Protocol I8F-MC-GPGL(b)

A Phase 3, Randomized, Open-Label Trial Comparing Efficacy and Safety of Tirzepatide Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Patients With Type 2 Diabetes (SURPASS-2)

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Confidential Information

Tirzepatide (LY3298176)

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1. Synopsis

Title of Study:
A Phase 3, Randomized, Open-Label Trial Comparing Efficacy and Safety of Tirzepatide versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Patients with Type 2 Diabetes (SURPASS-2)

Rationale:

Current incretin-based injectable treatment options for type 2 diabetes mellitus (T2DM) are directed at a single incretin molecular target (GLP-1 [glucagon-like peptide-1]). These treatment options offer improved glycemic control, low risk of hypoglycemia, and the potential for clinically relevant weight loss. However, a proportion of patients do not reach treatment targets despite high levels of compliance with the treatment regimens. Therefore, there is an unmet need for additional treatment options that enhance glycemic control, promote weight loss, and preserve an acceptable benefit/risk profile (Stark Casagrande et al. 2013; Zaccardi et al. 2016).

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety that CCI
It is administered once weekly (QW) by subcutaneous (SC) injection.

Study I8F-MC-GPGL (GPGL) is a Phase 3, randomized, open-label, active-controlled, parallel group, multicenter, multinational, 4-group trial to assess the safety and efficacy of tirzepatide 5 mg, 10 mg, and 15 mg QW compared to semaglutide 1 mg QW in patients with type 2 diabetes inadequately controlled with ≥1500 mg/day metformin alone. Study GPGL will provide a comparative assessment of tirzepatide versus the highest approved dose of semaglutide (1 mg) with respect to glycemic control and other clinically relevant outcomes, including weight change, hypoglycemia incidence, and tolerability profile.

Objectives/Endpoints:

Objectives	Endpoints
Primary • To demonstrate that tirzepatide 10 mg and/or 15 mg QW are noninferior to semaglutide 1 mg QW for glycemic control at 40 weeks	• Mean change in HbA1c from baseline
Key Secondary (controlled for type 1 error) Efficacy • To demonstrate that tirzepatide 5 mg QW is noninferior to semaglutide 1 mg QW for glycemic control at 40 weeks for: • To demonstrate that tirzepatide 5 mg, 10 mg, and/or 15 mg QW is superior to semaglutide 1 mg QW at 40 weeks for:	• Mean change in HbA1c from baseline • Mean change in body weight from baseline • Mean change in HbA1c from baseline • Proportion of patients with HbA1c target values of <7.0% (53 mmol/mol)
Additional Secondary (not controlled for type 1 error) Efficacy • To compare tirzepatide 5 mg, 10 mg, and/or 15 mg QW to semaglutide 1 mg QW at 40 weeks for:	• Proportion of patients achieving an HbA1c target value of ≤6.5% (48 mmol/mol) • Proportion of patients achieving an HbA1c target value of <5.7% (39 mmol/mol) • Mean change in fasting serum glucose (central laboratory) from baseline • Mean change in 7-point SMBG profiles from baseline • Proportion of patients who achieved weight loss of ≥5%, ≥10%, and ≥15% from baseline • Patient-reported outcomes: o DTSQs (baseline only)/DTSQc (end of treatment only) o IW-SP (baseline and end of treatment) o APPADL (baseline and end of treatment)
Safety • To compare the safety of tirzepatide 5 mg, 10 mg, and 15 mg QW to that of semaglutide 1 mg QW to the end of safety follow-up for:	• TEAEs • Early discontinuation of study drug due to AEs • Adjudicated pancreatic AEs • Serum calcitonin • Incidence of allergic and hypersensitivity reactions • Incidence of treatment-emergent anti-drug antibodies to tirzepatide • Mean change in systolic and diastolic blood pressure and heart rate from baseline • Occurrence of hypoglycemic episodes • Incidence of initiation of rescue therapy for severe, persistent hyperglycemia

Abbreviations: AE = adverse event; APPADL = Ability to Perform Physical Activities of Daily Living; DTSQc = Diabetes Treatment Satisfaction Questionnaire change; DTSQs = Diabetes Treatment Satisfaction Questionnaire status; HbA1c = hemoglobin A1c; IW-SP = Impact of Weight on Self-Perception; QW = once weekly; SMBG = self-monitored blood glucose; T2DM = type 2 diabetes mellitus; TEAEs = treatment-emergent adverse events.

Summary of Study Design:

Study I8F-MC-GPGL is a Phase 3, 40-week, randomized, open-label, active-controlled, parallel group, multicenter, multinational, 4-group trial to assess the safety and efficacy of tirzepatide compared to semaglutide 1 mg in patients with type 2 diabetes inadequately controlled with ≥1500 mg/day metformin alone.

Treatment Groups and Duration:

Study GPGL will consist of 3 sequential periods:

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

Patients will be randomly assigned 1:1:1:1 to 1 of the 4 treatments:

- Tirzepatide (doses will be double-blinded)
  - 5 mg
  - 10 mg
  - 15 mg, or
- Semaglutide 1 mg (not blinded).

Patient randomization will be stratified based on country and baseline HbA1c (≤8.5% or >8.5% [69 mmol/mol]).

Tirzepatide treatment will follow a fixed dose escalation. It will be

- initiated at 2.5 mg QW for 4 weeks, and
- 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 desired dose is achieved and maintained for the duration of the study.

Semaglutide treatment will follow a fixed dose escalation. It will be

- initiated at 0.25 mg QW for 4 weeks
- increased to 0.5 mg QW for 4 weeks, and
- increased to and maintained at 1 mg QW for the duration of study.

Number of Patients:

Approximately 1872 patients will be randomly assigned to treatment groups, with 468 patients in each group.

Statistical Analysis:

Efficacy Analyses

Efficacy and safety will be assessed using the modified intention-to-treat (mITT) population, which consists of all randomly assigned patients who are exposed to at least 1 dose of study drug. There will be 2 estimands of interest in comparing efficacy of tirzepatide doses with semaglutide relative to the primary measure of mean change in HbA1c from baseline to the 40-week visit. The "efficacy" estimand represents efficacy prior to discontinuation of study drug without confounding effects of antihyperglycemic rescue therapy. The "treatment-regimen" estimand represents the efficacy irrespective of adherence to investigational product or introduction of rescue therapy for persistent severe hyperglycemia.

For the FDA and possibly other regulatory agencies, the primary efficacy assessment will be guided by the "treatment-regimen" estimand. This assessment will analyze change in HbA1c values from baseline to the 40-week visit using an analysis of covariance (ANCOVA) with terms: treatment, country, and baseline HbA1c as a covariate. The ANCOVA analysis will be conducted using the full analysis set at the 40-week visit, which consists of all available changes from baseline in HbA1c data at the 40-week visit, irrespective of whether they were obtained while the participants had discontinued the study drug or whether the participant had been given rescue medication. Additionally, missing HbA1c values at the 40-week visit will be imputed based on observed data in the same treatment group from patients who had their efficacy assessed after early discontinuation of study drug and/or initiation of rescue antihyperglycemic medication. This analysis will be conducted with multiple imputations, and statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

For all other purposes, the primary efficacy assessment will be guided by the "efficacy" estimand. This assessment will use the efficacy analysis set that consists of data obtained before the initiation of any rescue therapy and before premature treatment discontinuation. The analysis model for change from baseline in HbA1c assessed over time will be a mixed-effects model for repeated measures (MMRM) with terms: treatment, visit, treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c as a covariate. An unstructured covariance structure will model relationship of within-patient errors.

A 0.3% boundary will be used for noninferiority evaluations between tirzepatide and semaglutide relative to mean change in HbA1c from baseline.

Since they are intended for different purposes, each of the 2 primary efficacy assessments relative to the two estimands will be conducted at a family-wise type 1 error rate of 0.05. Additional details, including analysis methods for key secondary endpoints and a strategy for controlling overall family-wise type 1 error rate at a 2-sided alpha of 0.05 of primary and key secondary endpoint evaluation, will be provided in the statistical analysis plan (SAP).

Safety Analyses

Safety assessment will be based on all available data through safety follow-up visit, irrespective of whether they were obtained after study drug discontinuation or whether the participant received rescue medication. Summary statistics will be provided for incidence of TEAEs, serious AEs, and study discontinuation due to AEs or deaths from the time of first dose through end of safety follow-up. Counts and proportions of patients experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups. For continuous laboratory analytes, summary statistics will be provided by visit, with statistical comparisons among treatment at each visit conducted using an MMRM analysis. Selected safety analysis (for example, hypoglycemia) may be conducted excluding data after introducing another antihyperglycemic therapy. Additional details, including analysis of AEs of special interest, will be provided in the SAP.

2. Schedule of Activities

The Schedule of Activities described below should be followed for all patients enrolled in Study GPGL. However, for those patients whose participation in this study is affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes the novel Coronavirus Disease 2019 (COVID-19), please refer to Appendix 8 for additional instructions.

Table GPGL.1. Schedule of Activities

	Study Period I		Study Period II										Study Period III
	Screening/ Lead-in		Treatment Period										Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**		**4 weeks post end of tx**
Allowable Deviation (days)[c]	-	±3	±7	±3	±3	±3	±3	±3	±3	±7	±7		±7
Fasting Visit[d]			X	X	X	X	X	X	X		X	X	X
Informed consent	X												
Randomization			X										
Clinical Assessments													
Medical history[e]	X												
Physical examination	X										X	X	
Height	X												
Weight[f]	X		X	X	X	X	X	X	X	X	X	X	X
Waist circumference			X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram			X								X	X	X
Vital signs (2 sitting BP and HR)[g]	X		X	X	X	X	X	X	X	X	X	X	X
Dilated fundoscopic examination[h]		X											
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Review hypoglycemic events collected in the diary[i]			X	X	X	X	X	X	X	X	X	X	X

	Study Period I		Study Period II										Study Period III
	Screening/ Lead-in		Treatment Period										Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**		**4 weeks post end of tx**
Allowable Deviation (days)[c]	-	±3	±7	±3	±3	±3	±3	±3	±3	±7	±7		±7
Fasting Visit[d]			X	X	X	X	X	X	X		X	X	X
Patient Education													
Diabetes education[i,j]		X											
BG meter, SMBG training[i]		X											
Dispense BG meter/supplies, as needed		X	X	X	X	X	X	X	X	X	X	X	
Study drug injection training with demo device[i]			X										
Hand out diary, instruct in use[i]		X	X								X	X	
Remind patients about 7-point SMBG[k]		X						X		X			
Review 7-point SMBG values collected in the diary			X						X		X		
Dispense study drug			X	X	X	X	X	X	X	X			
Study Drug Compliance													
Observe patient administer study drug[l]			X										

	Study Period I		Study Period II										Study Period III
	Screening/ Lead-in		Treatment Period										Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**		**4 weeks post end of tx**
Allowable Deviation (days)[c]	-	±3	±7	±3	±3	±3	±3	±3	±3	±7	±7		±7
Fasting Visit[d]			X	X	X	X	X	X	X		X	X	X
Patient returns study drugs and injection supplies				X	X	X	X	X	X	X	X	X	
Assess study drug compliance				X	X	X	X	X	X	X	X	X	
Laboratory Tests													
Serum pregnancy test[m]	X												
Urine pregnancy test[n]			X			X			X		X		
Follicle-stimulating hormone[o]	X												
Estradiol[o]	X												
Chemistry panel	X[p]					X			X		X	X	X
Fasting glucose			X	X	X	X	X	X	X		X	X	X
Fasting insulin			X		X		X		X		X	X	X
Fasting glucagon			X		X		X		X		X	X	X
Fasting C-peptide			X		X		X		X		X	X	X
Lipid panel			X		X		X		X		X	X	X
Urinary albumin/creatinine ratio	X[p]								X		X	X	X
eGFR (CKD-EPI)[q]	X[p]					X			X		X	X	X
Calcitonin	X[p]					X			X		X	X	X
Hematology	X[p]					X			X		X	X	X

