be measured. All weights for a given patient should be measured in a consistent manner using a calibrated scale (mechanical or digital scales are acceptable), using the same scale whenever possible, and after the patient has emptied their bladder. Patients should be lightly clothed but not wearing shoes while their weight is measured.

Waist Circumference

Two waist circumference measurements should be obtained with the patient in the recommended standing position. In the event, the patient is unable to stand for the measurement it may be taken in a seated position. All subsequent waist measurement are to be taken in the same position. The waist circumference should be measured immediately above the iliac crest and the measuring tape should be removed between the 2 measurements. Measurements should be rounded to the nearest 0.5 cm.

9.4.3. Electrocardiograms

Twelve-lead ECGs will be obtained locally at Visit 2 (randomization) according to Schedule of Activities (Section 2). Electrocardiograms should be recorded after the patient has been supine for 5 minutes in a quiet room.

The ECGs must be interpreted by a qualified physician (the investigator or designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, for immediate patient management, if needed. The investigator or designee must document their review of the ECG. If a clinically relevant abnormality is observed on the patient's ECG, then the investigator should assess the patient for symptoms (such as palpitations, near syncope, syncope, or chest pain).

The original ECG must be retained at the investigative site. As appropriate, all new endpoint events of MI/myocardial ischemia not already reported by the site will be submitted for adjudication.

The investigator or qualified designee's interpretation will prevail for immediate patient management purposes.

9.4.4. Laboratory Tests

Clinical laboratory tests (Appendix 2) should be conducted according to the Schedule of Activities (Section 2).

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via the eCRF.

9.4.5. Safety Monitoring

Safety will be monitored by Lilly and an IDMC with membership external to Lilly.

The IDMC will monitor patient safety in an unblinded fashion.

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

The blinded Lilly clinical research physician (CRP) will monitor safety data throughout the course of the study. The Lilly CRP will consult, as is appropriate, with the blinded Global Patient Safety (GPS) therapeutic area physician or clinical scientist outside the study team and review trends in laboratory analyses and SAEs at periodic intervals.

Lilly GPS will review SAEs within time frames mandated by company procedures and regulatory agency expectations.

If Lilly safety monitoring reveals an issue or signal, the safety internal review committee within Lilly GPS will determine if unblinding is necessary. If needed, the safety internal review committee will then perform an unblinded review of the data specific to the identified issue or signal. The IDMC will be informed of the unblinding. These data will then be provided to the IDMC for further review. These measures will preserve the integrity of the data collected during this study and minimize any potential for bias while providing for appropriate safety monitoring.

9.4.5.1. Hepatic Safety Monitoring

Close hepatic monitoring

Laboratory tests (Appendix 4), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin (D. Bil), gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 3 to 5 days 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 results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP <1.5x ULN	ALP ≥2x ULN
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)

TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for participants with Gilbert's syndrome)

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

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

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

Comprehensive hepatic evaluation

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

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

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

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

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

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels,

acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

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

Additional hepatic safety data collection in hepatic safety case report forms (eCRF) should be performed in study participants who meet 1 or more of the following 5 conditions:

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

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

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

9.7.1. Whole Blood Sample(s) for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to tirzepatide and to investigate genetic variants thought to play a role in T2DM and T2DM-related metabolic

abnormalities. This will include, but not limited to, TCF7L2, HNF1A, CTRB1/2 IRS1 etc., known genes that have shown shared genetic contribution for T2DM and CV diseases. In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic analysis will be performed to evaluate genetic variants in the GLP-1 and GIP signaling pathway genes for association with efficacy responses to tirzepatide (such as change from baseline in HbA1c, body weight, BMI etc.), and known CV disease risk genes with efficacy response. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/investigational review boards impose shorter time limits. This retention period enables the use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of tirzepatide or after tirzepatide become(s) commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

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

Serum and plasma samples for nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

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

All samples will be coded with the patient identification number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables the use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the course of the development and commercialization of both study drugs.

9.9. Health Economics

The following questionnaires will be completed by the patients at specific clinic visits according to the Schedule of Activities (Section 2). At these visits, the questionnaires should be completed before the patient has discussed their medical condition or progress in the study with the investigator and/or site staff and before any other study procedures if the patient is not adversely affected by their fasting condition.

9.9.1. EQ-5D-5L

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

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

9.9.2. Ability to Perform Physical Activities of Daily Living

The Ability to Perform Physical Activities of Daily Living (APPADL) questionnaire contains 7 items that assess how difficult it is for patients to engage in certain activities considered to be integral to normal daily life, such as walking, standing, and climbing stairs (Hayes et al. 2011, 2012). Items are scored on a 5-point numeric rating scale, where 5 = "not at all difficult" and 1 = "unable to do." A raw overall score is calculated by simply summing the scores of the 7 items and dividing by the number of items. 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.

9.9.3. Impact of Weight on Self-Perception Questionnaire

The Impact of Weight on Self-Perception (IW-SP) questionnaire contains 3 items that assess how often the patient's body weight affects how unhappy they are with their appearance and how often they feel self-conscious when out in public (Hayes and DeLozier 2015). Each item is rated on a 5-point scale, where 1 = "always" and 5 = "never." Total scores for the IW-SP are derived

by summing the item scores and dividing by the number of items. The score can also be transformed to a range from 0 to 100. Higher IW-SP scores correspond to better self-perception (Hayes and DeLozier 2015).

10. Statistical Considerations

10.1. Sample Size Determination

This is an event-driven study. The study will be continued until at least 1615 patients experience 1 or more components of the CEC-confirmed MACE-3 endpoint. This sample size provides 90% power to demonstrate the superiority of tirzepatide compared to dulaglutide relative to MACE-3 risk at a 2-sided alpha of .0472 significance level, if tirzepatide is associated with a 15% reduction in hazard compared to dulaglutide for the MACE-3 endpoint (nQuery + nTerim 4.0 software). The significance level is adjusted to account for an efficacy assessment at an interim analysis (see Section 10.3.6). It is assumed that the log-rank test will be used for comparing the distribution of time-to-first occurrence of MACE-3 between tirzepatide and dulaglutide.

Although the sample size is guided by superiority, the primary study objective is to demonstrate NI of tirzepatide to dulaglutide. An NI boundary of 1.05 will be used, which represents the inverse of the 97.5th percentile of the posterior distribution of the hazard ratio (HR) for dulaglutide versus placebo for the MACE-3 endpoint. The posterior distribution of the HR was derived using a Bayesian hierarchical meta-analysis of patients with a history of CVD from 6 completed GLP-1 RA CVOTs, including the REWIND CVOT (Gerstein et al. 2019). Additionally, the NI margin of 1.05 ensures preservation of at least 50% of dulaglutide efficacy estimated using the Bayesian hierarchical meta-analysis. Additional details regarding the justification of the NI boundary of 1.05 will be provided in the statistical analysis plan (SAP). The accrual of 1615 patients with at least 1 component of MACE-3 provides 90% power to establish NI of tirzepatide to dulaglutide (upper bound of the 95.3% CI of the HR, tirzepatide versus dulaglutide, is ≤1.05) provided that tirzepatide is associated with a 10.5% reduction in hazard compared to dulaglutide relative MACE-3 endpoint.

Extrapolated on evidence from previous trials (Zinman et al. 2015; Marso et al. 2016b; Hernandez et al. 2018; Gerstein et al. 2019), approximately 35 patients are expected to experience MACE-3 outcome for 1000 patient years of exposure in the dulaglutide treatment group. Therefore, approximately 12,500 patients enrolled and followed for an average of 4 years will lead to the accrual of at least 1615 primary endpoints. It is assumed that 2% of the potential exposure will not be realized due to discontinuations from study and deaths unrelated to CV causes. The number of patients enrolled may be changed based on the observed blinded aggregate event rate during the enrollment period. Duration of follow-up may change based on the observed blinded aggregate event rates, number of patients enrolled, and lost exposure due to study discontinuations.

10.2. Populations for Analyses

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

Analysis data set/Population	Description
Screened	All participants who sign informed consent.
Randomized	All patients who are randomly assigned to a study treatment group.
Intention-to-treat (ITT) Dataset	Data from all randomized patients during the follow-up period (date of randomization to the date of patient's end-of-follow-up, see Section 10.3.1).
Modified intention-to-treat efficacy (mITTE) Dataset	Data from all randomized patients excluding those who were inadvertently enrolled during the follow-up period (date of randomization to the date of patient's end-of-follow-up, see Section 10.3.1).
Modified intention-to-treat safety (mITTS) Dataset	Data from all randomized patients who take at least 1 dose of double-blind study drug during the follow-up period (date of first dose to the date of patient's end-of-follow-up, see Section 10.3.1).

