Protocol I8F-MC-GPGK(b)

A Randomized, Double-blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Three Tirzepatide Doses Versus Placebo in Patients With Type 2 Diabetes, Inadequately Controlled With Diet and Exercise Alone

NCT03954834

Approval Date: 15-Apr-2020

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A Randomized, Double-blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Three Tirzepatide Doses versus Placebo in Patients with Type 2 Diabetes, Inadequately Controlled with Diet and Exercise Alone (SURPASS-1)

Tirzepatide (LY3298176)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly: 13-Dec-2018
Amendment (a) Electronically Signed and Approved by Lilly: 03-May-2019
Amendment (b) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 15-Apr-2020 GMT

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1. Synopsis

Title of Study:

A Randomized, Double-blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Three Tirzepatide Doses versus Placebo in Patients with Type 2 Diabetes, Inadequately Controlled with Diet and Exercise Alone (SURPASS-1)

Rationale:

Type 2 diabetes mellitus (T2DM) is a metabolic condition characterized by impaired glycemic control caused by increased insulin resistance and progressive beta-cell failure and consequently inadequate insulin secretion. In addition to lifestyle intervention including medical nutrition therapy and physical therapy, glucose-lowering medications are usually required for improving glycemic control in patients with T2DM (ADA 2018; Davies et al. 2018).

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

Study I8F-MC-GPGK (Study GPGK) is a Phase 3, multicenter, randomized, double-blind, parallel, international, placebo-controlled, 40-week study that will assess the efficacy and safety of 3 doses of tirzepatide versus placebo in patients with T2DM naive to diabetes injectable therapy, inadequately controlled with diet and exercise alone, and have not been treated with any oral antidiabetic medication during the 3 months preceding to the start of the study.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To demonstrate that tirzepatide QW 5 mg, and/or 10 mg, and/or 15 mg are superior to placebo in HbA1c change from baseline to 40 weeks	• Mean change in HbA1c
Key Secondary (controlled for type 1 error) • To demonstrate superiority of tirzepatide QW 5 mg, and/or 10 mg, and/or 15 mg to placebo at 40 weeks for:	• Mean change in body weight • Proportion of patients with HbA1c target values of <7.0% (<53 mmol/mol) • Mean change in fasting serum glucose (central laboratory) • Proportion of patients with HbA1c target values of <5.7% (<39 mmol/mol)

Objectives	Endpoints
Additional Secondary (not controlled for type 1 error) • To compare tirzepatide QW 5 mg, 10 mg, and 15 mg to placebo at 40 weeks for:	• Proportion of patients with HbA1c target of ≤6.5% (≤48 mmol/mol) • Mean change in daily average 7-point self-monitored blood glucose profiles from baseline • Proportion of patients who achieved weight loss of ≥5%, ≥10%, and ≥15%
Safety • To compare the safety of tirzepatide QW 5 mg, 10 mg, and 15 mg to placebo for:	• Treatment-emergent adverse events (TEAEs) • Early discontinuation of study drug due to adverse events (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 • Time to initiation of rescue therapy for severe persistent hyperglycemia
Pharmacokinetics • To characterize the pharmacokinetics of tirzepatide QW 5 mg, 10 mg, and 15 mg and the relationships between tirzepatide exposure and safety, tolerability, and efficacy measures	• Population pharmacokinetic and pharmacodynamic parameters

Summary of Study Design:

Study GPGK is a multicenter, randomized, double-blind, parallel, international, placebo-controlled, 40-week study which will assess the efficacy and safety of 3 doses of tirzepatide versus placebo in approximately 472 randomized patients with T2DM who are not controlled on diet and exercise alone, naïve to diabetes injectable therapy, and have not been treated with any oral antidiabetic medication during the 3 months preceding to the start of the study.

Treatment Arms and Duration:

Study GPGK will consist of 3 periods: an approximately 3-week screening/lead-in period, followed by a 40-week treatment period, and a 4-week safety follow-up period. Patients will be randomized in a 1:1:1:1 ratio (tirzepatide 5 mg QW, 10 mg QW, 15 mg QW, and injectable placebo). Patients will be stratified based on country, baseline HbA1c [≤8.5% (≤69 mmol/mol) or >8.5% (>69 mmol/mol)], and any past prior use (Yes or No) of any oral antidiabetic medication).

Number of Patients:

A total of approximately 472 patients (118 patients per treatment group) will be randomized.