	Study Period I		Study Period II										Study Period III
	Screening/ Lead-in		Treatment Period										Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**		**4 weeks post end of tx**
Allowable Deviation (days)[c]	-	±3	±7	±3	±3	±3	±3	±3	±3	±7	±7		±7
Fasting Visit[d]			X	X	X	X	X	X	X		X	X	X
HbA1c	X		X	X	X	X	X	X	X		X	X	X
Pancreatic amylase, lipase	X[p]					X			X		X	X	X
Immunogenicity[r]			X	X		X			X		X	X	X
PK sample for immunogenicity[s]			X	X		X			X		X	X	X
Anti-GAD antibodies			X										
Stored Samples													
Pharmacogenetic stored sample			X										
Nonpharmacogenetic stored sample EDTA plasma, serum, P800 plasma			X			X			X		X	X	X
Patient-Reported Outcomes[t]													
DTSQs			X										
DTSQc											X	X	
IW-SP			X								X	X	
APPADL			X								X	X	
EQ-5D-5L			X								X	X	
IWQOL-Lite-CT			X								X	X	

Abbreviations: ADA = anti-drug antibodies; APPADL = Ability to Perform Physical Activities of Daily Living; BG = blood glucose; BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; DTSQc = Diabetes Treatment Satisfaction Questionnaire change; DTSQs = Diabetes Treatment Satisfaction Questionnaire status; ECG = electrocardiogram; eCRF = electronic case report form; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Qualtiy of Life: 5 dimensions, 5 levels; ET = early termination; F/U = follow-up; FSH = follicle-stimulating hormone; GAD = glutamic acid decarboxylase; HbA1c = hemoglobin A1c; HR = heart rate; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version; IW-SP = Impact of Weight on Self-Perception; PK = pharmacokinetics; SMBG = self-monitored blood glucose; tx = treatment.

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

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

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

[d] For all the fasting visits (Visits 3-9 and 11), ET, and at follow-up, patients should be reminded to report to the site in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or any significant physical activity and before taking study drug(s) and metformin.

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

[f] Weight measurements must be in kilograms per instructions specified in Appendix 7.

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

[h] Dilated fundoscopic examination will be performed by an eye care professional (ophthalmologist or optometrist) for all patients between Visit 2 and Visit 3 to exclude patients with proliferative diabetic retinopathy, diabetic maculopathy, or nonproliferative diabetic retinopathy that requires acute treatment. The results from this examination will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy. Follow-up dilated fundoscopic examination should be performed when clinically indicated, and the results should be recorded on the retinopathy eCRF.

[i] All training should be repeated as needed to ensure patient compliance.
- Diaries will be provided to each patient. Patients will need to fill out their diary and bring it with them at each visit.
- The following delivery devices will be used: a single-dose pen for tirzepatide and a single-patient-use pen for semaglutide.

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

[k] Patient is required to collect two 7-point SMBGs on 2 nonconsecutive days prior to the next visit. A 7-point SMBG consists of measurements before and 2 hours after each of 3 main meals within the same day and at bedtime. These SMBG profiles will be collected by the patient within 2 weeks prior to the assigned visits. Patients will also be required to collect a weekly 4-point SMBG. If 7-point SMBG is not performed, then data from the most recent nonconsecutive 4-point SMBG profiles can be used. If more than two 7-point SMBG profiles are available, the 2 most recent nonconsecutive profiles should be used.

[l] Patients should administer their first dose of study drug at the end of this visit (Visit 3), after all the other study procedures and randomization. Patients will then continue self-administering their study drug QW, with their last dose administered on Week 39 (or week of ET visit).

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

[n] A local urine pregnancy test must be performed at Visit 3 with the result available prior to randomization and first injection of study drug(s) for women of childbearing potential only. Additional pregnancy tests will be performed at Visits 6, 9, and 11. Pregnancy tests may also 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.

[o] FSH test will be performed at Visit 1 only for postmenopausal women at least 45 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months and estradiol levels consistent with a postmenopausal state (FSH ≥40 mIU/mL and estradiol <30 pg/mL).

[p] Screening visit assessment will serve as baseline. If missed at Visit 1, results should be obtained and reviewed before Visit 3 (randomization).

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

[r] In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional blood samples will be collected including ADA, PK, and an exploratory biomarker sample.

[s] PK samples for immunogenicity must be taken prior to drug administration.

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

3. Introduction

3.1. Study Rationale

Type 2 diabetes mellitus (T2DM) is a metabolic condition characterized by impaired glycemic control caused by increased insulin resistance, progressive beta-cell failure and consequently, inadequate insulin secretion. T2DM is associated with comorbidities such as increased weight or obesity, hypertension, dyslipidemia, and a higher risk for macro- and microvascular complications. To prevent these complications, tight glycemic control is recommended (ADA 2019b; Davies et al. 2018).

Injectable incretin-based treatments (for example, glucagon-like peptide-1 [GLP-1] receptor agonists) are commonly used in combination with oral antihyperglycemic medication (OAMs) and basal insulin to achieve and maintain glucose control (Inzucchi et al. 2015; ADA 2019b). While associated with lower risk for hypoglycemia and either weight neutral or weight loss effects, current preparations are directed at a single incretin molecular target (for example, GLP-1 receptors). These treatment options offer improved glycemic control, low risk of hypoglycemia, and the potential for clinically relevant weight loss. However, a proportion of patients do not reach treatment targets despite high levels of compliance with the treatment regimens. Therefore, there is an unmet need for additional treatment options that enhance glycemic control, promote weight loss, and preserve an acceptable benefit/risk profile (Stark Casagrande et al. 2013; Zaccardi et al. 2016).

The metabolic effects of GLP-1 receptor agonists can be enhanced by combining them with the actions of other enteropancreatic hormones. Glucose-dependent insulinotropic polypeptide (GIP) 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 receptor agonists (for example, improved lipid homeostasis and whole-body energy metabolism) (Asmar et al. 2016; Nauck and Meier 2018).

Tirzepatide (LY3298176) is a 39-amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety that CCI [redacted] It is administered as once-weekly (QW) subcutaneous (SC) injection (Coskun et al. 2018).

Study I8F-MC-GPGL (Study GPGL) is a Phase 3, randomized, open-label, active-controlled, parallel-group, multicenter, multinational, 4-group trial to assess the safety and efficacy of tirzepatide 5 mg, 10 mg, and 15 mg QW compared to semaglutide 1 mg QW in patients with type 2 diabetes inadequately controlled with ≥1500 mg/day metformin alone. Study GPGL will provide a comparative assessment of tirzepatide versus the highest approved dose of semaglutide (1 mg) with respect to glycemic control and other clinically relevant outcomes, including weight change, hypoglycemia incidence, and tolerability profile.

3.2. Background

Four tirzepatide clinical studies have completed dosing and analysis: two Phase 1 studies, Study I8F-MC-GPGA (Study GPGA) and Study I8F-MC-GPGC (Study GPGC) in Japanese

patients, two Phase 2 studies, Studies I8F-MC-GPGB (Study GPGB) and I8F-MC-GPGF (Study GPGF).

Phase 1 Study GPGA was a combination of single ascending dose (SAD) and multiple ascending dose study in healthy subjects followed by a multiple dose proof-of-concept study in patients with T2DM. Study GPGA investigated safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of tirzepatide administered as weekly SC injections. A total of 142 subjects (89 healthy subjects 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 SAD (with maximum tolerated dose achieved at 5 mg) in healthy subjects; multiple doses from 0.5 mg to 4.5 mg QW and titrated doses up to 10 mg QW for 4 weeks in healthy subjects; and multiple doses ranged from 0.5 mg to 5 mg QW and titrated doses up to 15 mg QW for 4 weeks in patients with T2DM. 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 (Coskun et al. 2018) .

A 26-week Phase 2 study (Study GPGB) assessed the efficacy, tolerability, and safety of 4 doses (1 mg, 5 mg, 10 mg, and 15 mg) of tirzepatide 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).

Study GPGB demonstrated that tirzepatide 5-mg, 10-mg, and 15-mg 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 significantly greater than with dulaglutide 1.5 mg QW. Similar to the GLP-1 receptor agonist 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 severity. Serious AEs (SAEs) were balanced across the treatment groups, and none of the groups in either study reported severe hypoglycemia (Frias et al. 2018).

As it was recognized that the titration scheme employed in Study GPGB was not optimal, Study GPGF was designed to explore alternative titration schemes (longer time intervals between dose escalations and different dose increments) to support evaluation of optimized dosing regimen(s) in Phase 3. Data from the Phase 1 and Phase 2 studies were used to model the escalation scheme to be used in the Phase 3 program and to minimize GI-related AEs.

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

3.3. Benefit/Risk Assessment

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

In addition, detailed information about the known and expected benefits and risks of semaglutide may be found in the semaglutide package insert (Ozempic® USPI [WWW]; Ozempic® SmPC [WWW]).

4. Objectives and Endpoints

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

Table GPGL.2. Objectives and Endpoints

Objectives	Endpoints
Primary • To demonstrate that tirzepatide 10 mg and/or 15 mg QW are noninferior to semaglutide 1 mg QW for glycemic control at 40 weeks	• Mean change in HbA1c from baseline
Key Secondary (controlled for type 1 error) Efficacy • To demonstrate that tirzepatide 5 mg QW is noninferior to semaglutide 1 mg QW for glycemic control at 40 weeks for: • To demonstrate that tirzepatide 5 mg, 10 mg, and/or 15 mg QW is superior to semaglutide 1 mg QW at 40 weeks for:	• Mean change in HbA1c from baseline • Mean change in body weight from baseline • Mean change in HbA1c from baseline • Proportion of patients with HbA1c target values of <7.0% (53 mmol/mol)
Additional Secondary (not controlled for type 1 error) Efficacy • To compare tirzepatide 5 mg, 10 mg, and/or 15 mg QW to semaglutide 1 mg QW at 40 weeks for:	• Proportion of patients achieving an HbA1c target value of ≤6.5% (48 mmol/mol) • Proportion of patients achieving an HbA1c target value of <5.7% (39 mmol/mol) • Mean change in fasting serum glucose (central laboratory) from baseline • Mean change in 7-point SMBG profiles from baseline • Proportion of patients who achieved weight loss of ≥5%, ≥10%, and ≥15% from baseline • Patient-reported outcomes: o DTSQs (baseline only)/DTSQc (end of treatment only) o IW-SP (baseline and end of treatment) o APPADL (baseline and end of treatment)
Safety • To compare the safety of tirzepatide 5 mg, 10 mg, and 15 mg QW to that of semaglutide 1 mg QW to the end of safety follow-up for:	• TEAEs • Early discontinuation of study drug due to AEs • Adjudicated pancreatic AEs • Serum calcitonin • Incidence of allergic and hypersensitivity reactions

Objectives	Endpoints
	• Incidence of treatment-emergent anti-drug antibodies to tirzepatide • Mean change in systolic and diastolic blood pressure and heart rate from baseline • Occurrence of hypoglycemic episodes • Incidence of initiation of rescue therapy for severe persistent hyperglycemia
Exploratory Objective To compare tirzepatide 5 mg, 10 mg, and 15 mg QW to semaglutide 1 mg QW at 40 weeks for: • Patient-reported outcomes at baseline and end of treatment: o EQ-5D-5L o IWQOL-Lite-CT • Changes in fasting glucagon, C-peptide, and insulin levels • Changes in lipids (total cholesterol, HDL, VLDL, and triglycerides) • Changes from baseline in mean BMI • Mean change in waist circumference • Biomarkers	

Abbreviations: AE = adverse event; APPADL = Ability to Perform Physical Activities of Daily Living; BMI = body mass index; DTSQc = Diabetes Treatment Satisfaction Questionnaire change; DTSQs = Diabetes Treatment Satisfaction Questionnaire status; EQ-5D-5L = European Quality of Life: 5 dimensions, 5 levels; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IW-SP = Impact of Weight on Self-Perception; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version; QW = once weekly; SMBG = self-monitored blood glucose; T2DM = type 2 diabetes mellitus; TEAEs = treatment-emergent adverse events; VLDL = very low-density lipoprotein.