Abbreviations: ITT = intention-to-treat; mITTE = modified intention-to-treat efficacy; mITTS = modified intention-to-treat safety.

10.3. Statistical Analyses

10.3.1. General Statistical 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 clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate. In statistical summaries and analyses, patients will be analyzed as randomized.

Summary of patient disposition will be based on the ITT dataset. Safety summaries and analyses will be carried out using the modified intention-to-treat safety (mITTS) dataset. Efficacy summaries and analyses will be carried out using the mITTE dataset.

For patients with a final visit where primary endpoint status is ascertained, the patient's end-of-follow-up will be defined as the earliest of a) date of death, or b) date of the patient's final visit. For patients with documented withdrawal of consent (Section 8.2), the end-of-follow-up will be the date they confirm withdrawal of consent. For patients prematurely discontinuing study but without documented withdrawal of consent (Section 8.2), the patient's end-of-follow-up will be the latest of a) date of the patient's post-ETV, b) date of ETV, or c) date of last contact when the primary end point status is ascertained prior to date of discontinuation. For patients who have neither a final visit where primary endpoint status is ascertained nor are prematurely discontinuing from study, the patient's end-of-follow-up will be the date of last contact when the primary endpoint status is ascertained.

Efficacy and safety measures will be summarized by treatment group as randomized. Summary statistics for continuous measures will include sample size, mean, standard deviation, median,

minimum, and maximum. Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. All tests of treatment effects, except for the final efficacy analysis subject to type 1 error rate control, will be conducted at a 2-sided alpha level of .05 and the level of confidence of 2-sided CI will be 95%, unless otherwise stated.

Listing of efficacy or safety events occurring after patient's end-of-follow-up will be provided.

Additional statistical analysis 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 SAP, where appropriate.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

Frequency counts and percentages of all patients screened will be provided. Frequency counts and percentages of all patients randomized, as well as those receiving at least 1 dose of study drug, will be presented by treatment. A listing of patients not receiving study drug will be provided. Frequency counts and percentages of patients completing the study or prematurely discontinuing the study, including reason for premature discontinuation, will be presented by treatment group. A Kaplan-Meier analysis of time from randomization to premature discontinuation from study by treatment group will be provided.

10.3.2.2. Patient Characteristics

Demographic information, medical history (including qualifying CV entry criteria), concomitant illness, and medications (including antihyperglycemic drugs used at baseline) will be summarized by treatment group.

10.3.2.3. Concomitant Therapy

Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification and treatment. In particular, modifications to baseline antihyperglycemic therapy will be summarized by treatment group.

10.3.2.4. Treatment Compliance

Frequency counts and percentages of patients' prematurely and permanently discontinuing study drug, overall and by reasons for discontinuation, will be summarized by treatment group. The Kaplan-Meier method will be used for illustrating the time profile of the cumulative proportion of patients discontinuing from the study drug over time by the treatment group. Study drug compliance will be defined by ([total number of single dose pens dispensed – total number of unused single dose pens returned]/number of weeks from the date of first dose to the date of last dose)*100%. The proportion of patients with compliance <75% will be reported by treatment group.

10.3.3. Efficacy Analyses

10.3.3.1. Analyses of Primary Outcome

The primary outcome is the occurrence of CEC-confirmed CV death, MI, or stroke. The primary endpoint is the time from randomization to first occurrence of any component of the primary outcome. The primary analysis is time-to-first event analysis via Cox proportional hazards regression model with sodium glucose cotransporter 2 inhibitor use (Yes/No) at baseline as a stratification factor.

The study includes a single planned interim efficacy analysis (Section 10.3.6) conducted using an alpha spending function (Hwang et al. 1990) with Gamma= -4.75. The alpha level will be determined based on the number of primary endpoints at the interim analysis, and the number of primary endpoints at the final analysis. For example, if the number of endpoints at interim and final analyses are 1075 and 1615, respectively, the interim analysis will be conducted at a 2-sided .01 significance level and the final analyses will be conducted at a 2-sided .0472 significance level with non-inferiority assessment guided by a 95.3% CI of HR (tirzepatide versus dulaglutide). To account for multiple comparisons related to the primary outcome conducted at the final analysis, the following analyses will be conducted hierarchically in the order specified:

The first assessment is conducted to discharge US FDA regulatory requirement to rule out >30% increase CV risk with tirzepatide compared to placebo by a direct comparison between tirzepatide and dulaglutide. The requirement calls for demonstrating that the upper bound of the 95% CI of HR (test drug versus placebo) is <1.3 in a CVOT. Typically, this requirement is discharged using a CVOT with 611 primary endpoints, which provides 90% power to discharge >30% increase in hazard (i.e., the upper bound of the 95% CI of HR <1.3) when HR in truth is 1. A CVOT comparing the experimental agent to placebo with 1615 primary endpoints provides 90% power to discharge >17% increase in hazard (i.e., the upper bound of 95% CI of HR <1.17) when HR in truth is 1. Since the comparison is to dulaglutide, if the upper bound of the 95.3% CI of HR (tirzepatide versus dulaglutide) = HR (tirzepatide versus placebo) × HR (placebo versus dulaglutide) <1.17×1.05 =1.23 is met, then the regulatory requirement is considered met. See Section 10.1 for the justification of the choice of 1.05 as a conservative estimate of HR (placebo versus dulaglutide).

Contingent upon successfully demonstrating above, NI of tirzepatide to dulaglutide will be assessed by inspecting the upper bound of the 2-sided 95.3% CI of HR (tirzepatide versus dulaglutide), and NI will be established if that upper bound is less than 1.05.

Contingent on establishing NI of tirzepatide to dulaglutide, superiority of tirzepatide would be claimed if upper bound of the 2-sided 95.3% CI <1.

10.3.3.2. Secondary Analyses Subject to Type 1 Error Rate Control

If superiority of tirzepatide compared to dulaglutide is met for the primary endpoint, then separate statistical testing of each component of the primary composite endpoint, death due to any cause, expanded composite CV outcome defined as either CV death, MI, stroke, coronary revascularization or hospitalization for unstable angina, and cumulative number of CV deaths

and total (first and recurrent) HF events requiring hospitalization and/or urgent HF visits, will be conducted. Graphical testing strategy will be employed in controlling for type 1 error rate when conducting these analyses, details of which will be outlined in the SAP.

In analyzing the secondary endpoints above, time-to-first occurrence of the specific endpoint, whether or not it occurred as the first event, will be considered. For an example, time-to-death due to CV cause analysis will include all deaths due to CV cause even if a CEC-confirmed nonfatal MI or nonfatal stroke preceded the death. Additionally, time-to-first occurrence of MI analysis will include all first occurrences of MIs even if it was preceded by a CEC-confirmed nonfatal stroke.

10.3.3.3. Other Efficacy Analyses

Details regarding analysis of other efficacy endpoints will be outlined in the SAP.

10.3.4. Safety Analyses

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 by treatment for incidence of TEAEs, SAEs, study drug discontinuation due to AEs, and deaths. The Fisher's exact test will be used to compare the treatment groups.

Additional details regarding safety analyses including those for AEs of special interest will be outlined in the SAP.

10.3.5. Other Analyses

10.3.5.1. Health Outcomes

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

10.3.5.2. Subgroup Analyses

Subgroup analyses relative to the primary efficacy endpoint will be conducted using a Cox proportional hazards model with subgroup, treatment group, and the interaction between the levels of the subgroup and treatment group as categorical variables. Planned subgroup analyses will include but are not limited to:

Demographics:

Sex, age (<65, ≥65), region of enrollment, race, ethnic group, BMI (<27, 27-30, >30).

Medical History and Baseline Antihyperglycemic Medication Use:

Hemoglobin A1c (≤8.5%, >8.5%), duration of diabetes (<10 years, ≥10 years), history of MI, history of stroke, CHF (yes, no), impaired renal function (yes, no), and baseline SGLT-2i use (yes, no).

10.3.6. Interim Analyses

The IDMC is authorized to evaluate unblinded interim efficacy and safety analyses prior to database lock. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients. The study team will remain blinded until final database is locked, unless the study is prematurely terminated.

The first scheduled IDMC review will occur approximately 6 months after first patient visit. Thereafter, IDMC reviews will be planned approximately every 6 months throughout the study.

Tabular summaries of clinical endpoint events (reported and adjudicated) including deaths, MIs, and strokes, selected potentially clinically significant laboratory values, AEs, SAEs, discontinuations due to AEs, and other relevant safety information by treatment group will be sent to the IDMC by a Statistical Analysis Center external to and independent from the sponsor.