Statistical Analysis:

Efficacy Analyses

Efficacy will be assessed using the modified intent-to-treat population, which consists of all randomly assigned participants who are exposed to at least 1 dose of study drug. There will be 2 estimands of interest in comparing efficacy of QW tirzepatide doses with placebo relative to the primary measure of mean change in HbA1c values from baseline to 40-week visit. The "efficacy" estimand, represents efficacy prior to discontinuation of study drug without confounding effects of rescue therapy for persistent severe hyperglycemia. 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 40-week visit using an analysis of covariance (ANCOVA) with terms: treatment, country, any past prior use (Yes or No) of any oral antidiabetic medication, and baseline HbA1c as a covariate. The ANCOVA analysis will be conducted using the full analysis set at 40-week visit, which consists of all available change 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, data for patients with missing values will be imputed based on observed data in the same treatment arm from patients who had their efficacy measure at the Week 40 visit assessed after early discontinuation of study drug and/or initiation of rescue medication (retrieved dropouts).

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, guided by the "efficacy" estimand, will use efficacy analysis set which consists of data obtained before the initiation of any rescue therapy and before premature treatment discontinuation. The analysis model for change in HbA1c values from baseline assessed over time will be a mixed model for repeated measures (MMRM) with terms: treatment, visit, treatment-by-visit interaction, country, any past prior use (Yes or No) of any oral antidiabetic medication as fixed effects, baseline HbA1c as a covariate, and patient as a random effect. An unstructured covariance structure will model relationship of within-patient errors.

Since they are intended for different purposes, each of the 2 primary efficacy assessments relative to two estimands will be conducted at 2-sided alpha of 0.05. Additional details, including analysis methods for key secondary endpoints and a strategy for controlling overall 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 first dose to 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. 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 GPGK. 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 GPGK.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	12	13	14	ET[b]	801
Week of Treatment	-3	-2	0	4	7	8	12	15	16	20	23	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	X
PK specific Visit[e]					X			X			X					
Informed consent	X															
Randomization			X													
Clinical Assessments																
Medical history[f]	X															
Physical	X													X	X	X
Height	X															
Weight[g]	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[h]			X											X	X	X
Vital signs (2 sitting BP and HR)[i]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundoscopic Examination[j]		X														
Adverse events	X	X	X	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	X	X	X
Review hypoglycemic events collected in the diaries			X	X		X	X		X	X		X	X	X	X	X

	Study Period I		Study Period II												Study Period III
	Screening/ Lead in		Treatment Period												Safety F/U
Visit	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	ET[b]	801
Week of Treatment	-3	-2	0	4	7	8	12	15	16	20	23	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	X
PK specific Visit[e]					X			X			X					
Diabetes education[k,l]		X														
BG meter, SMBG training[m]		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[l]			X													
Hand out diaries, instruct in use[l]		X	X											X	X	
Remind patients about 7-point SMBG[m]		X				X							X	X	X	
Review 7-point SMBG values collected in the diaries			X				X							X		X

	Study Period I		Study Period II													Study Period III
	Screening/ Lead in		Treatment Period													Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**4**	**7**	**8**	**12**	**15**	**16**	**20**	**23**	**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**	**X**
PK specific Visit[e]					**X**			**X**			**X**					
Dispense study drug			X	X		X	X		X	X		X	X			
Observe patient administer study drug[n]			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	

	Study Period I		Study Period II													Study Period III
	Screening/ Lead in		Treatment Period													Safety F/U
Visit	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	ET[b]	801
Week of Treatment	-3	-2	0	4	7	8	12	15	16	20	23	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	X
PK specific Visit[e]					X			X			X					
Laboratory Tests																
Serum pregnancy test[o]	X															
Urine pregnancy test[p]			X				X					X		X		
Follicle-stimulating hormone test, estradiol[q]	X															
Chemistry panel	X[r]						X					X		X	X	X
Fasting serum glucose			X	X		X	X		X	X		X	X	X	X	X
Fasting insulin			X			X			X			X		X		X
Fasting glucagon			X			X			X			X		X		X
Fasting C-peptide			X			X			X			X		X		X
Lipid panel			X			X			X			X		X	X	X
Urinary albumin/creatinine ratio	X[r]													X	X	X
Serum creatinine, eGFR (CKD-EPI)[s]	X[r]						X					X		X	X	X
Calcitonin	X[r]						X					X		X	X	X
Hematology	X[r]						X					X		X	X	X
HbA1c	X		X	X		X	X		X	X		X	X	X	X	X
Pancreatic amylase, lipase	X[r]						X					X		X	X	X
Immunogenicity[t]			X	X			X					X		X	X	X
PK sample for immunogenicity[u]			X	X			X					X		X	X	X