5. Study Design

5.1. Overall Design

Study GPGL is a Phase 3, 40-week, randomized, open-label, active-controlled, parallel-group, multicenter, multinational, 4-group trial to assess the safety and efficacy of tirzepatide compared to semaglutide 1 mg in patients with type 2 diabetes inadequately controlled with ≥1500 mg/day metformin alone.

Study periods

Study GPGL will consist of 3 sequential periods:

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

Randomization to study treatment

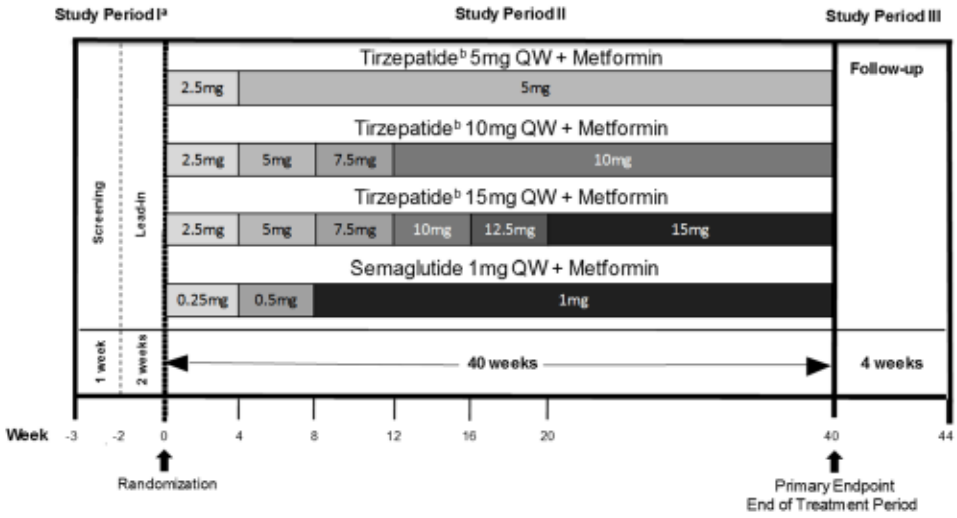
Patients will be randomly assigned 1:1:1:1 to 1 of 4 QW treatments:

- Tirzepatide (doses will be double-blinded)
  - 5 mg
  - 10 mg
  - 15 mg, or
- Semaglutide 1 mg (not blinded).

Patient randomization will be stratified based on country and baseline HbA1c (≤8.5% or >8.5% [69 mmol/mol]).

Study governance considerations are described in detail in Appendix 3.

Figure GPGL.1 illustrates the study design.



Abbreviation: QW = once weekly.

[a] Stable doses of metformin ≥1500 mg/day for at least 3 months prior to Visit 1 and during the screening/lead-in period.

[b] All tirzepatide doses will be double-blinded.

Figure GPGL.1. Illustration of study design for Clinical Protocol I8F-MC-GPGL.

Study Period I (screening and lead-in)

Screening (Visit 1)

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

Lead-in (Visit 2 to Visit 3)

The purpose of Visit 2 is to review the results of the screening laboratory measures to further assess patient eligibility. For those patients meeting all other eligibility requirements, a dilated fundoscopic examination, performed by an ophthalmologist or optometrist, must be completed between Visit 2 and Visit 3. The purpose of this examination is to ensure that patients who meet Exclusion Criterion [11] are excluded from the study (Section 6.2).

- Patients and their caregiver(s), if applicable, will receive a glucometer and training on how to perform self-monitoring of blood glucose (SMBG).
    - Patients will be asked to monitor 4-point SMBG profiles weekly and 7-point SMBG profiles twice on 2 nonconsecutive days in the 2-week period prior to Visit 3 (randomization), Visit 9 (Week 24), and Visit 11 (Week 40).

- Patients will be provided diaries and will be trained as appropriate to record blood glucose (BG) values and hypoglycemic events.
- During this period, patients will also be trained on disease management (symptoms of hypoglycemia and hyperglycemia) and study procedures; this training can be repeated at subsequent visits as deemed appropriate.
    - Patients should monitor BG any time a hypoglycemic event is suspected.
- During the lead-in period, patients should continue their diet and exercise routine and must not use any OAMs other than metformin, or change their metformin dose or formulation, to allow reliable assessment of HbA1c at baseline (Visit 3).

Study Period II (40-week treatment period)

Randomization (Visit 3)

- At Visit 3, prior to randomization and prior to taking the first dose of study drug, eligible patients will complete all required baseline study procedures (including the collection of all baseline laboratory measures and electrocardiogram [ECG]).
- Patient should arrive to the clinic in the fasting state that should have lasted at least 8 hours without having taken any doses of their metformin during that time.
- The patient-reported outcomes questionnaires should be completed before any other study procedures if the patient is not adversely affected by the fasting condition or completed after the patient has sufficiently recovered from the preceding visit procedures.
- Patients will be instructed on how to use their delivery devices: a single-dose pen for patients randomized to tirzepatide and a single-patient-use pen for patients randomized to semaglutide. They will inject their first dose of study drug while in the clinic for Visit 3.
- The date and time of the first dose of study drug should be recorded on the electronic case report form (eCRF).

Following randomization, patients will participate in a 40-week treatment period.

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

See the Schedule of Activities (Section 2) for details about the study procedures and Treatments Administered (Section 7.1) for details about the study drug doses.

Study Period III (safety follow-up period)

Safety follow-up (final treatment visit to Visit 801):

All patients who complete the treatment period are required to complete Visit 801, a safety follow-up visit, approximately 4 weeks after their last treatment visit. Patients discontinuing the study early and performing an early termination (ET) visit will also be asked to perform the safety follow-up visit, so that the safety follow-up visit will be their final visit. During the safety follow-up period, patients will not receive study drug. Patients will be treated with another glucose-lowering intervention decided upon by the investigator. If any new antihyperglycemic medication is initiated during the safety follow-up period, it will not be classified as rescue therapy. Patients are also required to return any remaining study diaries to the study site at the end of this period.

Study Procedures

Patients will perform study procedures listed in the Schedule of Activities (Section 2).

Patients will continue to use concomitant metformin throughout the treatment period; discontinuation or changes to the dose or formulation are not permitted, except in the situations where dose adjustment or complete discontinuation is required per country-specific label or when allowed per study protocol (for further details, see Section 7.7.1).

Patients will be instructed to perform 4-point SMBG measurements (consisting of fasting, pre-midday meal, pre-evening meal, and bedtime BG measurements) once weekly and to record all results in diaries. These results will be used for glucose management only. In addition, a 7-point SMBG profile (prior to and 2 hours after the 3 main meals and at bedtime) on 2 nonconsecutive days will be collected during the 2 weeks preceding prespecified clinic visits, as shown in the Schedule of Activities (Section 2), and will be used for efficacy analyses. During the weeks when the 7-point SMBG profiles are to be collected, patients will not be required to collect 4-point SMBG profiles, and the 7-point profiles will be used for glucose management instead. Data from the 7-point profiles will be entered into the eCRF as shown in the Schedule of Activities (Section 2). If the 7-point SMBG is not performed, then data from the most recent nonconsecutive 4-point SMBG profiles can be used. If more than two 7-point SMBG profiles are available, the 2 most recent nonconsecutive profiles should be used.

Patients who develop severe, persistent hyperglycemia based on prespecified thresholds (see Sections 7.4.2.3 and 9.2.2.2) will receive a new glucose-lowering intervention ("rescue therapy") and will also continue to administer study drug. Patients who need hyperglycemic rescue therapy will continue in the trial until they complete all study visits.

Patients who permanently discontinue study drug prior to the safety follow-up period should continue in the trial and should receive a new glucose-lowering intervention (Section 7.7.2).

5.2. Number of Participants

Approximately 1872 patients will be randomly assigned to treatment groups, with 468 patients in each group.

5.3. End of Study Definition

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 patient.

5.4. Scientific Rationale for Study Design

Study GPGL will provide a comparative assessment of tirzepatide versus semaglutide 1 mg with respect to glycemic control and other clinically relevant outcomes, including weight change, hypoglycemia incidence, and tolerability profile.

Semaglutide 1 mg was chosen as the active comparator because it is the highest approved dose of semaglutide for patients with T2DM that has shown superiority in improving glycemic control

and reducing body weight compared to 2 other GLP-1 receptor agonists in the class, dulaglutide and exenatide QW, with a similar safety profile (Ahmann et al. 2018; Pratley et al. 2018).

Metformin was chosen as the required concomitant antihyperglycemic medication because it is commonly used in clinical practice as first-line therapy and when used in combination, the risk of hypoglycemia is low. The minimum dose (at least 1500 mg/day) was chosen to ensure maximizing efficacy of metformin prior to adding additional therapy (Nathan et al. 2009). To minimize the potential confounding effect of changes to concomitant metformin, patients will be expected to maintain metformin throughout the treatment period until the last dose of randomized treatment, other than for the situations described in Section 7.7.1.

The parallel-group design for treatment comparison was chosen to avoid any interaction between treatments that may interfere with the interpretation of the study outcome. Patients will be permitted to use concomitant medications that they require during the study. Medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments will not be allowed (Section 7.7).

The open-label design is used for this study because of the different devices used for administering tirzepatide and semaglutide. The tirzepatide doses will be blinded for better assessment of efficacy and safety outcomes of individual doses.

The planned treatment duration of 40 weeks is considered appropriate to assess the full effects and benefit/risk of each maintenance dose of tirzepatide on both glycemic control and body weight as requested by the FDA.

5.5. Justification for Dose

Tirzepatide Doses

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

These doses and associated escalation schemes were selected based on the 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 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 would permit time for development of tolerance to GI events and are predicted to improve GI tolerability.

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

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

Semaglutide Dose

To allow the most robust comparison of tirzepatide and semaglutide, the highest approved dose of semaglutide (1 mg) for T2DM was chosen to be studied.

Semaglutide has 2 effective doses, 0.5 mg QW and 1 mg QW. Whereas the lower dose (0.5 mg) is recognized as an effective dose for glycemic control, the 1-mg dose provides some additional benefit in glycemic control and weight reduction, with relatively similar tolerability (Marso et al. 2016; Ahrén et al. 2017; Aroda et al. 2017; Sorli et al. 2017; Pratley et al. 2018; Rodbard et al. 2018). Semaglutide dose will be escalated to 1 mg as recommended in the prescribing information (Ozempic® USPI [WWW]).

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are 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:

Type of Patient and Disease Characteristics

[1] Have been diagnosed with T2DM based on the World Health Organization classification or other locally applicable diagnostic standards

Patient Characteristics

[2] Have HbA1c ≥7.0% (≥53 mmol/mol) to ≤10.5% (≤91 mmol/mol), as determined by the central laboratory at Visit 1

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

[4] Have body mass index (BMI) ≥25 kg/m^2 at Visit 1

[5] Have been on stable diabetes treatment with metformin ≥1500 mg/day during the 3 months prior to Visit 1 and between Visits 1 and 3

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

Male patients (See Appendix 6 for more details):

- Male patients should be willing to use reliable contraceptive methods throughout the study and for at least 3 months after last injection

Female patients:

- Female patients not of childbearing potential due to surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation), congenital anomaly (that is, Mullerian agenesis), or menopause
  - Women with an intact uterus are deemed postmenopausal if they are at least 45 years old and
    - have not taken hormones or oral contraceptives within the last year and had cessation of menses for at least 1 year

      OR

    - have had at least 6 months and less than 12 months of spontaneous amenorrhea with follicle-stimulating hormone (FSH) and estradiol levels consistent with a postmenopausal state (FSH ≥40 mIU/mL and estradiol <30 pg/mL).