A single planned interim efficacy analysis will be performed once approximately 1075 CEC-confirmed MACE-3 endpoints have been accrued to evaluate the need for further continuation of the study. At the interim analysis with 1075 CEC-confirmed MACE-3 endpoints, tirzepatide will be compared to dulaglutide relative to the primary endpoint at a 2-sided .01 significance level. Consideration will be given to terminate the trial if tirzepatide is superior to dulaglutide. If not, the trial will continue until at least 1615 patients experience at least 1 component of the composite MACE-3 endpoint and the final primary endpoint analyses will be conducted at a 2-sided .0472 level. If the number of CEC-confirmed MACE-3 endpoints at the interim and the final analyses are different from planned, alpha levels for interim and final analyses will be guided by using an alpha spending function (Hwang et al. 1990) with Gamma= -4.75. Details of interim stopping rules, membership, operations, and the communication plan will be documented in the IDMC Charter.

Details regarding maintaining blind during the conduct of this study will be specified in the blinding and unblinding plan document.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Additional Dose Escalation	The process of dose escalation in participants who do not reach the maximum dose during the initial dose escalation for any reason. This process may occur 2 times after the initial escalation.
Alternative visit methods	Telephone or remote methods of direct patient contact, contact with the patient's family or the patient's primary physician or medical record review during the study and at the end of the study to ascertain vital status and record safety and efficacy endpoints.
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
authorized AxMP	*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 auxiliary medicinal product
AxMP	auxiliary medicinal product. See also NIMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial
baseline	Data captured at randomization unless data is only collected at screening, in which case screening is considered baseline
BG	blood glucose

BMI	body mass index
BP	blood pressure
CAD	Coronary artery disease
CEC	Clinical Endpoint Committee
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase (also known as creatine phosphokinase [CPK])
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, GCP, and applicable regulatory requirements.
CRP	clinical research physician
CRF	case report form
CSR	clinical study report
CTCA	computed tomography coronary angiography
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
DPP-4	dipeptidyl peptidase-4
DR	diabetic retinopathy
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency

End of follow-up	For patients with a final visit where primary endpoint status is ascertained, the patient's end-of-follow-up will be defined as the earliest of a) date of death, or b) date of the patient's final visit. For patients with documented withdrawal of consent (Section 8.2) the patient's end-of-follow-up will be the date they confirm withdrawal of consent. For patients prematurely discontinuing study but without documented withdrawal of consent (Section 8.2), the patient's end-of-follow-up will be the latest of a) date of the patient's post-ETV, b) date of ETV, or c) date of last contact when the primary end point status is ascertained prior to date of discontinuation. For patients who have neither a final visit where primary endpoint status is ascertained nor are prematurely discontinuing from study, the patient's end-of-follow-up will be the date of last contact when the primary end point status is ascertained.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ETV	early termination visit
FDA	Food and Drug Administration
GCP	good clinical practice
GDPR	EU General Data Protection Regulation
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide 1 receptor
GPS	Global Patient Safety
HbA1c	hemoglobin A1c
HF	heart failure
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee.
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 patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board.
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 patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
IW-SP	Impact of Weight on Self-Perception
Lilly	Eli Lilly and Company
MACE	major adverse cardiovascular events
MACE-3	myocardial infarction, stroke, or death from cardiovascular causes
MACE-4	cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina
MACE 5	cardiovascular death, myocardial infraction, stroke, hospitalization for unstable angina, or coronary revascularization

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, prefilled pens, or both.
ME	macular edema
MI	myocardial infarction
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
mITTE	modified intention-to-treat efficacy
mITTS	modified intention-to-treat safety
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NI	noninferior(ity)
NIMP	Non-investigational Medicinal Product. See AxMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment.
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRO	patient-reported outcome
QW	once weekly
RA	receptor agonist
Restart	Any reinitiation of study drug dose escalation after a temporary interruption at any time during the study.

SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
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.
SGLT-2i	sodium-glucose cotransporter-2 inhibitor
study drug	refer to investigational product definition
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reactions Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TIA	transient ischemic attack
ULN	upper limit of normal
UV	unscheduled visit
WOCBP	women of childbearing potential

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry[a]**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
Mean cell volume	Direct bilirubin
Mean cell hemoglobin concentration	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT)
Neutrophils, segmented	Aspartate aminotransferase (AST)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Creatinine
Eosinophils	Uric acid
Basophils	Calcium
Platelets	Glucose
Cell morphology (RBC, WBC)	Albumin
	Creatine kinase (CK) (Also known as creatine phosphokinase [CPK])
	Cystatin-C
	eGFR (calculated by CKD-EPI equation)[b]
	Hormones (females only)
	Urine pregnancy[c]
	Serum pregnancy[a]
	Follicle-Stimulating Hormone (FSH)[a,e]
Stored Samples[d]	**Lipid Panel[a]**
Nonpharmacogenetic Samples:	Total cholesterol
Serum	Triglycerides
EDTA Plasma	HDL-cholesterol
P800 Plasma	LDL-cholesterol (Calculated)
Pharmacogenetic Sample	
	Pancreatic (Exocrine)[a]
	Pancreatic amylase
	Lipase
	Other Tests
	Calcitonin[a]
	HbA1c[a]
	Serum glucose, fasting
	Urine Chemistries[a]
	Albumin
	Creatinine
	Albumin/Creatinine Ratio (ACR)

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RBC = red blood cells; WBC = white blood cells; WOCBP = women of childbearing potential.

[a] All tests will be performed by a Lilly-designated central laboratory, unless otherwise noted in the Schedule of Activities.
[b] The CKD-EPI equation will be used by the central lab to estimate and report eGFR.
[c] A urine pregnancy test must be performed at Visit 2 with the result available prior to randomization and first injection of study drug(s) for WOCBP only. Additional urine pregnancy tests may be performed at the investigator's discretion during the study and if required by local regulations.
[d] These samples are being stored. If tested at a later time, results will not be reported to the sites but will be utilized for analysis purposes only.
[e] Follicle-stimulating hormone test performed at Visit 1 for women 40 to 55 years of age in order to determine pre-postmenopausal stage. Postmenopausal stage is defined in Inclusion Criterion 5 (Section 6.1).

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for the following:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as 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. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel 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 information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

Appendix 3.1.4. Ethical Review

The investigator or an appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current IB, and updates during the course of the study
- ICF
- other relevant documents (eg, curricula vitae, advertisements)

Appendix 3.1.5. Regulatory Considerations

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

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party.

The investigator will be responsible for reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Appendix 3.1.6. Investigator Information

Physicians with a specialty in diabetes/endocrinology, cardiology, nephrology, internal medicine, family medicine, general medicine, or any other specialty physician who has experience treating T2DM with clinical research experience will participate as investigators in this clinical trial.

Appendix 3.1.7. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.8. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

A qualified investigator will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. 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 dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Appendix 3.3. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate

- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the investigator site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.3.1. Data Capture System

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

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

Additionally, clinical outcome assessment data (scales, questionnaires) will be collected by the patient/investigator site personnel via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Data collected via the sponsor-provided data capture systems 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 systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

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

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

Appendix 3.4. Study and Site Closure

Appendix 3.4.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

In the event of study site closure, every effort should be made to transfer patients to another site. If patient transfer is not possible, a plan must be put into place to ascertain vital status and assess endpoints at study end for all randomized patients.

Appendix 3.4.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.5. Publication Policy

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the sponsor CRP or its designee.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by central laboratory.

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

Appendix 5. Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and BMI

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

Measuring Height

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

Step 2. Ask the patient 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 back board or the stadiometer or the wall.

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

Step 4. Ask the patient 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 patient's head. Record the patient's height in centimeters (cm).

Measuring Weight

Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms (kg) to one decimal place. All weights for a given patient should be measured using the same scale, whenever possible, after the patient has emptied their bladder. Patients should be lightly clothed but not wearing shoes while their weight is measured.

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

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

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

Step 4. Ask the patient to stand still with their arms by their sides and then record their weight in kilograms (kg).

Measuring Waist Circumference

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

Step 1. Ask the participant to wear light clothing (if available, patient gowns could also be used).

Step 2. Ask the participant to stand with their feet close together, arms at their side, body weight evenly distributed.

Step 3. Ask the participant to relax and measure the participant's waist circumference.

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 following: Amputee Coalition – https://www.amputee-coalition.org/limb-loss-resource-center/resources-filtered/resources-by-topic/healthy-living/about-bmi/.

Appendix 6. Recommended Laboratory Testing for Hypersensitivity Events

Recommended laboratory tests should be performed at the time of a systemic hypersensitivity event. The management of the AE may warrant laboratory testing beyond that described below and should be performed as clinically indicated.