	Study Period I		Study Period II													Study Period III
	Screening/ Lead in		Treatment Period													Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**4**	**7**	**8**	**12**	**15**	**16**	**20**	**23**	**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	X
PK specific Visit[e]					X			X			X					
Stored samples																
Tirzepatide PK[v]			X[w]		X			X			X			X[x]	X	
Pharmacogenetic stored sample			X													
Nonpharmacogenetic stored sample EDTA plasma, serum, P800 plasma-2.0 mL			X				X					X		X	X	
Patient-Reported Outcomes[y]																
APPADL			X											X	X	
EQ-5D-5L			X											X	X	
IW-SP			X											X	X	

Abbreviations: ADA = anti-drug antibody; APPADL = Ability to Perform Physical Activities of Daily Living; BG = blood glucose; BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life-dimensions; ET = early termination; F/U= follow-up; HbA1c = hemoglobin A1c; HR = heart rate; IW-SP = Impact of Weight on Self-Perception; PK = pharmacokinetics; PRO = patient-reported outcome; SMBG = self-monitoring of blood glucose; Tx = treatment.

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

[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] On visits 3, 4, 6, 7, 9, 10, 12, 13, 14, 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.

[e] Visit is for tirzepatide PK blood draws

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

[g] Weight measurements must be in kilograms.

[h] Electrocardiograms occurring on visits with tirzepatide PK collection should be collected at least 30 minutes prior to obtaining the sample for tirzepatide PK measurement.

[i] 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.

[j] 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 were recorded on the retinopathy eCRF.

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

[l] All training should be repeated as needed to ensure patient compliance.

[m] Patient is required to collect two 7-point SMBGs on 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. If more than 2 SMBG profiles are available, the 2 most recent nonconsecutive profiles should be used.

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

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

[p] 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 7, 12, and 14. 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.

[q] Follicle-stimulating hormone (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).

[r] Screening visit assessment will serve as baseline.

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

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

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

[v] PK samples will be collected at these visits except for Visit 3 and Visit 14 at time windows of 1 to 24 hours, 24 to 96 hours, OR 120 to 168 hours post dose, as assigned by IWRS. Dependent on the time windows to which a patient gets assigned, they may be required to come to site for PK-specific visits.

[w] The PK sample after the first dose at Visit 3 should be collected anytime on the same day after administration of the first dose at the site.

[x] The PK sample after the last dose administered at Week 39 will be collected at Visit 14 (Week 40).

[y] All PROs 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.

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 and progressive beta-cell failure and consequently inadequate insulin secretion. Type 2 diabetes mellitus is associated with comorbidities such as increased weight or obesity, hypertension, increased blood lipoprotein concentrations, and a higher risk for macro- and microvascular complications. To prevent these complications, tight glycemic control is recommended (ADA 2018; 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) to achieve and maintain glucose control (Inzucchi et al. 2015; ADA 2018). While associated with lower risk for hypoglycemia and either weight neutral or weight loss effects, current preparations are directed at a single molecular target (GLP-1 receptors) and provide dose-dependent glucose-lowering effects, which can be limited by gastrointestinal (GI) tolerability (Nauck 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 some other actions beyond its role as an incretin that could potentially improve therapeutic efficacy in combination with GLP-1 receptor agonists alone (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 It is administered as once-weekly (QW) subcutaneous (SC) injection (Coskun et al. 2018).

Study I8F-MC-GPGK (Study GPGK) is a Phase 3, multicenter, randomized, double-blind, parallel, international, placebo-controlled, 40-week study that will assess the efficacy and safety of 3 doses of tirzepatide versus placebo in patients with T2DM naive to diabetes injectable therapy, inadequately controlled with diet and exercise alone, and have not been treated with any oral antidiabetic medication during the 3 months preceding to the start of the study.

3.2. Background

Three tirzepatide clinical studies have completed dosing and analysis: a Phase 1 study, Study I8F-MC-GPGA (Study GPGA), and 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 study in patients with T2DM. Study GPGA investigated safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of tirzepatide administered as SC injections. A total of 142 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 multiples 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.