- Female patients of childbearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must
  - test negative for pregnancy at Visit 1 based on a serum pregnancy test

  AND
  - if sexually active, agree to use 2 forms of effective contraception, where at least 1 form is highly effective for the duration of the trial and for 30 days thereafter).
  - not be breastfeeding

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

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

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

(c) inject tirzepatide or semaglutide once weekly

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

(e) sufficiently understand one of the provided languages of the country such that they will be able to complete the patient questionnaires

Informed Consent

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

6.2. Exclusion Criteria

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

Medical Conditions

[9] Have type 1 diabetes mellitus (T1DM)

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

[11] Have a history of any of the following:

- proliferative diabetic retinopathy,

OR

- diabetic maculopathy,

OR

- nonproliferative diabetic retinopathy that requires acute treatment (a dilated fundoscopic examination performed by an ophthalmologist or optometrist between Visit 2 and Visit 3 is required to confirm eligibility)

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

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

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

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

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

[17] Have acute or chronic hepatitis, signs and symptoms of any liver disease other than nonalcoholic fatty liver disease (NAFLD), or alanine aminotransferase (ALT) level >3.0 times the upper limit of normal (ULN) for the reference range, as determined by the central laboratory at study entry. Patients with NAFLD are eligible to participate in this trial if their ALT level is ≤3.0 times the ULN for the reference range

[18] Have an estimated glomerular filtration rate <45 mL/min/1.73 m^2 (or lower than the country-specific threshold for discontinuing metformin therapy per local label), calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory at Visit 1

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

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

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

[22] Have known or suspected hypersensitivity to trial product(s) or related products

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

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

[25] Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years

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

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

Prior/Concomitant Therapy

[28] Have been treated with any antihyperglycemic medication (other than metformin) within the 3 months prior to Visit 1. An exception is for the use of insulin for gestational diabetes or short-term use (<14 days) for acute conditions such as acute illness, hospitalization, or elective surgery

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

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

Prior/Concurrent Clinical Trial Experience

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

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

[33] Have previously completed or withdrawn from this study or 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 unwilling or unable to comply with the use of a data collection device to directly record data from the patient

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. Per Inclusion Criterion [3] (Section 6.1), patients should not initiate an organized diet and/or exercise (weight reduction) program during the study other than the lifestyle and dietary measures for diabetes treatment.

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

6.4. Screen Failures

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

7. Treatments

7.1. Treatments Administered

Patients will be randomized in a 1:1:1:1 ratio to 1 of the 4 study treatments:

- Tirzepatide (doses will be double-blinded)
  - 5 mg
  - 10 mg
  - 15 mg, or
- Semaglutide 1 mg (not blinded).

Study drug will be administered QW as SC injection in patients with T2DM inadequately controlled with ≥1500 mg/day metformin alone.

Table GPGL.3 shows the randomized treatments for the entire treatment period.

The date and time of all doses of study drug should be recorded on the eCRF.

Table GPGL.3. Treatment Regimens

Name of Drug	Dosage	Frequency	Drug Formulation	Route of Administration
Investigational compound				
Tirzepatide[a]	5 mg	QW	Single-dose pen	SC
	10 mg	QW	Single-dose pen	SC
	15 mg	QW	Single-dose pen	SC
Comparator				
Semaglutide[b]	1 mg	QW	Single-patient-use pen	SC

Abbreviations: SC = subcutaneous; QW = once weekly.

[a] Tirzepatide treatment will follow a fixed dose escalation. It will be
- initiated at 2.5 mg QW for 4 weeks, and
- 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 desired dose is achieved and maintained for the duration of the study.

[b] Semaglutide treatment will follow a fixed dose escalation. It will be
- initiated at 0.25 mg QW for 4 weeks
- increased to 0.5 mg QW for 4 weeks, and
- increased to and maintained at 1 mg QW for the duration of study.

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

- explaining the correct use of the study drugs and delivery devices (that is, single-dose pen for tirzepatide and single-patient-use pen for semaglutide) to the patient or patient representative. For single-dose pens, a demonstration device will be used
- explaining the correct use of concomitant metformin to the patient or patient representative, including any contraindications and appropriate dosing per country-specific labeling
- verifying that instructions are followed properly by the patient
- maintaining accurate records of investigational product dispensing and collection

Patients should return all unused study drugs to the site according to the Schedule of Activities (Section 2). Patients should be instructed to discard all used delivery devices in a closeable, puncture-resistant container according to local regulations.

7.1.1. Packaging and Labelling

The sponsor will provide tirzepatide in single-dose pens and semaglutide, in single-patient-use pens. These will be dispensed via an interactive web-response system (IWRS). Single-dose pens and single-patient-use pens will be packaged in cartons to be dispensed. Clinical study materials will be labeled according to the country's regulatory requirements.

7.1.2. Medical Devices

The combination products provided for use in the study are investigational prefilled single-dose pens for tirzepatide and marketed prefilled single-patient-use pens for semaglutide.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomly assigned to 1 of the study treatment groups at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. Patients will be randomly assigned in a 1:1:1:1 ratio to receive tirzepatide 5 mg, 10 mg, 15 mg, or semaglutide 1 mg. Patient randomization will be stratified based on country and baseline HbA1c (≤8.5% or >8.5% [69 mmol/mol]).

7.2.1. Selection and Timing of Doses

Assignment to tirzepatide (3 doses) or semaglutide will occur at randomization.

Tirzepatide

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, with or without meals. The actual date and time of all dose administrations will be recorded by the patient in the patient diary. If a dose of study drug is missed, the patient should take it as soon as possible unless it is within 72 hours of the next scheduled dose, in which case, that dose should

be skipped and the next dose should be taken at the appropriate time. The day of weekly administration can be changed if necessary, as long as the last dose was administered 72 or more hours before.

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

Semaglutide

Semaglutide should be administered QW on the same day each week, at any time of the day, with or without meals. The day of weekly administration can be changed if necessary, as long as the time between 2 doses is at least 2 days (>48 hours). If a dose is missed, semaglutide should be administered as soon as possible within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular QW dosing schedule (Ozempic® USPI [WWW]).

Patients will inject semaglutide SC in the abdomen or thigh using the single-patient-use pen using the injection supplies provided; a caregiver may administer the injection in the patient's upper arm. When study drug is always injected in the same body region, patients should be advised to use a different injection site each week. A single-patient-use pen may be used for multiple injections.

7.3. Blinding

This is an open-label study with respect to assignment to semaglutide versus tirzepatide. Within the tirzepatide arms, the dose of tirzepatide will be double-blinded. Investigators, site staff, clinical monitors, and patients will remain blinded to the tirzepatide doses until the study is complete.

If an investigator, site personnel performing assessments, or patient is unblinded to the tirzepatide dose, the patient will continue on the assigned therapy through the end of the study, if medically appropriate. Study site personnel and the sponsor will document any unblinding events.

7.4. Dosage Modification

7.4.1. Study Drugs

No adjustment in study drug doses will be allowed unless for safety reasons. Details about dose administration of tirzepatide and semaglutide during the study are described in Sections 7.2.1 and 8.1.2.

7.4.2. Special Treatment Considerations

This section provides guidance on management of episodes of hypoglycemic events; severe, persistent hyperglycemia during the treatment period; patients who permanently discontinue study drug prior to Visit 11; and patients with GI symptoms. For effective implementation of measures described here, it is important that patients, and their caregivers, if applicable, be well educated about the signs and symptoms of hyperglycemia (for example, severe thirst, dry mouth, frequent micturition, or dry skin) and hypoglycemia (for example, intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep, or transient neurological disorders). Patients should be instructed to contact the investigative site in the event of severe, persistent hyperglycemia or severe hypoglycemia between study visits or in the event when a patient intends to permanently discontinue study drug.

7.4.2.1. Standards of Medical Care

Investigators and other study team members are expected to treat patients according to the nationally established standards of care for diabetes management in respective participating countries, except where that treatment would be in conflict with the protocol-provided treatment requirements. If there are no local standards of care for diabetes, the investigators should follow current published standards of care from the American Diabetes Association and the European Association for Study of Diabetes (Davies et al. 2018) during their patients' participation in this study.

7.4.2.2. Management of Hypoglycemia Risk

In this study, increased risk of hypoglycemia is defined as having a single episode of severe hypoglycemia or having more than 1 episode of documented symptomatic hypoglycemia within a 1-week period at any time during the treatment period. In cases where a patient experiences hypoglycemia as described above, to confirm the increased risk, the study sites must ensure that the patient has been fully compliant with the assigned therapeutic regimen and also that there is no evidence of other possible causes of hypoglycemia (for example, omission of meal, unexpected increase in exercise). The investigator must also confirm they have reduced or discontinued metformin as described in Section 7.7.1. If the patient fulfills the definition of increased risk of hypoglycemia even when metformin has been discontinued, the investigator should discontinue the patient from study treatment and follow the guidance for management of patients to permanently discontinue the study drugs as outlined in Section 8.1.1.

7.4.2.3. Management of Patients with Severe, Persistent Hyperglycemia during the Treatment Period

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

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

dipeptidyl peptidase-4 (DPP-4) inhibitors, or GLP-1 receptor agonists will not be allowed. See Section 7.7.2 for details about the allowed antihyperglycemic medication.

Add-on glycemic rescue therapy will be allowed for patients who meet any one of the following prespecified criteria for severe, persistent hyperglycemia and no intercurrent cause of the hyperglycemia can be identified (investigators should first confirm that the patient is fully compliant with the assigned therapeutic regimen and that he or she does not have an acute condition causing severe hyperglycemia):

(a) average daily BG from the once-weekly 4-point SMBG profile >270 mg/dL (>15.0 mmol/L) over at least a consecutive 2-week period any time during the first 8 weeks post randomization;

OR

(b) average daily BG from the once-weekly 4-point SMBG profile >240 mg/dL (>13.3 mmol/L) over a consecutive 2-week period at any time 9 to 16 weeks post randomization;

OR

(c) average daily BG from the once-weekly 4-point SMBG profile >200 mg/dL (>11.1 mmol/L) over a consecutive 2-week period at any time beyond the first 16 weeks post randomization;

OR

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

7.4.2.4. Management of Patients Permanently Discontinuing Study Drugs

Circumstances under which patients may be required to prematurely discontinue study drug are outlined in Section 8.1. 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 and should receive another antihyperglycemic medication (Section 7.7.2). The new antihyperglycemic medication will be recorded on the eCRF specified for collecting such medications.

To assure timely initiation of another antihyperglycemic medication after permanent discontinuation of study drug, patients should be advised to promptly notify the site when this situation occurs. The investigator should evaluate the need for additional antihyperglycemic medication at this time (as outlined in Section 7.7.2) and initiate the additional intervention accordingly. An unscheduled visit should be used as needed for more timely initiation if warranted based on the investigator's clinical judgment.

7.4.2.5. Management of Patients with Gastrointestinal Symptoms

Tirzepatide

In the Phase 2 program, the most commonly reported treatment-emergent AEs (TEAEs) for patients receiving tirzepatide were nausea, vomiting, and diarrhea.