Laboratory testing during a Systemic Hypersensitivity Event is performed to:

- help characterize and classify systemic hypersensitivity reactions,
- meet regulatory expectations, and
- improve subsequent clinical management by helping to distinguish between the various mechanistic bases of anaphylaxis.

If anaphylaxis is suspected or generalized urticaria is present, then:

1. obtain a sample within 1 to 2 hours of the event,
    a. samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time
2. record the time at which the sample was collected, and
3. obtain a follow up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

Laboratory Tests for Hypersensitivity Events

Test	Details
Tryptase	If a tryptase sample is obtained more than 2 hours after the event (ie, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, then obtain urine for *N*-methylhistamine (NMH) testing. For tryptase serum samples obtained within 2 to 12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.
ADA	ADA testing should include drug specific IgE or the basophil activation test (BAT). The BAT requires a serum sample
tirzepatide pharmacokinetic concentration	
Complement	C3a, C5a
Cytokines	IL-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines)

All tests will be performed by a Lilly-designated central laboratory.

Appendix 7. Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Informed consent

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

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

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

> **Telemedicine:** Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to,

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations. Local laboratory results should be retained in the patient's study file.

Study drug and ancillary supplies

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 drug 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.

Adjustments to visit windows

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

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visits After Visit 16	The Visit window may be expanded to ±28 Days

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

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study drug 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.

Appendix 8. Country-Specific Requirements

Appendix 8.1. Changes to the Protocol for Study Sites in Europe who Follow General Data Protection Regulation

In this appendix, additions are designated using underline. Deletions are designated using strikethrough.

This appendix is specific to the study sites in Europe, including Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Italy, Netherlands, Poland, Romania, Slovakia, Spain, Sweden, and the United Kingdom.

Changes to the protocol:

- To remove all references to third party patient locator services from the Study GPGN protocol for the 15 countries in Europe who follow GDPR data privacy regulations.

Appendix 8.1.1. Section 5.1. Overall Design

If an on-site clinic or remote final visit with the patient is not possible, contact with the patient's family or the patient's primary physician or medical record review during the close out period of the study to ascertain vital status and record safety and efficacy endpoints is required. National registries/databases, medical records, voter records~~, third-party patient locator services,~~ or other means may be used to ascertain this information. At a minimum, vital status (alive or dead) should be ascertained for all randomized study participants, including participants who are considered high risk of being lost to follow-up or participants who have withdrawn consent.

Appendix 8.1.2. Section 8.3. Lost to Follow-Up

A patient will be considered high risk for lost to follow-up if he or she repeatedly fails to return for scheduled visits. A patient will be considered as lost to follow-up only if the patient is unable to be contacted by the study site during the study close-out period, and no data on vital status (alive or dead) is available through accepted methods for ascertainment, including query of public databases. Investigator site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

For endpoint/end of study purposes, investigator site personnel should make every effort to ascertain endpoints by contacting the patient's family or designee/personal contact (eg, friend), family doctor, or attempt to determine vital status via other means (if not prohibited by local laws) (eg, national registries/databases, medical records, and voter records~~, and third-party patient locator services~~). At a minimum, vital status should be ascertained for all randomized study participants, including participants who are considered high risk of being lost to follow-up or participants who have withdrawn consent.

Appendix 8.2. Changes applicable to Study Sites in EU

In this appendix, additions are designated using underline. Deletions are designated using strikethrough.

This appendix to Study I8F-MC-GPGN is specific to study sites in the European Union (EU).

The purpose of this appendix is to incorporate feedback from the competent authorities within the EU.

Appendix 8.2.1. Section 2. Schedule of Activities

Table GPGN.1. Schedule of Activities: Screening through to 24 Weeks (Visit 14)

	Screening	Dose Escalation Period												
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week of Treatment	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Allowable Window (days)		**+7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Fasting (>8 hours)		**X**												
Optional Telephone Visit[a]			**X**		**X**		**X**		**X**		**X**		**X**	
Laboratory Tests (Performed at a Central Laboratory except Urine Pregnancy)														
Serum pregnancy [g]	X													
Urine pregnancy [h]		X												

g A serum pregnancy test must be performed at Visit 1 in WOCBP.

h A local urine pregnancy test must be performed at Visit 2 with the result available prior to randomization and first injection of study drug(s) for WOCBP only. Additional local urine pregnancy tests may be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period. A pregnancy test will be performed at the time of permanent study drug discontinuation (i.e., at the end of relevant systemic exposure).

Appendix 8.3. Substudy to Investigate the Diabetic Retinopathy Progression

This appendix only applies to investigative sites participating in retinopathy substudy.

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy (DR). Type 1 diabetes patients on intensive glycemic control in the Diabetes Control and Complication Trial (DCCT) has demonstrated increased DR progression in the first 1 to 2 years when compared with patients on standard glycemic control management. However, in longer follow-up, the DR progression was markedly reduced in the intensive arm (DCCT Research Group 1993). Results of recent cardiovascular outcome trials (CVOTs) with glucagon-like peptide-1 receptor agonists (GLP1-RAs) led to a similar hypothesis.

Most evidence of the effect of GLP1-RAs on DR is indirect, based on safety findings from interventions frequently associated with DR progression. The 2-year Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) reported a significantly higher rate of interventions associated with retinopathy complications on semaglutide versus placebo (hazard ratio [HR] 1.76 [95% confidence interval [CI] 1.11–2.78]) (Marso et al. 2016a). The incidence of these interventions on semaglutide was larger in patients with marked early hemoglobin A1c (HbA1c) reduction (Vilsbøll et al. 2018). Liraglutide treatment in the LEADER CVOT has been associated with numerically increased incidences of interventions due to retinopathy complications (HR 1.15 [0.87–1.52]) (Marso et al. 2016b). Similarly, dulaglutide, the active comparator in the present study, was also associated with numerically increased incidence (1.9%) of treatments of retinopathy complications compared with placebo (1.5%, p =.16) in the REWIND CVOT (Gerstein et al. 2019). On the other hand, none of the GLP1-RA treatments were associated with clinically meaningful visual loss. Consequently, regulatory labels of these drugs include warnings that patients with a history of DR should be monitored for progression of DR. No results from incretin studies have been reported so far with systematic evaluation of DR.

Protocol I8F-MC-GPGN (SURPASS-CVOT) is a prospective, double-blind study with expected average follow-up of 4 to 5 years of tirzepatide versus dulaglutide in patients with atherosclerotic cardiovascular disease. Patients have uncontrolled (HbA1c: 7% to 10.5%) diabetes with longer duration, and a large proportion of patients have DR or have increased risk for DR.

Tirzepatide, a GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) dual agonist and a potential new incretin therapeutic agent, has been shown to reduce blood glucose and HbA1c more than dulaglutide 1.5 mg (Frias et al. 2018). Due to the rapid blood glucose reduction, both treatments may be associated with increased progression of DR in the first 1 to 2 years, especially in patients with preexisting DR or increased risk due to other conditions such as long-term diabetes duration. Subsequently, the progression could potentially slow down due to anticipated improved chronic glycemic control. On the other hand, tirzepatide can significantly reduce the serum triglyceride levels which again could potentially be protective of DR progression (Lloyd et al. 1995). Both in the FIELD and ACCORD Eye studies, fenofibrate

therapy, a triglyceride-lowering agent, was associated with less DR progression in patients with type 2 diabetes (Keech et al. 2007; ACCORD Study 2010).

The aim of the present substudy is to investigate the DR progression on tirzepatide based on systematic, repeated collection and analyses of retinopathy images and to evaluate these changes when compared to dulaglutide.

This appendix to Study I8F-MC-GPGN (SURPASS-CVOT) describes the eligibility criteria and procedures to be followed for those participants enrolled in this appendix in addition to all procedures required by protocol SURPASS-CVOT or any subsequent amendments to that protocol.

Appendix 8.3.1. Section 2. Schedule of Activities

For the purposes of the appendix, the SoA tables are labeled 1-3.

For clarity in the SoA only, additions to the main protocol SoA 1 and 2 are underscored and deletions have been identified with ~~strikethroughs~~.

An additional SoA table 3 outlines procedures if the main study is terminated early after receiving the planned interim efficacy analysis results.

If the main study continues after receiving the planned interim efficacy analysis results, use SoA tables 1 and 2.