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 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 GI related, consisting mainly of nausea, vomiting, and diarrhea and were dose-dependent. The GI AEs were usually mild to moderate in intensity. 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 unlikely to be optimal for the reduction of GI-related AEs expected with tirzepatide, Study GPGF was designed to explore alternative titration schemes (longer time intervals between dose escalations and different dose escalations) to support evaluation of optimized dosing regimen(s) in Phase 3. This was a 12-week, placebo-controlled study to assess the efficacy and 3 different titration schemes to attain doses as high as 15 mg of tirzepatide in patients with T2DM.

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

3.3. Benefit/Risk Assessment

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

4. Objectives and Endpoints

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

Table GPGK.2. Objectives and Endpoints

Objectives	Endpoints
Primary • To demonstrate that tirzepatide QW 5 mg, and/or 10 mg, and/or 15 mg are superior to placebo in HbA1c change from baseline to 40 weeks	• Mean change in HbA1c
Key Secondary (controlled for type 1 error) • To demonstrate superiority of tirzepatide QW 5 mg, and/or 10 mg, and/or 15 mg to placebo at 40 weeks for:	• Mean change in body weight • Proportion of patients with HbA1c target values of <7.0% (<53 mmol/mol) • Mean change in fasting serum glucose (FSG) (central laboratory) • Proportion of patients with HbA1c target values of <5.7% (<39 mmol/mol)
Additional Secondary (not controlled for type 1 error) • To compare tirzepatide QW 5 mg, 10 mg, and 15 mg to placebo at 40 weeks for:	• Proportion of patients with HbA1c target of ≤6.5% (≤48 mmol/mol) • Mean change in daily average 7-point self-monitored blood glucose profiles from baseline • Proportion of patients who achieved weight loss of ≥5%, ≥10%, and ≥15%
Safety • To compare the safety of tirzepatide QW 5 mg, 10 mg, and 15 mg to placebo for:	• Treatment-emergent adverse events (TEAEs) • Early discontinuation of study drug due to adverse events (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 • Time to initiation of rescue therapy for severe persistent hyperglycemia

Objectives	Endpoints
Pharmacokinetics • To characterize the pharmacokinetics (PK) of tirzepatide QW 5 mg, 10 mg, and 15 mg and the relationships between tirzepatide exposure and safety, tolerability, and efficacy measures	• Population PK and PD parameters
Tertiary/Exploratory • To compare tirzepatide QW 5 mg, 10 mg, and 15 mg with placebo with respect for the following:	• Change in fasting glucagon, C-peptide, and insulin level • Mean change in lipids (total cholesterol, HDL, LDL, VLDL, and TG) • Mean change in waist circumference • Changes from baseline in mean body mass index • Biomarkers • Patient-reported outcomes o Ability to Perform Physical Activities of Daily Living o European Quality of Life-Dimensions (EQ-5D-5L) scores o Impact of Weight on Self-Perception

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; PD = pharmacodynamics; QW = once weekly; TG = triglycerides; VLDL = very low-density lipoprotein.