The tirzepatide dose escalation scheme has been designed to minimize the development of GI symptoms. The escalation period is considered to be 24 weeks, which allows 20 weeks to escalate to 15 mg and additional 4 weeks to reach steady state. During the dose escalation period, every effort should be made by the investigator to be able to escalate and maintain patients on the corresponding study drug dosage.

To mitigate GI symptoms and manage patients with intolerable GI AEs during the escalation period (Week 0 to 24), 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.
- prescribe symptomatic medication (for example, 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.
- before permanently discontinuing tirzepatide, consider a temporary interruption (for example, omit 1 dose, the patient will take 3 of 4 doses at that dose level).
    - At a maximum, 1 dose can be omitted per 4 weeks (up to 6 doses could be omitted during the escalation period, 24 weeks).
    - After interruption, the investigator should restart the dose, or escalate the dose as required, with the patient taking medication to alleviate their GI symptoms.
    - The data related to temporary interruption of study treatment should be documented in source documents and entered on the eCRF.

If intolerable GI symptoms or events persist despite the above measures, the investigator may decide to discontinue study drug. De-escalation of study drug will not be allowed. Patients who stop the study drug permanently will receive another glucose-lowering intervention (Section 7.7.2) and will continue participating in the study according to the protocol to collect all planned efficacy and safety measurements. The new glucose-lowering intervention will be recorded on the eCRF specified for collecting antihyperglycemic medications.

In the event of intolerable persistent GI symptoms that occur after the escalation period (after Week 24), the investigator can advise on behavioral changes and consider prescribing symptomatic medication to keep the patient on study treatment before stopping the study drug permanently and initiating another glucose-lowering intervention.

Semaglutide

In the semaglutide Phase 3 program, the most commonly reported TEAEs were nausea, vomiting, and diarrhea (Marso et al. 2016; Ahrén et al. 2017; Aroda et al. 2017; Sorli et al. 2017; Pratley et al. 2018; Rodbard et al. 2018).

To mitigate GI symptoms and manage patients with intolerable GI AEs during the escalation period, with an additional 4 weeks to reach steady state with 1 mg dose (Week 0 to 12), 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.
- prescribe symptomatic medication (for example, 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.
- before permanently discontinuing semaglutide, consider a temporary interruption (for example, omit 1 dose, and have the patient take 3 of 4 doses at that dose level).
    - At a maximum, up to 3 doses could be omitted during the escalation period (12 weeks).
    - After interruption, the investigator should restart the dose, or escalate the dose as required, with the patient taking medication to alleviate their GI symptoms.
    - The data related to temporary interruption of study treatment should be documented in source documents and entered on the eCRF.

If intolerable GI symptoms or events persist despite the above measures, the investigator may decide to discontinue study drug. De-escalation of study drug will not be allowed. Patients who stop the study drug permanently will receive another glucose-lowering intervention (Section 7.7.2) and will continue participating in the study according to the protocol to collect all planned efficacy and safety measurements. The new glucose-lowering intervention will be recorded on the eCRF specified for collecting antihyperglycemic medications.

In the event of intolerable persistent GI symptoms that occur after the escalation period (after Week 12), the investigator can advise on behavioral changes and consider prescribing symptomatic medication to keep the patient on study treatment before stopping the study drug permanently and initiating another glucose-lowering intervention.

7.5. Preparation/Handling/Storage/Accountability

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

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply study treatment. All study treatments 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 the head of the medical institution (where applicable) is responsible for study treatment 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. Please refer to the study drug label for specific storage conditions. Patients may receive insulated bags with cooling gel packs for use in transporting the study drug carton from the site to home.

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

Study drug compliance will be determined by the following:

- Study drug administration data will be recorded by the patient into the patient diary and reviewed by the investigator at each study visit.
- The patients will be instructed to return any unused study drug in the original carton and/or empty cartons at the next visit to the study site for the purpose of performing drug accountability. Patients will be instructed to discard used pens in a closeable, puncture-resistant container according to local regulations.

In the 3 tirzepatide treatment groups, as well as the semaglutide group, treatment compliance for each visit interval is defined as taking at least 75% of the required doses of study drug. Similarly, a patient will be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

In addition to the assessment of a patient's compliance with the study drug administration, other aspects of compliance with the study procedures will be assessed at each visit based on the patient's adherence to the visit schedule, compliance with the required concomitant therapy with metformin, completion of study diaries, the results of home BG monitoring, and any other parameters the investigator considers necessary.

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

7.7. Concomitant Therapy

7.7.1. Background Therapy with Metformin

Patients in this study must be treated with metformin for at least 3 months prior to Visit 1; the minimum required dose during this time will be 1500 mg/day. The prescreening dose and

formulation (short-acting or long-acting) should be maintained during the screening and lead-in periods, through randomization at Visit 3.

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

1. In the event of a hypoglycemic episode(s) (clinical symptoms of hypoglycemia and/or BG-confirmed symptomatic BG hypoglycemia: glucose concentration <3.0 mmol/L [54 mg/dL]): Patients may reduce/discontinue the dose of metformin.
2. In certain situations that require short-term discontinuation in line with the product(s) labeling for each respective country (for example, for metformin: severe dehydration, elective surgery, or need for radiologic examination involving IV iodinated contrast dye). Once the situation that led to temporary discontinuation of the drug is resolved, treatment should be restarted at investigator discretion.
3. If a patient develops contraindications to metformin such that the use of the drug is contraindicated according to the country-specific label.
4. If patient meets the criteria for severe, persistent hyperglycemia (Section 7.4.2.3) or discontinues study drug, then metformin dose may be increased according to country-specific label as long as that is not the sole intervention (Table GPGL.4).

A patient will be considered noncompliant with the protocol (protocol deviation) if he or she changes the dose or discontinues metformin for reasons other than those described here.

Dose reduction/discontinuation of metformin during the trial should be properly documented and recorded on the appropriate eCRF.

7.7.2. Initiation of New Antihyperglycemic Medication

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

- As an antihyperglycemic intervention for severe, persistent hyperglycemia ("rescue therapy"), as defined in Section 7.4.2.3
- In those patients who require permanent discontinuation of study drug, but remain in the study (Section 8.1.1)
- During the safety follow-up period (between Visit 11 [Week 40] or ET and Visit 801)

If a new antihyperglycemic medication is introduced during the treatment period (that is, prior to Visit 11), the patient should be treated with a locally approved glucose-lowering agent (except other GLP-1 receptor agonists, DPP-4 inhibitors, and pramlintide) according to the following order of preference based on the updated 2018 ADA/EASD consensus statement (Davies et al. 2018):

1. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are recommended first, unless a contraindication is present.
2. If a contraindication to SGLT2 inhibitor is present, then a sulfonylurea or thiazolidinedione can be considered.

3. If glycemic control remains inadequate despite introduction of new antihyperglycemic medication (for example, after 3 months or within a timeframe determined by the investigator), then addition of basal insulin therapy should be considered. If insulin is prescribed as a rescue therapy for hyperglycemia or as a new antihyperglycemic medication in patients requiring study drug discontinuation, it must be differentiated from short-term use of insulin therapy for medical emergencies when reported in the eCRF.
4. Initiation of insulin as the first rescue intervention for hyperglycemia should be reserved for patients with severe, persistent hyperglycemia (Section 7.4.2.3) with an average fasting serum glucose ≥300 mg/dL (≥16.7 mmol/L), in patients with symptoms of hyperglycemia, or in other clinical situations where the investigator believes more rapid glycemic control is warranted.

7.7.3. Other Concomitant Medications

Patients will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments (Table GPGL.4).

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 OTC drugs, such as paracetamol or aspirin) must be documented, and the name of the drug and the date(s) of administration must be recorded on the "Concomitant Medications" section of the eCRF.

Antihyperglycemic medications other than study drugs and metformin are not allowed at any time during the study except as allowed for those patients who require permanent discontinuation of study drug, but remain in the study; rescue therapy after randomization due to severe, persistent hyperglycemia; or during the safety follow-up period (Section 7.7.2). Short-term insulin use for up to 14 days is allowed for certain clinical situations (for example, elective surgery, during hospitalization, hyperosmolar states) and must be differentiated from insulin use as rescue therapy when reported in the eCRF.

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

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

Table GPGL.4. Criteria for Use of Concomitant Medications that May Interfere with Efficacy and Safety Assessments in Study GPGL

Drug Class	Use during Screening/Lead-In	Conditions for Use after Randomization		
		Acute Therapy[a]	Rescue Therapy/Post Study Drug Discontinuation	During Safety Follow-Up Period
Drugs with approved weight loss indication[b]	Excluded	N	N/A	Y
Systemic glucocorticoid therapy[c]	Excluded except for acute therapy[a]	Y	N/A	Y
Antihyperglycemia medications				
Other GLP-1 RAs	Excluded	N	N	N
DPP-4 inhibitors	Excluded	N	N	N
Pramlintide	Excluded	N	N	N
SGLT-2i	Excluded	N	Y	Y
Insulins	Excluded except for acute therapy[a]	Y	Y	Y
Meglitinides	Excluded	N	Y	Y
Alpha-glucosidase inhibitors	Excluded	N	Y	Y
Sulphonylureas	Excluded	N	Y	Y
Thiazolidinediones	Excluded	N	Y	Y
Metformin[d]	Required	N/A	Y[e]	Y

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

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

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

[c] From 1 month prior to Visit 1 or between Visits 1 and 3; does not apply to topical, intraocular, intranasal, intra-articular, or inhaled preparations.

[d] Metformin prescreening dose and formulation (short-acting or long-acting) should be maintained throughout the study, except as specified in Section 7.7.1.

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

7.8. Treatment after the End of the Study

Study completion will occur after all patients complete the follow-up visit. Investigators will continue to follow Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

Tirzepatide will not 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 Treatment

Possible reasons leading to permanent discontinuation of investigational product:

- **Patient Decision**
  - The patient requests to discontinue investigational product.
- **Discontinuation due to increased risk of hypoglycemia**

  Please refer to Section 7.4.2.2 for details.

- **Discontinuation due to a hepatic event or liver test abnormality**
  Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via an eCRF.

  Discontinuation of the investigational product for abnormal liver tests **should be** considered by the investigator when a patient meets one of the following conditions after consultation with the Lilly-designated medical monitor:

  - 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
  - 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
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

- If a patient is inadvertently enrolled and it is determined that continued treatment with study drug would not be medically appropriate or is not allowed per local laws or regulations, see Section 8.1.3
- Acute or chronic pancreatitis
- If a patient is diagnosed with MTC after randomization or has a postrandomization calcitonin value ≥35 ng/L that has increased at least 50% over baseline

- If a patient is diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
- Any significant study drug-related hypersensitivity reaction
- Any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
- If female patient becomes pregnant
- If a patient is diagnosed with T1DM

Patients who stop the study drug permanently will receive another glucose-lowering intervention (Section 7.7.2) and will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements. The new glucose-lowering intervention will be recorded on the eCRF specified for collecting antihyperglycemic medications.

Patients discontinuing from the investigational product prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Discontinuation from Study Treatment

In certain situations after randomization, the investigator may need to temporarily interrupt study drug (for example, acute illness, surgery, or hospitalization). 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. 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.

Tirzepatide

- If the number of consecutive missed doses is ≤2, tirzepatide can be restarted at the same dose, if the drug was well tolerated prior to discontinuation.
- If the number of consecutive missed doses is ≥3, then tirzepatide should be restarted at 5 mg irrespective of the dose the patient was receiving before the interruption and subsequently escalated as required by protocol (see Table GPGL.3).
- The investigator will use the IWRS to receive the appropriate study drug dispensing information to preserve blinding of the tirzepatide dose.
- If the above situations occur again during the course of the study, the investigator in consultation with sponsor or designee will discuss the next treatment option.