Table GPGN.1. Schedule of Activities 1 and 2

Schedule of Activities: Screening through to 24 Weeks (Visit 14)

	Screening	Dose Escalation Period												
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Week of Treatment	-2	0	2	4	6	8	10	12	14	16	18	20	22	24
Allowable Window (days)		+7	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±~~3~~28
Fasting (>8 hours)		X												
Optional Telephone Visit[a]			X		X		X		X		X		X	
Ophthalmology Assessments[t]														
Visual acuity checks	X													X
Dilated fundoscopic examination[f]	X													X[f]
Standard retinal fundus photographs	X													X

Schedule of Activities: 9 Months to Final Visit

	Maintenance Period															Extended Maintenance Period[n]				Early Termination[o]		Unscheduled Visit (UV)[p]			Final Visit
Visit	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	EVa (31, 35, etc.)	EVb (32, 36, etc.)	EVc (33, 37, etc.)	EVd (34, 38, etc.)	ETV	Post-ETV (60)	UV	Dosing UV	Phone Follow-Up Dosing UV	99
Study Month	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	(+3)	(+6)	(+9)	(+12)		(+1)				-
Allowable Window (days)	±15	±~~15~~ 28	±15	±~~15~~ 28	±15	±~~15~~ 28	±15	±15	±15	±~~15~~ 28	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15		±7				
Fasting (>8 hours)		X				X								X							X		X[r]			X
Ophthalmology Assessments[t]																										
Visual acuity check		X		X		X				X											X					X
Dilated fundoscopic examination[f]		X[f]		X		X				X											X					X
Standard retinal fundus photographs		X		X		X				X											X					X

~~f Dilated fundoscopic exam will be evaluated by an eye care professional (ophthalmologist or optometrist) for all patients (after signed informed consent and prior to randomization). This diagnostic procedure can be either a direct fundus examination or a review of fundus photographs. Either of the 2 procedures must be finalized prior to randomization. The results from this exam will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy. If based on a recent (performed ≤ 90 days prior to randomization) fundus examination, the eCRF could be completed, there is no need for repeated procedure during screening period (after signed informed consent and prior to randomization). A follow up dilated fundoscopic exam should be performed when clinically indicated by any adverse event suspected of worsening retinopathy, and the findings should be recorded on the retinopathy eCRF. For participants with severe non-proliferative retinopathy or proliferative retinopathy and/or macular edema at baseline, a follow up fundoscopic exam at Visit 14 ±30 days and Visit 16 ±30 days is required and should be recorded in the eCRF.~~

t Ophthalmology assessments will be performed at screening (between Visit 1 and 2), 6-months (Visit 14), 12-months (Visit 16), 18-months (Visit 18), 24-months (Visit 20), and 36-months (Visit 24) visits, or at the early termination visit (ETV) for participants who discontinue early from the study. If the participant is in the rescreening process for the study and ophthalmology assessments for this substudy were completed for the previous screening process (performed ≤90 days prior to currently planned randomization date), there is no need to repeat assessments during the rescreening period. The data of this previous screening ophthalmology assessment can be accepted as part of the ongoing rescreening process. If the ETV is scheduled within 6 months of the previous ophthalmology assessment, there is no need for an additional ophthalmology assessment visit. If the final visit (Visit 99) is reached before 36 months (Visit 24), the ophthalmology assessment should be performed also at the final visit unless the previous ophthalmology assessment was within 6 months of the final visit. In the event the participant discontinues study intervention, the ophthalmology assessments should continue on schedule.

NOTE: Study visit windows for ophthalmology assessments have been changed to ±28 days.

Schedule of Activities 3

Schedule of Activities if the main study is terminated early after receiving the planned interim efficacy analysis results: 9 Months to Final Visit

	Maintenance Period										Early Termination[a]		Unscheduled Visit[b]		
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**ETV**	**Post-ETV (60)**	**UV**	**Dosing UV**	**Phone Follow-Up Dosing UV**
Study Month	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**		**(+1)**			
Allowable Window (days)	**±7**	**±28**	**±15**	**±28**	**±15**	**±28**	**±15**	**±15**	**±15**	**±28**		**±7**			
Reconsent for continuation of Appendix			X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]					
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual acuity check[d]		X		X		X				X	X				
Dilated fundoscopic examination[d]		X		X		X				X	X				
Standard retinal fundus photographs[d]		X		X		X				X	X				
Pulse rate and blood pressure[e]		X		X		X		X		X	X	X	X	X	
Dispense study drug	X	X	X	X	X	X	X	X	X	X				X	
Collect and record unused study drug	X	X	X	X	X	X	X	X	X	X	X			X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry panel		X				X				X	X		X[f]		
Lipid panel		X				X					X		X[f]		
Hematology											X		X[f]		
Pancreatic amylase, lipase		X				X				X	X		X[f]		
Calcitonin		X				X				X	X		X[f]		
HbA1c		X				X				X	X		X[f]		
eGFR (CKD-EPI)		X				X				X	X		X[f]		

	Maintenance Period										Early Termination[a]		Unscheduled Visit[b]		
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**ETV**	**Post-ETV (60)**	**UV**	**Dosing UV**	**Phone Follow-Up Dosing UV**
Study Month	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**		**(+1)**			
Allowable Window (days)	**±7**	**±28**	**±15**	**±28**	**±15**	**±28**	**±15**	**±15**	**±15**	**±28**		**±7**			
Urine ACR		X				X				X	X		X[f]		
Urine pregnancy											X		X[f]		
Cystatin-C		X				X				X	X		X[f]		
Nonpharmacogenetic samples						X					X				

[a] Patients discontinuing from the study prematurely per criteria outlined in Section 8.2 of the main protocol should complete an early termination visit (ETV), followed by a post-ETV 1 month later, and follow up for annual vital status should be entered into the case report form (CRF).

[b] There are 3 types of Unscheduled Visits (UV):

- Unscheduled Visits (UV) – Unscheduled Visit per investigator discretion. The study site will determine if fasting status is needed prior to the visit. Concomitant medications and adverse events are required and should be recorded in the eCRF.
- Dosing Unscheduled Visit (UV) (required use of IWRS unscheduled A / B visit starting at Visit 14) – these visits will include dose re-escalation and dose restart (reinitiation). The study drug must be restarted when it is safe to do so and only on a clinic visit. This visit must include collection of concomitant medications, pulse rate and blood pressure and adverse events in the eCRF. The subsequent dosing visits will be scheduled every 4 weeks (±7 days) until maximum tolerated dose is achieved.
- Phone Follow-up Dosing Unscheduled Visit (UV) – these visits are optional phone visits.

[c] Patients must be reconsented at their first Visit after closure of the main study.

[d] Ophthalmology assessments will be performed at 12-months (Visit 16), 18-months (Visit 18), 24-months (Visit 20), and 36-months (Visit 24), or at the early termination visit (ETV) for participants who discontinue early from the study.
If the ETV is scheduled within 6 months of the previous ophthalmology assessment, there is no need for an additional ophthalmology assessment visit.
If the participant discontinues study intervention, the ophthalmology assessments should continue on schedule.

[e] The order of conducting the local ECG, vital sign measurements, and blood samples for laboratory testing is determined at the investigator site. At unscheduled visits, ECG is per investigator discretion.

[f] Unscheduled Visit: laboratory tests may be drawn according to investigator discretion or to repeat laboratory tests as needed.

Appendix 8.3.2. Section 4. Objectives and Endpoints

Table GPGN.2. Objectives and Endpoints

Objectives	Endpoints
Primary • To compare the effect of tirzepatide dose up to 15 mg QW with dulaglutide 1.5 mg QW on DR progression.	• At least 2 grades worsening of DR per person on Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) - (ETDRS2+) from baseline at 36 months visit
Key Secondary • To compare the effect of tirzepatide dose up to 15 mg QW with dulaglutide 1.5 mg QW on DR progression.	• Time to first onset of ETDRS2+ per person • Time to first onset of worsening of visual acuity of at least 3 lines (15 letters) on either eye
Exploratory To assess the safety of tirzepatide dose up to 15 mg QW when compared with dulaglutide 1.5 mg QW on DR.	• ETDRS3+ from baseline at 36 months visit • Time to first onset of ETDRS3+ • ETDRS2+ at 36 months or photocoagulation, intravitreal injections (anti-VEGF, steroid treatment, or both), or vitrectomy in response to ETDRS2+ from baseline • Time to first onset of new diagnosis of PDR • Time to first onset new diagnosis of ME • Time to first onset of treatment by photocoagulation, intravitreal injections (anti-VEGF, steroid treatment, or both), or vitrectomy • Time to first onset of treatment by photocoagulation, intravitreal injections (anti-VEGF, steroid treatment, or both), or vitrectomy followed by ETDRS2+ • Mean change of ETDRS DRSS • Presence of at least 2 grade ETDRS2+ DRSS progression and improvement per either eye • Presence of at least 3 grade ETDRS DRSS progression and improvement per either eye • Presence of at least 2 grade ETDRS DRSS progression and improvement per person • Presence of at least 3 grade ETDRS DRSS progression and improvement per person

Objectives	Endpoints
	• Time to first occurrence of treatment for at least one of the following: o focal/grid laser photocoagulation o pan-retinal laser photocoagulation o intravitreal injection with anti-VEGF o intravitreal injection with steroid o vitrectomy • Change in visual acuity in the worse- or better-seeing eye as measure in the number of letters using best correction

Abbreviations: DR = diabetic retinopathy; ETDRS DRSS = Early Treatment Diabetic Retinopathy Study, Diabetic Retinopathy Severity Scale; ETDRS2+ = progression of at least 2 grades per person on the Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale; ETDRS3+ = progression of at least 3 grades per person on the Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale; ME = macular edema; PDR = proliferative diabetic retinopathy; QW = once weekly; VEGF = vascular endothelial growth factor.