Semaglutide

- If the number of consecutive missed doses is ≤2, semaglutide can be restarted at 1 mg during the maintenance period. If the doses are missed during the escalation period, the investigator should evaluate each case based on his/her clinical judgement and decide how to restart semaglutide.

- If the number of consecutive missed doses is 3 or 4, semaglutide treatment should be continued with 4 weeks on 0.5 mg QW before escalation to the maintenance dose of 1 mg QW.
- If the number of consecutive missed doses is 5 or more, a full dose escalation should be performed (0.25 mg QW for 4 weeks followed by 0.5 mg QW for 4 weeks, and then escalation to the maintenance dose of 1 mg).
- If the above situations occur again during the course of the study, the investigator in consultation with sponsor or designee will discuss the next treatment option.

If the study drug interruption is due to intolerable persistent GI AE (for example, nausea, vomiting, or diarrhea), the patients should be treated as suggested in Section 7.4.2.5.

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

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor clinical research physician (CRP) agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow-up should be performed as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

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:

- adherence to study drug,
- adherence to visit schedule,
- missing assessments,
- study drug discontinuation due to an AE,
- development of comorbidities, and
- development of clinical outcomes.

The circumstances listed above are not valid reasons for discontinuation from the study.

Patients will be discontinued from the study in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice
- If a female patient becomes pregnant
- If a patient is diagnosed with T1DM
- Patient requests to be withdrawn from the study

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

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

Prior to early study discontinuation, the patient may discontinue study drug and will have end-of-study procedures (ET visit) performed as shown in the Schedule of Activities (Section 2). During the ET visit, the patient will initiate a new glucose-lowering therapy per the discretion of the investigator. Visit 801 (safety follow-up visit) should be performed approximately 4 weeks after the ET visit as the final study visit.

Patients discontinuing from the study prematurely for any reason should complete adverse event and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Every attempt will be made to minimize the number of patients considered lost to follow-up at the end of the study. Patients will be informed about the importance of completing the study and providing updated contact information to the study site when necessary.

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 Assessment

The primary efficacy measurement in this study is mean change in HbA1c values from baseline to 40 weeks, as determined from the central laboratory values. Blood samples for HbA1c measurements will be collected at specific clinic visits as summarized in the Study Schedule, Section 2.

9.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be assessed at 40 weeks based on data collected at the times shown in the Study Schedule (Section 2):

- **Key secondary efficacy assessment (controlled for type 1 error)**
  - Mean change in HbA1c from baseline
  - Mean change in body weight from baseline
  - Proportion of patients with HbA1c target values of <7.0% (53 mmol/mol)
- **Additional secondary efficacy assessment (not controlled for type 1 error)**
  - Proportion of patients achieving an HbA1c target value of ≤6.5% (48 mmol/mol)
  - Proportion of patients achieving an HbA1c target value of <5.7% (39 mmol/mol)
  - Mean change in fasting serum glucose (central laboratory) from baseline
  - Mean change in 7-point SMBG profiles from baseline
  - Proportion of patients who achieved weight loss of ≥5%, ≥10%, and ≥15% from baseline
  - Patient-reported outcomes:
    - DTSQs/DTSQc
    - IW-SP
    - APPADL

9.1.3. Exploratory Assessments and Procedures

The following exploratory measures will be calculated based on data collected at the times shown in the Study Schedule (see Section 2).

- Patient-reported outcomes:
  - EQ-5D-5L
  - IWQOL-Lite-CT
- Changes in fasting glucagon, C-peptide, and insulin levels
- Changes in lipids (total cholesterol, HDL, VLDL, and triglycerides)
- Changes from baseline in mean BMI
- Mean change in waist circumference
- Biomarkers

9.1.4. Body Weight, Height, and Body Mass Index

Body weight will be measured at prespecified time points (Schedule of Activities, Section 2).

Each patient's weight should be measured according to a standardized protocol and recorded on the eCRF to the nearest one-tenth kg (Appendix 7).

BMI will be computed from the patient's weight and height. BMI should be rounded to the nearest whole number for purposes of Inclusion Criterion [4] (Section 6.1).

9.1.5. 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 or stabilizes with appropriate diagnostic evaluation. 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.

The investigator will record all relevant AE and SAE information in the eCRF. After the ICF is signed, study site personnel will record via 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, site personnel will record any change in the condition(s) and any new conditions as AEs. For each AE, the onset and duration, the seriousness and severity, and the actions taken with respect to study treatment will be recorded. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and investigational product via an eCRF.

Procedures and assessments performed prior to Visit 3 are considered screening procedures. The results of these procedures and assessments should be considered preexisting conditions and should be reported as medical history or concomitant illness.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, 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, study site personnel must report this to Lilly or its designee via an 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 one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the 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.

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.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. 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 following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, 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.

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 procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

9.2.2.1. Hypoglycemia

Patients will collect information on episodes of hypoglycemia starting from Visit 3 until the last study visit (follow-up visit or ET visit). For that purpose, patients will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia in the study according to the Schedule of Activities (Section 2). Site personnel will enter this information into the eCRF at each visit.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the plasma glucose [PG] values in this section refer to values determined by a laboratory or International Federation of Clinical

Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips) (ADA 2019a, 2019b):

Glucose alert value (Level 1):

- **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 PG level of ≤70 mg/dL (≤3.9 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).

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 PG 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 PG <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 PG <54 mg/dL (<3.0 mmol/L).

Severe hypoglycemia (Level 3):

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

Other hypoglycemia categories:

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

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

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

In each case of suspected or confirmed hypoglycemia, it is important that the event be properly categorized, the effect of the intervention be assessed, and the frequency of hypoglycemia be evaluated. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established. The patient should receive additional education, if deemed appropriate. Please refer to Section 7.4.2.3 for guidance on management of increased hypoglycemia risks. The dose of metformin may need to be reduced as outlined in Section 7.7.1.

9.2.2.2. Severe, Persistent Hyperglycemia

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

Investigators will be trained on the application of criteria for deciding when and how to intervene with patients who do not reach glycemic targets. An additional therapeutic intervention should be considered in patients who develop severe, persistent hyperglycemia after randomization. Rescue medication will be prescribed as an add-on to randomized treatment, and patients will continue to follow the protocol-specified visit schedule as described in Section 7.4.2.3.

9.2.2.3. Pancreatitis

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

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

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase [p-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 discontinue therapy with investigational product(s), but will continue in the study on another glucose-lowering regimen (details on rescue intervention will be provided). The most appropriate diabetes therapeutic regimen will be decided by the investigator, based on the patient's clinical status. A review of the patient's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Each case of an AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or

pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug(s).

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

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent clinical endpoint committee (CEC). In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from 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 or Lilly staff. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

9.2.2.4. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or MEN-2 will be excluded from the study. The assessment of thyroid safety during the study will include reporting of any case of thyroid malignancy including MTC and papillary carcinoma and measurements of calcitonin. This data will be captured in specific eCRFs. The purpose of calcitonin measurements is to assess the potential of tirzepatide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Tirzepatide should be discontinued (after first confirming the value) if postrandomization calcitonin value is ≥35 ng/L and has increased at least 50% over baseline. A consultation with a thyroid specialist (if not available, an endocrinologist) should be obtained. If the increased calcitonin value (≥35 ng/L and increases by ≥50% compared with baseline) is observed in a patient who has administered a medication that is known to increase serum calcitonin, this medication should be stopped and calcitonin levels should be measured after an appropriate washout period. If the confirmed calcitonin value is <35 ng/L, tirzepatide should be restarted when it is safe to do so.

9.2.2.5. Major Adverse Cardiovascular Events

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

- myocardial infarction
- hospitalization for unstable angina

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

9.2.2.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders will be further evaluated. Patients who develop any event from this group of disorders should undergo an ECG, which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 9.2.1 must be reported as SAEs.

9.2.2.7. Hypersensitivity Events

All allergic or hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, SAEs. Additional data, such as type of reaction and treatment received, will be collected on any AEs or SAEs that the investigator deems related to study drug(s) via a CRF created for this purpose. Additional samples should also be collected as outlined in Section 9.4.4. Study drug(s) should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to the study drug(s). Study drug(s) may be restarted when/if it is safe to do so, in the opinion of the investigator. If study drug(s) is permanently discontinued, the patient will receive another glucose-lowering treatment, judged by the investigator to be appropriate based on the patient's clinical status, and will continue in the trial to collect all planned efficacy and safety measurements.

9.2.2.7.1. Injection Site Reactions

Injection site reactions will be collected on the eCRF separate from the hypersensitivity reaction eCRF. At the time of AE occurrence in the tirzepatide group, samples will be collected for measurement of tirzepatide anti-drug bodies (ADAs) and tirzepatide concentration.

9.2.2.7.2. Anti-Drug Antibodies

The occurrence of ADA formation will be assessed as outlined in Section 9.4.4.

9.2.2.8. Diabetic Retinopathy Complications

Dilated retinal fundoscopic examination will be performed by a qualified eye care professional (ophthalmologist or optometrist) for all patients between Visit 2 and Visit 3 to exclude patients with proliferative retinopathy and/or maculopathy. The results from this examination will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy.

A follow-up dilated fundoscopic examination should be performed by a qualified eye care professional (ophthalmologist or optometrist) when clinically indicated by any AE suspected of worsening retinopathy, and the findings should be recorded on the retinopathy eCRF.

9.2.2.9. Hepatobiliary Disorders

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

elevated liver markers, hepatic monitoring should be initiated as outlined in Section 9.4.5.1 and Appendix 4.

9.2.2.10. 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. For detailed information concerning the management of GI AEs, please refer to Section 7.4.2.5.

9.2.2.11. Acute Renal Events

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

9.2.2.12. Metabolic Acidosis, Including Diabetic Ketoacidosis

Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been reported rarely in patients with T2DM. Patients who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting BG levels, as ketoacidosis may be present even if BG levels are less than 250 mg/dL. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement. Routine bicarbonate assessment will be performed during the course of the study. If lactic acidosis is suspected, metformin should be temporarily discontinued until the resolution of the event.

9.2.2.13. Amputation/Peripheral Revascularization

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

9.2.2.14. Major Depressive Disorder/Suicidal Ideation

The prevalence of depressive symptoms and disorders is increased in patients with T1DM or T2DM (ADA 2019a). Any AE of major depressive disorder or suicidal ideation should be reported.

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.

9.3. Treatment of Overdose

Study drug overdose (more than the specified number of injections) will be reported as an AE. In the event of overdose, refer to the IB for tirzepatide or the Product Label for semaglutide, as applicable (Ozempic® USPI [WWW]).

9.4. Safety

9.4.1. Electrocardiograms

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2). ECGs should be performed after vital signs are collected and prior to the collection of blood samples for laboratory testing if the patient is not adversely affected by the fasting condition. Patients should be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection. Electrocardiograms should be recorded according to the study-specific recommendations.

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

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

9.4.2. Vital Signs

Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required. The participant should sit quietly for 5 minutes before vital sign measurements are taken. For each patient, vital sign measurements should be conducted according to the Schedule of Activities (Section 2) and following the study-specific recommendations.

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

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

Unless otherwise noted in Appendix 2, 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 eCRF.

9.4.4. Immunogenicity Assessments

Where local regulations and ERBs allow, blood samples for immunogenicity testing will be collected to determine antibody production against tirzepatide as specified in the Schedule of Activities (Section 2).

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against tirzepatide. To interpret the results of immunogenicity, a PK sample will be collected at the same time points as the immunogenicity sample. All samples for immunogenicity should be taken before dose when applicable and possible. In the event of drug hypersensitivity reactions (immediate or nonimmediate), additional samples will be collected (including ADA, PK, and exploratory immune safety sample) as close to the onset of the event as possible, at the resolution of the event, and 30 days following the onset of the event. Instructions for the collection and handling of blood samples will be provided by the sponsor. Sample collected at Visit 801 will assess immunogenicity at washout of tirzepatide (5 half-lives post end of treatment).

Treatment-emergent ADAs are defined in Section 10.3.5.

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

Samples will be retained for a maximum of 15 years after the last patient visit or for a shorter period if local regulations and ERBs allow at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to tirzepatide. Any samples remaining after 15 years will be destroyed.

9.4.5. Safety Monitoring

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

9.4.5.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in

consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection
Additional safety data should be collected via the eCRF if 1 or more of the following conditions occur:

- Elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- Elevation of serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- Patient discontinuation from treatment due to a hepatic event or abnormality of liver tests
- Hepatic event considered to be an SAE

9.5. Pharmacokinetics

A PK sample will be collected at the same time points as the immunogenicity sample per the Study Schedule of Activities (Section 2). All samples for PK assessment should be taken predose.

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry method.

Bioanalytical samples collected to measure tirzepatide concentrations will be retained for a maximum of 1 year after the last patient visit for the study.

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. 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

ERBs/IRBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the 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 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 DNA, RNA, proteins, lipids, and other cellular elements.

Serum and plasma samples for 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 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 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 Events (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. Diabetes Treatment Satisfaction Questionnaire

The status (s) and change (c) versions of the DTSQ will be used during the study to assess the patient's satisfaction with their diabetes treatment and the perceived frequency of hyperglycemia and hypoglycemia. The questionnaire contains 8 items (Bradley 1994). Each item is rated on a 7-point Likert scale. Six items (1 and 4 through 8) are summed to produce a measure of

treatment satisfaction ranging from 0 "very dissatisfied" to 6 "very satisfied." The remaining 2 items (2 and 3) are treated individually. Item 2 measures the perceived frequency of hyperglycemia on a scale ranging from 0 "none of the time" to 6 "most of the time," and Item 3 measures the perceived frequency of hypoglycemia on the same scale. The change version has the same 8 items as the status version with a small alteration of the wording of Item 7. The DTSQ change response options differ from those of the DTSQ status to produce measures of relative change rather than absolute satisfaction (3 "much more satisfied now" to -3 "much less satisfied now").

9.9.2. Impact of Weight on Self-Perception Questionnaire

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

9.9.3. Ability to Perform Physical Activities of Daily Living

The 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. 2012). Items are scored on a 5-point numeric rating scale, where 5 = "not at all difficult" and 1 = "unable to do." A raw overall score is calculated by simply summing the scores of the 7 items, and a transformed overall score is obtained by linearly transforming the raw overall score to a 0 to 100 scale. A higher raw overall score and a higher transformed overall score are indicative of better ability to perform activities of daily living.

9.9.4. European Quality of Life

Generic health-related quality of life will be assessed using the EQ-5D-5L (EuroQoL Group 2015). The EQ-5D-5L is a standardized 5-item instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, 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) and 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 2015).

9.9.5. Impact of Weight on Quality of Life-Lite Clinical Trials Version

The IWQOL-Lite-CT is a 20-item, obesity-specific patient-reported outcome (PRO) instrument developed for use in obesity clinical trials. It assesses 2 primary domains of obesity-related health-related quality of life: physical (7 items), and psychosocial (13 items). A 5-item subset of the physical domain – the physical function composite is also supported. Items in the physical function composite describe physical impacts related to general and specific physical activities. All items are rated on either a 5-point frequency ("never" to "always") scale or a 5-point truth ("not at all true" to "completely true") scale (Kolotkin et al. 2017, 2018).

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 1872 patients (468 per group) will be randomly assigned in a 1:1:1:1 ratio to tirzepatide 5 mg, 10 mg, 15 mg QW, or semaglutide 1 mg QW. Patient randomization will be stratified based on country and baseline HbA1c (≤8.5% or >8.5% [69 mmol/mol]).

The trial is powered to assess noninferiority of tirzepatide 10 mg and/or tirzepatide 15 mg QW to semaglutide 1 mg QW, relative to the primary endpoint: mean change in HbA1c from baseline to 40 weeks.

The power is assessed based on the following assumptions:

- each of the 10-mg and 15-mg tirzepatide QW treatment groups will be tested in parallel against semaglutide 1 mg QW at 2-sided 0.025 significance level
- use of 2-sample *t* test utilizing HbA1c data collected before initiation of any rescue medication or premature treatment discontinuation with no more than 28% of patients initiating any rescue medication or premature treatment discontinuation in each treatment group
- no difference between tirzepatide doses and semaglutide 1 mg relative to the primary endpoint
- a noninferiority margin of 0.3%, and
- a common standard deviation (SD) of 1.1%.

On the basis of these assumptions, randomly assigning approximately 1872 patients to the 4 treatments using a 1:1:1:1 ratio will provide at least 90% power to demonstrate noninferiority of tirzepatide 10 mg and/or 15 mg QW doses to semaglutide 1 mg QW, relative to the primary endpoint for the "efficacy" estimand. Furthermore, this sample size will ensure 90% power to demonstrate noninferiority for the "treatment-regimen" estimand conducted using an analysis of covariance (ANCOVA) utilizing all available HbA1c data at 40 weeks. Missing data will be imputed with a conservative multiple imputation method (as described in Section 10.3.3) if SD were to increase up to 1.3% due to the inclusion of data on rescue medications, inclusion of data after premature treatment discontinuation, and imputation of the missing data.

10.2. Populations for Analyses

For purposes of the analyses, the following populations are defined:

Population	Description
Screened patients	All participants who sign informed consent
Randomly assigned patients	All patients who are randomly assigned to a treatment group
Modified intent-to-treat (mITT) population	All randomly assigned patients who are exposed to at least 1 dose of study drug. In the event of a treatment error, patients will be analyzed according to the treatment they were randomly assigned to.
Efficacy analysis set (EAS)	Data obtained during Study Period II from the mITT population, excluding data after initiating rescue antihyperglycemic medication or stopping study drug.
Full analysis set (FAS)	Data obtained during Study Period II from the mITT population, regardless of adherence to study drug or initiation of rescue antihyperglycemic medication.
Safety analysis set (SS)	Data obtained during Study Period II or III from the mITT population, regardless of adherence to study drug or initiation of rescue antihyperglycemic medication.

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 statistical analysis plan (SAP) or the clinical study report. Additional exploratory analyses of the data may be conducted as deemed appropriate.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval (CI) will be calculated at 95%, 2-sided. In statistical summaries and analyses, patients will be analyzed as randomly assigned.

There will be 2 estimands of interest in comparing efficacy of tirzepatide doses with semaglutide. The first estimand, "efficacy," represents efficacy prior to discontinuation of study drug without confounding effects of antihyperglycemic rescue therapy. The second estimand, "treatment-regimen," represents the efficacy irrespective of adherence to study drug or initiation of rescue antidiabetic drugs.

The primary efficacy assessment for change from baseline in HbA1c, guided by the "efficacy" estimand, will be conducted using the efficacy analysis set (EAS). The primary efficacy assessment, guided by the "treatment-regimen" estimand, will be conducted using the full analysis set (FAS). As they are intended for different purposes, no multiplicity adjustments will be made for conducting 2 primary efficacy assessments relative to the "efficacy" and "treatment-regimen" estimands.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses with semaglutide irrespective of adherence to study drug or initiation of

antihyperglycemic rescue therapy. Thus, safety analysis will be conducted using the safety analysis set (SS). Selected safety analyses may be conducted after excluding data on rescue therapy or data after starting another antihyperglycemic medication.

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

- treatment
- visit
- treatment-by-visit interaction
- country
- baseline HbA1c category (≤8.5% or >8.5% [69 mmol/mol]), and
- baseline measurement as a covariate.

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

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

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

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

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

Frequency counts and percentages of all patients screened, randomly assigned, and receiving at least 1 dose of study drug will be presented by treatment groups. A listing of randomly assigned patients not receiving study drug will be provided. Of the patients in the mITT set, frequency, counts, and percentages of patients completing the study; prematurely discontinuing the study including the reason for premature discontinuation; and prematurely discontinuing study drug including the reason for premature discontinuation of study drug will be presented by treatment groups. A Kaplan-Meier analyses of time from randomization to premature discontinuation from study and premature discontinuation from study drug by treatment group will be provided.

10.3.2.2. Patient Characteristics

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

10.3.2.3. Concomitant Therapy

Concomitant medications will be summarized by anatomical therapeutic chemical classification and treatment group using the mITT population. In particular, the incidence of initiation of rescue therapy for severe, persistent hyperglycemia will be analyzed and summarized as an exploratory safety endpoint. Dose modifications of metformin will also be summarized.

10.3.2.4. Treatment Compliance

Treatment compliance for each visit interval is defined as taking at least 75% of required injections of study drugs. Overall treatment compliance for each patient will be computed by the number of injections divided by the total planned number of injections the patient should take during the study. Frequency counts and percentages of patients compliant to study drug will be summarized by treatment groups using the mITT population.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

As indicated in Section 10.3.1, there will be 2 primary efficacy analyses conducted to establish noninferiority of tirzepatide 10 mg and/or 15 mg QW to semaglutide 1 mg QW relative to mean change in HbA1c values from baseline to the 40-week visit.

For the FDA and possibly other regulatory agencies, the primary efficacy analysis will be guided by the "treatment-regimen" estimand defined in Section 10.3.1 using the FAS dataset. This assessment will analyze change in HbA1c values from baseline obtained at the 40-week visit using an analysis of covariance (ANCOVA) with terms for:

- treatment
- country, and
- baseline HbA1c as a covariate.

As initial step, a 2-sided 97.5% CI for the difference in mean change in HbA1c from baseline to the 40-week visit between 10 mg tirzepatide QW and semaglutide 1 mg QW, as well as between 15 mg tirzepatide QW and semaglutide 1 mg QW, will be constructed. If the upper limit of the CI is below 0.3%, the tirzepatide dose will be declared noninferior to semaglutide. A graphical testing approach (Bretz et al. 2011) will be employed to control the family-wise type 1 error at 5% level for the primary and key secondary endpoints. Details will be described in the SAP.

Missing HbA1c values at the 40-week visit will be imputed based on observed data in the same treatment group from patients who had their efficacy assessed after early discontinuation of study drug and/or initiation of rescue antihyperglycemic medication. This analysis will be conducted with multiple imputations, and statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

For all other purposes, the primary efficacy analysis will be guided by the "efficacy" estimand defined in Section 10.3.1. This assessment will be conducted using the EAS. The primary analysis model for HbA1c measurements over time will be an MMRM. The response variable of MMRM will be change in HbA1c values from baseline obtained at each scheduled postbaseline

visit. The independent variables of the MMRM model are treatment, visit, treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c as a covariate.

Since they are intended for different purposes, each of the 2 primary efficacy assessments relative to the "efficacy" and "treatment-regimen" estimands will be conducted at a family-wise type 1 error rate of 0.05. Additional details, including analysis methods for key secondary endpoints and a strategy for controlling the overall family-wise type 1 error rate at an alpha of 0.05 for primary and key secondary endpoint evaluation, will be provided in the SAP.

10.3.3.2. Secondary Analyses

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

- Noninferiority of tirzepatide 5 mg QW to semaglutide 1 mg QW relative to mean change in HbA1c from baseline to the 40-week visit
- Superiority of tirzepatide 5 mg, 10 mg, and/or 15 mg QW to semaglutide 1 mg relative to:
    - mean change in body weight from baseline to the 40-week visit
    - mean change in HbA1c from baseline to the 40-week visit
    - proportion of patients achieving the target value of HbA1c <7% (<53 mmol/mol) at the 40-week visit.

The type 1 error-controlled strategy for the primary and secondary endpoints will be described in the SAP. All type 1 error-controlled secondary efficacy analyses will be conducted separately for both estimands, the "efficacy" estimand and the "treatment-regimen" estimand.