Appendix 8.3.3. Section 6.1. Inclusion Criteria

Patients who agree to participate in this substudy, which requires periodic visual acuity testing and dilated fundoscopic exams, must be eligible for the main study and fulfill one of the following criteria at baseline:

[38] Any evidence of diabetic retinopathy (DR) or macular edema (ME) in either eye according to the baseline ophthalmologic investigation

[39] Irrespective from retinal status, the patient is at high risk for developing/recurring/progressing DR due to the duration of T2DM ≥15 calendar years and HbA1c ≥ 8% at screening

Appendix 8.3.4. Study Design for Substudy

Section 5.1. Overall Design

Patient can qualify for the substudy based on the presence of any severity of DR and/or ME described during the ophthalmology assessment at screening. Furthermore, a patient with a diagnosis of T2DM ≥15 calendar years and HbA1c ≥ 8% at screening (determined in the central laboratory), irrespective of retinal status, also qualifies for the substudy.

The ophthalmology assessment at screening includes the determination of visual acuity and DR/ME status and will be performed by an eye care professional (ophthalmologist, optometrist, or other qualified person) during the screening period (between Visit 1 and Visit 2). Visual acuity, DR, and ME status will be determined by dilated fundoscopic examination. When qualified for the substudy, the patient will also undergo standard 7-field or 4-field-wide digital color fundus photography for central reading. All results of the screening will serve as baseline.

If the participant is in the rescreening process for the study and the ophthalmology assessments for the substudy were completed for the previous screening process (performed ≤90 days prior to the currently planned randomization date), there is no need to repeat assessments during the rescreening period (between Visit 1 and Visit 2). The data from the previous screening ophthalmology assessment can be accepted as part of the ongoing rescreening process.

As part of the ongoing ophthalmology assessments, visual acuity checks, fundoscopic evaluation, and standard retinal fundus photographs will be performed during the screening period (between Visit 1 and Visit 2 [see above]) and repeated at 6-months (Visit 14), 12-months (Visit 16), 18-months (Visit 18), 24-months (Visit 20), and 36-months (Visit 24) visits, or at the early termination visit (ETV) for patients who discontinue early from the study. If the ETV is scheduled within 6 months of the previous ophthalmology assessment, there is no need for repeated ophthalmology visit as part of the ETV. If the final visit (Visit 99) is reached before 36 months (Visit 24), the ophthalmology assessment should be performed also at the final visit (Visit 99) unless the previous ophthalmology visit was within 6 months of the final visit. In the event the participant discontinues study treatment, the ophthalmology assessments should continue according to the Schedule of Activities (SoA). Furthermore, should the standard retinal fundus photographs need to be repeated for any reason, the repeated imaging should be completed within the same study visit window.

Visual acuity evaluation will be performed as part of the ophthalmology assessments prior to dilation. The results from this exam will be recorded on a specific eCRF.

Dilated fundoscopic exam will be evaluated to determine the presence or absence of DR or ME. This diagnostic procedure should be direct fundus examination. The results from this exam will be recorded on a specific retinopathy eCRF as a measure of retinopathy.

Standard retinal fundus photographs will be taken after the dilated fundoscopic exam for evaluation by the central reading center, blinded to study drug, and graded according to the modified Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale (DRRS) scale. The standard retinal digital color fundus photographs should be taken by the same methodology for a respective person: either 7-field or 4-field-wide photographs and preferably with the same optical device and by the identical eye care professional.

If the main study is terminated early for efficacy after receiving the planned interim efficacy analysis results, participants in this protocol appendix will be reconsented, continue to receive study intervention, and perform the required assessments outlined in the SoA in Section 2 until Visit 24 (3 years).

Blinding to investigators, site staff, clinical monitors and participants in this protocol appendix will be maintained until the protocol appendix is complete.

Appendix 8.3.5. Section 5.2. Number of Participants

Appendix 8.3.10.1 outlines the approximate number of participants originally planned for this substudy. Approximately 930 participants were randomized to ensure an adequate number of participants were able to complete this appendix.

Appendix 8.3.6. Section 5.4. Scientific Rationale for Study Design

The most relevant risk factors for the development of DR are the duration of diabetes and poor glycemic control (Jampol et al. 2020; Vujosevic et al. 2020). The study plan is to enroll patients with either preexisting DR or without preexisting DR but at high risk for DR determined by the long duration of diabetes of at least 15 years and poor glycemic control (HbA1c ≥8% at screening). In both groups, participants with existing DR and with risk for DR have similar and elevated risk for progression on DR and on the ETDRS DRSS (ETDRS Research Group 1991). The inclusion criteria enable the interpretation of the study results to a broader patient population.

Two-grade or more progression on the ETDRS DRSS (ETDRS2+) per person is frequently used as primary outcome for determination of DR progression, including the Wisconsin study (Klein et al. 1989, 1994), the UKPDS (Stratton et al. 2001) the ADVANCE retinal substudy AdRem (Beulens et al. 2009), and recent anti-VEGF studies (Bressler et al. 2017). Moreover, ETDRS2+ over 4 years strongly predicted the development of proliferative DR (PDR) during the upcoming 6 years (Klein et al. 2001). ETDRS2+ has been chosen for the primary outcome of this substudy due to the sensitivity for detecting changes. Measures of ETDRS2+ versus ETDRS3+ could be of particular interest for participants without baseline DR but with high risk for DR progression. The incidence rate for ETDRS2+ progression was similar in participants without or with various degrees of DR at baseline in the Wisconsin study (Klein et al. 1989, 1994) and in AdRem (Beulens et al. 2009). The incidence of 2 or more grade progression on the DRSS (ETDRS2+) is approximately 2- to 3-fold when compared with 3 or more grade progression (ETDRS3+). For example, in the first year of the secondary interventional cohort of the Diabetes Control and Complication Trial (DCCT) (participants with preexisting DR), the incidence rate of ETDRS2+ progression on the conventional and intensive treatment arms was 7.8% and 10.2%, respectively, while ETDRS3+ progression was 2.3 and 2.6%, respectively (DCCT Research Group 1993).

Similarly, approximately 2-fold progression in ETDRS2+ versus ETDRS3+ was observed in the ADVANCE retinal substudy AdRem (Beulens et al. 2009). In the placebo arm of the 4-year study, the incidence rate was 3.8 per 100 patient-years for ETSDR2+ but 1.3 per 100 patient-years for ETDRS3+. In the Wisconsin study, the population of patients in the second quartile of the HbA1c range of 7.7% to 8.6%, comparable glycemic control to the population of the present study, had an incidence rate of 4.2 to 6.5 per 100 patient-years for worsening DR by ETDRS2+ (Klein et al. 1989, 1994). In the 6-year retinopathy substudy of UKPDS, the ETDRS2+ incidence rate was approximately 3.7% and 6.1% for patients with no or preexisting DR, accordingly (Stratton et al. 2001). Based on the incidence rate of ETDRS3+ in the ACCORD Eye study (1.8 per 100 patient-years), an incidence rate of 3.5 to 4.5 per 100 patient-years for ETDRS2+ could be approximated in that study (ACCORD Study 2010).

Considering the various baseline characteristics including DR status in the studies referenced, an incidence rate of 5 per 100 patient-years of ETDRS2+ has been estimated for participants meeting entry criteria for this substudy.

The observation period for this substudy will be 36 months. This timing allows for evaluation of the risk of DR progression with tirzepatide versus dulaglutide treatment in the initial 1- to 2-year treatment period when fast progression in the DR status may occur due to markedly improved glycemic control. It also covers the period (Years 2 and 3) when potentially reduced DR progression could be anticipated. The observation period could be shorter by the ETV due to participant's discontinuation or termination of the study.

Visual acuity testing is part of the ophthalmology follow-up as a measure for potential complication of DR, focusing on the detection of at least moderate visual loss (defined as a 15 or more letters score or 3-lines decrease in visual acuity).

Based on preliminary data from enrolled study population, the large proportion of enrolled participants (approximately up to 90%) are anticipated to have no or mild non-PDR (NPDR) and the majority of the rest are anticipated to have moderate NPDR. In addition, none of them are planning treatment for DR and/or ME when entering the study. Thus, the substudy population consists of participants with low risk for treatment-emergent DR complications during the study course. When ophthalmology conditions for follow-up diagnostic and/or treatment procedures are identified during the ophthalmology visits, appropriate recordings in the study documentation should be performed (i.e., adverse event reporting, concomitant medication changes) and the subsequent ophthalmology follow-up should be performed in-line with local guidelines and as best possible patient care.

Photocoagulation, intravitreous treatment with steroids and/or anti-VEGF, and vitrectomy are increasingly frequent therapeutic interventions for PDR or central ME with vision loss. In some clinics, selected forms of severe NPDR are also a target for one of these treatments. Anti-VEGF treatment and, to a lesser extent, photocoagulation could result in marked improvement in the severity of DR (Bressler et al. 2017). However, the application of these treatments is influenced by the individual health care systems, access to these therapies, and socioeconomic circumstances. Thus, the initiation these treatments will be subject of exploratory analyses only.

Appendix 8.3.7. Randomization Scheme

Section 7.2. Method of Treatment Assignment

Participants enrolled into the substudy are a part of participants randomized in the main protocol and will receive study drug to which the patient was randomized in the main protocol. Therefore, participants will be randomly allocated in a 1:1 ratio to receive tirzepatide or dulaglutide stratified by country of enrollment and baseline sodium-glucose cotransporter-2 inhibitor (SGLT-2i) use, irrespective of substudy participation.

Appendix 8.3.8. Ophthalmology Evaluations

To determine visual acuity, either ETDRS or Snellen visual acuity test results using best correction will be collected at each scheduled visit. Evaluation of visual acuity by ETDRS chart is preferred for more precision (Kaiser 2009; Kalpana et al. 2013). The same study participants should be tested with the same method under identical conditions at every visit.

Dilated fundoscopic examination will be performed to evaluate the retinal status and in case of DR, to estimate the DR stages (Solomon et al. 2017).

The standard retinal fundus photographs will serve to determine the ETDRS DRSS by masked graders at the central reading center. The ETDRS is a tool for recording retinopathy status in a scale sensitive for well-defined changes within and between various severities of NPDR and PDR. The slightly modified and abbreviated ETDRS DRSS for individual eyes will be used. The ETDRS DRSS grades for the individual eyes will be combined per person, and these personal scores will be the primary subject of the analyses. The results of these evaluations will not be available for the investigators as these results does not contribute to an individual patient´s assessment beyond the findings of the dilated fundoscopic examination.

No additional ophthalmology evaluations are planned as part of the substudy. When ophthalmology condition for follow-up diagnostic and/or treatment procedures are identified during the ophthalmology visits, appropriate recordings in the study documentation should be performed (i.e., adverse event reporting, concomitant medication changes) and the subsequent ophthalmology follow-up should be performed in-line with local guidelines and as best possible patient care.

Appendix 8.3.9. Primary, Secondary, and Additional Study Endpoint Reporting

If the main study is terminated early after receiving the planned efficacy interim analysis results, then endpoint reporting for these events is no longer necessary after database lock for the main study:

- death
- myocardial infarction
- stroke or transient ischemic attack
- hospitalization for heart failure or an urgent heart failure visit
- hospitalization for unstable angina, and

- coronary revascularizations.

If these events occur, follow normal AE and SAE reporting guidelines using the appropriate CRF. All events meeting serious criteria must be reported using the SAE CRF.

Appendix 8.3.10. Section 10. Statistical Considerations

Appendix 8.3.10.1. Section 10.1. Sample Size Determination

Out of the randomized participants in the main protocol, approximately 700 participants will be enrolled into the substudy. This sample size provides 80% power for demonstrating non-inferiority of tirzepatide to dulaglutide with a margin of 1.8-fold in terms of hazard ratio for time to first onset of primary outcome, at least 2 grades worsening of DR per person using ETDRS.

The sample size determination assumes that 5 participants experiencing the primary outcome for 100 patient-years of follow-up, equally for both treatment exposures, and premature discontinuation from the evaluation of the primary outcome measures up to 5% per year.

This sample size also provides 77% power for demonstrating non-inferiority of tirzepatide to dulaglutide with a margin of 1.8-fold in terms of odds ratio for ETDRS2+ at 36 months or early termination.

Appendix 8.3.11. Section 10.3.1. General Statistical Considerations

Analyses for the substudy will be carried out using the modified intention-to-treat efficacy (mITTE) dataset. The substudy will conclude that tirzepatide is not associated with clinically meaningful increased risk for worsening DR status compared to dulaglutide, if the upper bound of the 95% CI for odds ratio (tirzepatide versus dulaglutide) for at least 2 grades worsening of DR per person using ETDRS scale from randomization through 36 months is less than a non-inferiority margin of 1.8-fold.

The primary analysis of the substudy for at least 2 grades worsening of DR using ETDRS scale at 36 months will be a logistic regression model using all available data regardless of adherence to study drug. The model will include treatment, country/pooled country, baseline SGLT-2i use, baseline HbA1c, and duration of T2DM as fixed effects, and baseline ETDRS score as a covariate. The analysis of time to first onset of at least 2 grades worsening of DR using ETDRS scale in the substudy will be a Cox proportional hazard model stratified by baseline SGLT-2i use with treatment, baseline HbA1c, and duration of T2DM as fixed effects, and baseline ETDRS score as a covariate.

Because the study duration of the main protocol is MACE-3 event-driven, some participants enrolled into the substudy may potentially not reach a 36-month visit before the last study visit. In analyses for primary and secondary objectives, if the ETDRS values at the scheduled visits through 36 months are missing, they will be imputed based on observed ETDRS values from participants in the same treatment group who performed dilated fundoscopic examination, prematurely discontinued study drug, and were in the same status whether treatment was used for retinopathy. Analysis will be conducted with multiple imputations. In cases where there are not

enough retrieved dropouts to provide a reliable imputation model (e.g., the model does not converge), alternative imputation methods will be considered.

The analyses intend to estimate the "treatment policy strategy" based parameters of interest, that is, irrespective of adherence to study drug or introduction of additional treatment for retinopathy.

Since the substudy is related to safety assessments, no multiplicity adjustments will be made.

If the main study is terminated early after receiving the planned efficacy interim analysis results, the AE data collected after stopping the main study will be analyzed and reported separately in the appendix CSR.

Appendix 8.4. Changes Applicable to Countries Allowing the Shipment of Study Drug Directly from Site to a Patient that Cannot Attend Clinic Visits

This appendix is specific to countries allowing the shipment of study drug directly from site to a patient that cannot attend clinic visits.

Patients that have remote visits should remain on study drug, if eligible. This appendix allows eligible patients to remain on study drug even if they are unable to have on-site clinic visits.

All deletions have been identified by ~~strikethroughs~~ and all additions have been identified by the use of underscore.

Appendix 8.4.1. Section 5.1. Overall Design

Remote visits may be considered at the discretion of the investigator if a patient is unable to come to their scheduled on-site visit. If a remote visit occurs, this should be entered in the patient's eCRF. If necessary, study drug may be shipped directly from the site to the patient. Alternative options to visit procedures must be considered with prior consultation and written approval of the sponsor.

Appendix 8.4.2. Section 7.5. Preparation/Handling/Storage/Accountability

The investigator or designee is responsible for the following:

- Confirming appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Ensuring that only ~~participants~~patients enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. Only authorized site staff may package study drug for shipment directly from the site to the patient. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

The study site must store the study drug in a locked and secure environment. The study drug should be refrigerated (not frozen) until use. Dry ice should not be used for cooling. Patients will receive insulated bags with cooling gel packs for use in transporting the study drug carton from the site to their home. For patients who require that study drug be shipped directly from site, study drug will be packaged in an appropriate manner.

Patients will be instructed to return any unused study drug at the next study visit. Used single dose pens should be disposed of in the sharp items container and the container should be returned to the site (or disposed of per local regulations) when full or sooner, unless the pen is damaged. In the case of a damaged pen, the patient is to report the product complaint to the site (per Section 9.2.3) and return the damaged pen in the original box provided to the site. Study site staff must regularly assess whether the patient is correctly administering the assigned study drug and storing the study drug according to the provided instructions. For patients who require that study drug be shipped directly from the site, a study drug return process should be established and communicated to the patient (for example, if patients will be instructed to keep study drug until next visit to site) as well a process on how compliance will be checked.