Analysis of change from baseline in body weight at the 40-week visit will be conducted in a manner similar to the primary efficacy analyses with baseline HbA1c category (≤8.5% or >8.5% [69 mmol/mol]) added in the model, and baseline of the corresponding variable as a covariate. The MMRM analyses are described in Section 10.3.1.

Comparisons among treatments relative to the proportion of patients achieving the HbA1c target value of <7.0% (<53 mmol/mol) at the 40-week visit will be conducted using a logistic regression analysis with terms for: treatment, country, and baseline HbA1c as a covariate. In the analysis of patients achieving the HbA1c target value relative to the "efficacy" estimand, patients with missing values at the 40-week visit will be excluded. In the analysis of patients achieving the HbA1c target value relative to the "treatment-regimen" estimand, missing values at the 40-week visit will be imputed based on observed data at respective visits from patients in the same treatment group who had their efficacy assessed after early discontinuation of study drug and/or initiation of rescue medication. The analysis will be conducted with multiple imputations and statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

10.3.3.3. Tertiary/Exploratory Analyses

All exploratory efficacy analyses will be guided by the "efficacy" estimand and will be conducted using the EAS. Details will be provided in the SAP.

10.3.4. Safety Analyses

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

AEs will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized MedDRA Queries. Summary statistics will be provided for incidence of TEAEs, SAEs, and study discontinuation due to AEs, study drug discontinuation due to AEs, or deaths from the time of first dose through end of safety follow-up. Counts and proportions of patients experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

10.3.4.1. Hypoglycemic Events

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

10.3.4.2. Gastrointestinal Events

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

10.3.4.3. Adjudicated Cardiovascular Events

Listings of deaths, myocardial infarctions, strokes, and hospitalization for unstable angina confirmed by an independent CEC will be provided. The event, first dose and last dose of study drug, and time from randomization to the event will be listed.

10.3.4.4. Central Laboratory Measures, Vital Signs, and Electrocardiograms

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

The percentages of patients with TE abnormal, high, or low laboratory measures at any time will be summarized and compared between treatment groups using Fisher's exact test. A TE abnormal value is defined as a change from normal value at baseline to a value greater than the

high limit at any time during Study Periods II and III. A TE low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time during Study Periods II and III. The high and low limits will be provided in the SAP.

10.3.5. Evaluation of Immunogenicity

The frequency and percentage of patients with preexisting ADA, with TE ADA, and with neutralizing TE ADA to tirzepatide will be tabulated by tirzepatide dose. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). The minimum required dilution of the ADA assay is 1:10. For the patients with TE ADA, the distribution of maximum titers will be described. The frequency of neutralizing antibodies to tirzepatide and/or cross-reactive and neutralizing antibodies to endogenous counterparts will be tabulated in patients with TE ADA.

The relationship between the presence of antibodies and tirzepatide PK and PD response including safety and efficacy to tirzepatide may be assessed.

10.3.6. Other Analyses

10.3.6.1. Health Economics

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

10.3.6.2. Subgroup Analyses

Subgroup analyses of mean change in HbA1c values from baseline to Visit 11 will be provided by

- age
- race
- ethnicity
- gender
- duration of diabetes, and
- baseline HbA1c (≤8.5% and >8.5% [69 mmol/mol]).

10.3.7. Interim Analyses

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

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APPADL	Ability to Perform Physical Activities of Daily Living
AST	aspartate aminotransferase
BG	blood glucose
blinding	In the context of this study, double-blind means that the patient, the investigator/site staff, and sponsor staff are blinded.
BMI	body mass index
CEC	clinical endpoint committee
CHF	congestive heart failure
CI	confidence interval
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related good clinical practice (GCP) and applicable regulatory requirements.
COVID-19	Coronavirus Disease 2019
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CT	computed tomography

CV	cardiovascular
DPP-4	dipeptidyl peptidase-4
DTSQc	Diabetes Treatment Satisfaction Questionnaire change
DTSQs	Diabetes Treatment Satisfaction Questionnaire status
EAS	efficacy analysis set
ECG	electrocardiogram
eCRF	electronic case report form
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.
EQ-5D-5L	European Quality of Life: 5 dimensions, 5 levels
ERB	ethical review board
ET	early termination
FAS	full analysis set
FSH	follicle-stimulating hormone
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICF	informed consent form
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.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intent 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.
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
IWRS	interactive web-response system
IW-SP	Impact of Weight on Self-Perception
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	multiple endocrine neoplasia type 2
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NAFLD	nonalcoholic fatty liver disease
OAM	oral antihyperglycemic medications
OTC	over the counter
p-amylase	pancreatic amylase
PG	plasma glucose
PK/PD	pharmacokinetics/pharmacodynamics
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QW	once weekly
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SMBG	self-monitored blood glucose
SS	safety analysis set
SUSARs	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VLDL	very low-density lipoprotein

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology
Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume
Mean cell hemoglobin concentration
Leukocytes (WBC)
Neutrophils, segmented
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Urine Chemistries
Microalbumin
Creatinine
Urine microalbumin/creatinine ratio[d]

HbA1c

Endocrine
Glucagon (fasting)
Insulin (fasting)
Calcitonin
C-peptide (fasting)

Immunogenicity
Tirzepatide anti-drug antibody
PK sample for immunogenicity

Anti-GAD Antibodies

Pharmacogenetic Stored Sample

Nonpharmacogenetic Stored Samples
EDTA plasma
Serum
P800 plasma

Chemistry Panel
Sodium
Potassium
Bicarbonate
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Blood urea nitrogen (BUN)
Creatinine
Uric acid
Calcium

Glucose (Fasting)

Pregnancy test (serum and urine; females only)[b]
Follicle-stimulating hormone (FSH)[c]
Estradiol[c]

eGFR (calculated by CKD-EPI equation)[d]

Pancreas (Exocrine) Panel
Pancreatic amylase
Lipase

Lipid Panel (Fasting)
Total cholesterol
LDL
HDL
VLDL
Triglycerides

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; GAD = glutamic acid decarboxylase; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RBC = red blood cells; VLDL = very low-density lipoprotein; WBC = white blood cells.

[a] All tests will be performed by a Lilly-designated central laboratory, unless otherwise noted.

[b] Serum pregnancy test will be performed by central laboratory at Visit 1 for women of childbearing potential. A local urine pregnancy test must be performed at Visit 3 with the result available prior to randomization and first injection of study drug(s) for women of childbearing potential only. Additional pregnancy tests will be performed at Visits 6, 9, and 11. Pregnancy tests may be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period.

[c] FSH test performed at Visit 1 for postmenopausal women at least 45 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months and estradiol levels consistent with a postmenopausal state (FSH ≥40 mIU/mL and estradiol <30 pg/mL).

[d] Urine microalbumin/creatinine ratio and estimated glomerular filtration rate will be calculated by the central laboratory and included in laboratory result reports.

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

- 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 informed consent form (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. Ethical Review

The investigator (or an appropriate local representative) must give assurance that the ethical review board (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 Good Clinical Practice (GCP).

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

- the protocol and related amendments and addenda, current Investigator Brochure (IB), and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

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

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) 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.

Appendix 3.1.5. Investigator Information

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

Appendix 3.1.6. 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 3.1.7. Final Report Signature

The Clinical Study Report (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. 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 CRFs, and study procedures.

- make periodic visits to the study site
- be available for consultation and stay in contact with the study 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 3.2.1. 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 source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment data (scales, self-reported diary data) 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 system(s) will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture 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 3.3. Study and Site Closure

Appendix 3.3.1. 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.

Appendix 3.3.2. 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 3.4. Publication Policy

The publication policy for Study I8F-MC-GPGL is described in the Clinical Trial Agreement.

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 Lilly, or its designee, clinical research physician.

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 = aspirate 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 Lilly-designated or local laboratory

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

Appendix 5. World Health Organization Classification of Diabetes and Diagnostic Criteria

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

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

Appendix 6. Classification of Contraceptive Methods

Highly Effective Methods of Contraception:

- Combined oral contraceptive pill and mini pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total abstinence (if this is their preferred and usual lifestyle) or in a same-sex relationship with no sexual relationship with males (as part of their preferred and usual lifestyle). Note: periodic abstinence (for example, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception
- Vasectomy – for men in clinical studies

Effective Methods of Contraception (must use combination of 2 methods):

- Male condom with spermicide
- Female condom with spermicide
- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

Men, regardless of their fertility status, with nonpregnant women of childbearing potential partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or effective method of contraception (such as diaphragms with spermicide or cervical sponge) for the duration of the study and for at least 3 months after the last injection.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in women of childbearing potential.

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

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

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2017) (Available at: https://www.who.int/ncds/surveillance/steps/Section%204%20Step%202%20Physical%20Measurements.pdf). Last accessed February 8, 2019.

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 backboard, 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.
- All weights for a given patient should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.
- Patients should be lightly clothed but not wearing shoes while their weight is measured.

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

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

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

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

Measuring Waist Circumference

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

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

Step 2. Ask patient to relax

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

Appendix 8. Changes to Study Procedures due to the COVID-19 Pandemic

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes the novel COVID-19 pandemic, has caused numerous global restrictions to be enacted that may impact a patient's ability and/or willingness to attend their onsite study visit as originally scheduled. In such a situation, please follow the guidance below:

1) Patients should come for the primary endpoint visit (Visit 11) at the originally planned 40-week (±7 days) schedule whenever possible and safe to do so, at the investigator's discretion. However, in order to maximize the ability for onsite visits for Visit 11, minimize missing data, and preserve the intended conduct of the study, the visit window for Visit 11 may be brought forward no sooner than 14 days (Week 38) or extended up to 28 days (Week 44). The subsequent safety follow-up visit (Visit 801) should take place 4 weeks ±7 days after Visit 11.

2) For patients requiring an extension for Visit 11 up to Week 44, additional study drug will be provided to allow patients to remain on study drug uninterrupted during the extended treatment period, to ensure patient safety, and to maintain the overall integrity of the trial.

3) Additional consent from the patient per local regulations will be obtained for those patients who will be dispensed additional study drug during the extended treatment period.

4) The sites will need to identify and document the details of how all patients and visits were affected by COVID-19 pandemic restrictions.

5) **Mobile (in-home) healthcare visits:**
   - Mobile visits may be performed at participants' homes when participants cannot travel to the site due to extenuating circumstances. These will be performed by a qualified home nursing service provider following sponsor approval, if permitted by local regulations. Procedures performed may include, but are not limited to, taking blood samples, conducting physical assessments, administering PROs, and collecting health information. Please note that requirements related to the reporting of SAEs remain unchanged. Every effort should be made for the participant to return to onsite visits as soon as reasonably possible, while ensuring the safety of the participant and investigational site staff.
   - Additional consent from the participant will be obtained for those who participate in home health services.

Appendix 9. Protocol Amendment I8F-MC-GPGL(b) A Phase 3, Randomized, Open-Label Trial Comparing Efficacy and Safety of Tirzepatide versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Patients with Type 2 Diabetes (SURPASS-2)

Overview

Protocol I8F-MC-GPGL titled "A Phase 3, Randomized, Open-Label Trial Comparing Efficacy and Safety of Tirzepatide versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Patients with Type 2 Diabetes (SURPASS-2)" has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table.

Amendment Summary for Protocol I8F-MC-GPGL Amendment (b)

Section # and Name	Description of Change	Brief Rationale
Appendix 8, Changes to Study Procedures due to the COVID-19 Pandemic	Added language about the mobile (in-home) healthcare visits.	This provides an option to conduct a clinical trial visit and all the applicable procedures in a mobile healthcare facility or at the home of a patient when the patient is not able or not willing to go to the site due to COVID-19 restrictions.

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