Appendix 9. Protocol Amendment History

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

Amendment [e]: (04-Sep-2023)
This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:
The primary rationale for this amendment is to align with new EU Clinical Trial Regulation requirements.

Section # and Name	Description of Change	Brief Rationale
1. Synopsis	Added • Regulatory Agency Identifier Number(s) • Study Population • Ethical Considerations of Benefit/Risk	For EU-CTR compliance
7. Treatments	Updated the definition of study intervention	For EU-CTR compliance
7.1. Treatments Administered	Added the table of interventions	For EU-CTR compliance
7.1.2. Packaging and Labeling	Updated the first paragraph	For EU-CTR compliance
9.2. Adverse Events	Added the events meeting the AE definition	For EU-CTR compliance
9.2.1. Serious Adverse Events	Added “SAE regulatory reporting” paragraph	For EU-CTR compliance
9.2.1.1. Suspected Unexpected Serious Adverse Reactions	Replaced “Clinical Trial Directive 2001/20/EC” to “European Union-Clinical Trial Regulation 536/2014”	Update
10.3.1. General Statistical Considerations	Added the paragraph regarding handling of missing, unused, and spurious data	For EU-CTR compliance
12. Appendices Appendix 1. Abbreviations and Definitions	Added • abuse • authorized IMP • authorized AxMP • AxMP • GDPR • IMP • medication error • misuse • NIMP • SUSAR	For EU-CTR compliance
12. Appendices Appendix 3.1.3. Data Protection	Added the section	For EU-CTR compliance

Section # and Name	Description of Change	Brief Rationale
12. Appendices Appendix 3.1.5. Regulatory Considerations	Added a bullet point regarding reporting of significant issues related to participant's safety, rights, or data integrity	For EU-CTR compliance
12. Appendices Appendix 3.2. Dissemination of Clinical Study Data	Added the section	For EU-CTR compliance
12. Appendices Appendix 8. Country-Specific Requirements	Added a new appendix applicable to EU only sites by including the content from Protocol Addenda 1.1, 6, and 7.1 8.1. Changes to the protocol for study sites in Europe who follow General Data Protection Regulation 8.2. Changes applicable to study sites in EU 8.3. Substudy to investigate the diabetic retinopathy progression	For harmonization of the protocol and to avoid country and region-specific protocol versions in the EU
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore, not detailed

Amendment [d]: (14-Dec-2021)

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the conduct or management of the trial.

Overall Rationale for the Amendment:

The protocol is being amended to maximize patient retention and thus endpoint reporting by allowing patients to adjust their dose, either by additional escalations or de-escalations throughout the entire study.

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis	Updated this section as per the changes made in the body of the protocol.	For consistency.
Section 2. Schedule of Activities: Table GPGN.1.	Updated to allow dose escalations to reach a maximum tolerated dose throughout the trial.	To maximize treatment benefits.
	Updated the allowable window to ±15 days at V15.	Update of study visit window to ±15 days at V15 to align with study treatment dispensing strategy
	Modified "collect (unused) study drug" to "collect and record unused study drug."	For clarification.
	Fasting labs need to be drawn at UV not dosing UV.	For clarification and correction.

Section # and Name	Description of Change	Brief Rationale
	Updated Footnote “e”, “o”, “p”, and “q”.	For clarification and correction.
Section 3.3. Benefit/Risk Assessment	Updated the reference citations for Trulicity USPI and SmPc from 2019 to 2021.	For clarification.
Section 5.1. Overall Design	Updated to allow dose escalations to reach a maximum tolerated dose throughout the trial.	To maximize treatment benefits.
	Updated language for remote visits, and to have study drug dispensing at unscheduled visits.	To allow flexibility.
Section 5.4. Scientific Rationale for Study Design	Updated to allow dose escalations to reach a maximum tolerated dose throughout the trial.	To maximize treatment benefits.
Section 7.1. Treatments Administered	Updated to allow dose escalations to reach a maximum tolerated dose throughout the trial.	To maximize treatment benefits.
	Updated language to allow re-start between scheduled clinic visits.	Reduce prolonged treatment interruptions or permanent discontinuation.
Section 7.1.1. Dose Escalation Scheme	Updated to allow dose escalations to reach a maximum tolerated dose throughout the trial.	To maximize treatment benefits.
	Updated language to allow re-start between scheduled clinic visits.	Reduce prolonged treatment interruptions or permanent discontinuation.
	Included additional language for de-escalation between clinic visits.	Reduce treatment interruptions or discontinuations between regularly scheduled visits.
Section 7.1.1.1. De-Escalation during Dose Escalation	Included additional language for de-escalation between clinic visits.	Reduce treatment interruptions or discontinuations between regularly scheduled visits.
Section 7.4.1. Dosage Modification After Initial Dose Escalation	Section title changed from “Dosage Modification during Maintenance Period” to “Dosage Modification After Initial Dose Escalation”.	For clarification.
	Updated language for de-escalation of 15 mg to 10 mg during the maintenance period.	Recent data demonstrate that patients with intolerable side effects on 15 mg tirzepatide could tolerate 10 mg. Having patients de-escalate to 10 mg rather than 5 mg is consistent with treating patients with the maximum tolerated dose.
Section 7.4.2. Additional Dose Escalations	Updated to allow dose escalations to reach a maximum tolerated dose throughout the trial.	To maximize treatment benefits.

Section # and Name	Description of Change	Brief Rationale
	Updated language to allow re-start between scheduled clinic visits.	Reduce prolonged treatment interruptions or permanent discontinuation.
	Section title changed from "Second Dose Escalation at Visit 16" to "Additional Dose Escalations".	For clarification.
Section 7.4.3. Reinitiating Study Drug After Interruptions Not Related to Tolerability	Updated language to allow re-start between scheduled clinic visits.	Reduce prolonged treatment interruptions or permanent discontinuation.
	Updated to allow dose escalations to reach a maximum tolerated dose throughout the trial.	To maximize treatment benefits.
	Section title changed from "Reinitiating Study Drug during Maintenance Period" to "Reinitiating Study Drug After Interruptions Not Related to Tolerability".	For Clarification
Section 7.6. Treatment Compliance	Text edited.	For consistency.
Section 7.7. Concomitant Therapy	Updated/Included wording on prohibited GLP-1 RAs use at any time during the trial.	For clarification.
Section 8.1.1. Permanent Discontinuation from Study Drug	Updated language • to clarify wording regarding AE/SAE collection for patients that have discontinued trial/study medication, and • on permanent discontinuation for hepatic event malignancy.	For clarification.
Section 8.1.2. Temporary Interruption of Study Drug	Updated to allow dose escalations to reach a maximum tolerated dose throughout the trial.	To maximize treatment benefits.
	Updated language about pregnancy.	For clarification.
	Updated "telephone" to "alternative visits" to allow less strict guidance.	For clarification.
Section 8.2. Discontinuation from the Study	• Deleted permanent discontinuation for pregnancy and other two criteria. • Added "consent" after "withdraw".	For clarification.
Section 9.2.1. Serious Adverse Events	Updated language about pregnancy.	For clarification.

Section # and Name	Description of Change	Brief Rationale
Section 9.2.2.2. Pancreatitis	• Applied structured authoring principles. • Updated language about all cases of suspected pancreatitis	For clarification.
Section 9.2.2.6. Diabetic Retinopathy Complications	• Included language about retinal diagnostic procedure and macular edema. • Changed the name of eCRF from "retinopathy" to "Fundoscopy Exam – Follow Up".	For clarification.
Section 9.2.3. Complaint Handling	Included language about product complaint form.	For clarification.
Section 9.4.5.1. Hepatic Safety Monitoring	Updated with standardized safety hepatic language.	Updated to align with current internal guidance.
Section 10.3.3.1. Analyses of Primary Outcome	Updated language about interim efficacy analysis.	For clarification.
Section 10.3.6. Interim Analyses	Updated language about interim and final analyses.	For clarification.
Appendix 1. Abbreviations and Definitions	Added definitions for "Additional dose escalation" and "Alternative visit methods"; added abbreviation for "CK"; updated definition of "Restart"; deleted "Second Dose Escalation".	For clarification.
Appendix 2. Clinical Laboratory Tests	Clarified the abbreviations CK and CPK.	For clarification.
Appendix 7. Provisions for Changes in Study Conduct During Exceptional Circumstances	Included this section.	Updated as per Exceptional Circumstances appendix posted on 25 Jan 2021.
Throughout the document	Minor editorial and formatting edits were made. These are minor changes; therefore, they have not been summarized.	Corrections were made for clarity and consistency.

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Approval	PPD Statistician 15-Apr-2024 11:38:08 GMT+0000

Approval	PPD Medical Director 16-Apr-2024 12:50:13 GMT+0000

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