5. Study Design

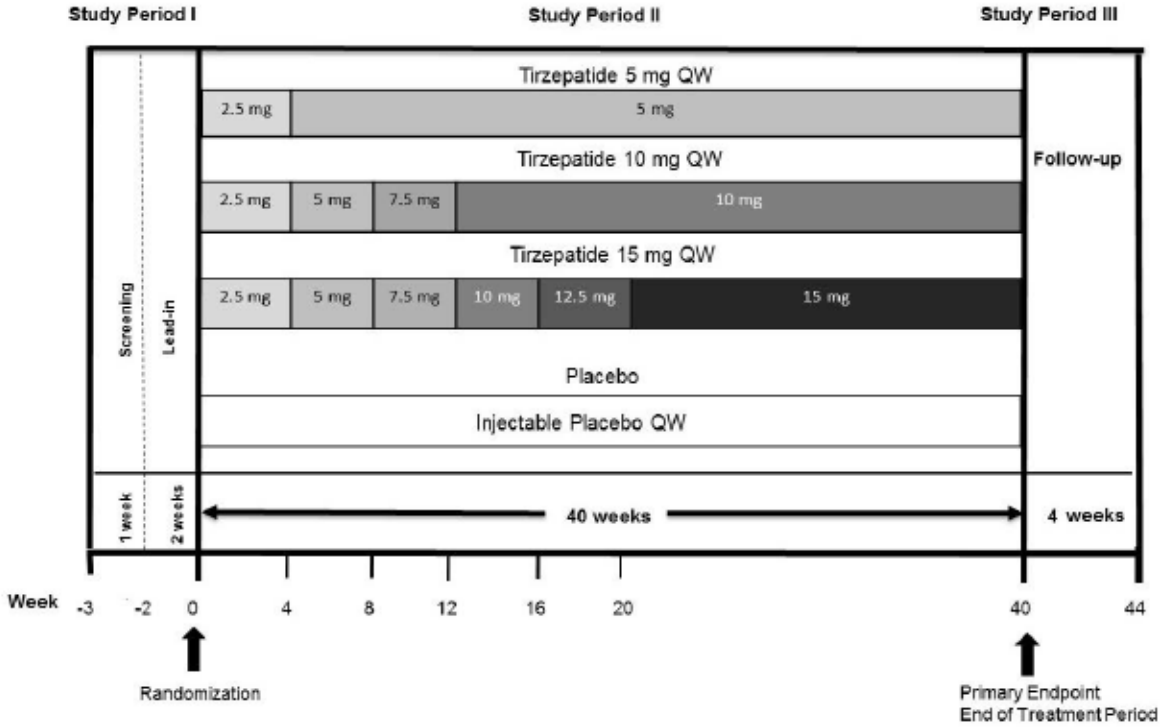
5.1. Overall Design

Study GPGK is a multicenter, randomized, double-blind, parallel, placebo-controlled, Phase 3 study with 3 study periods in patients with T2DM, naive to diabetes injectable therapy, inadequately controlled with diet and exercise alone, and have not been treated with any oral antidiabetic medication during the 3 months preceding to the start of the study.

Study GPGK will consist of 3 periods: an approximately 3-week screening/lead-in period, followed by a 40-week treatment period, and a 4-week safety follow-up period. Patients will be randomized in a 1:1:1:1 ratio (tirzepatide 5 mg QW, 10 mg QW, 15 mg QW, and injectable placebo). Patients will be stratified based on country, baseline HbA1c [≤8.5% (≤69 mmol/mol) or >8.5% (>69 mmol/mol)], and any past prior use (Yes or No) of any OAM.

Study governance considerations are described in detail in Appendix 3.

Figure GPGK.1 illustrates the study design.



Abbreviation: QW = once weekly.

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

Study Period I (screening and lead-in)

Screening (Visit 1)

The purpose of screening procedures at Visit 1 is to establish initial eligibility and to obtain blood samples for laboratory assessments needed to confirm eligibility at Visit 2. The 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)

At Visit 2, the screening laboratory results will be reviewed. 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 to ensure that patients with proliferative diabetic retinopathy, diabetic maculopathy, or nonproliferative diabetic retinopathy who require acute treatment, are identified and excluded. Additionally, at Visit 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 fasting blood glucose (FBG) 4 times a week and two 7-point SMBG profiles done on 2 nonconsecutive days in the 2-week period prior to Visit 3 (randomization), Visit 7 (Week 12), Visit 14 (Week 40), and Visit 801 (Week 44). 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 add any OAMs in order to allow reliable assessment of HbA1c at baseline (Visit 3).

Study Period II (40-week treatment period)

Randomization (Visit 3)

At Visit 3, eligible patients will perform all required baseline study procedures (including the collection of all baseline laboratory measures and electrocardiogram [ECG]) prior to randomization and prior to taking the first dose of study drug except for PK sample collection which will be collected anytime on the same day after administration at the site (see Section 2). Patient should arrive to the clinic in the fasting state; the fasting state should have lasted at least 8 hours. The questionnaires (European Quality of Life-Dimensions [EQ-5D-5L], Ability to Perform Physical Activities of Daily Living [APPADL], Impact of Weight on Self-Perception [IW-SP]) 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 the single-dose pen (SDP) and 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.

Postrandomization period (end of Visit 3 to Visit 14):

The starting dose of study drug will be 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW, for the duration of the study in the 5-mg group. For the 10-mg group, the starting dose of study drug will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study. For the 15-mg group, the starting dose of study drug will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg to 12.5 mg to 15 mg) until the 15-mg dose is reached and maintained for the duration of the study. For the placebo group, patients will inject matched QW placebo for the duration of the study.

Study Period III (safety follow-up period)

Safety follow-up (Visit 801) visits:

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 or initiate any new antihyperglycemic therapy. In the event a patient has persistent, severe hyperglycemia, defined as any FBG values within 1 week for 2 consecutive weeks is >200 mg/dL (>11.1 mmol/L) or HbA1c ≥8.5% (≥69mmol/mol), new antihyperglycemic medication can be initiated at the discretion of the investigator as described in Section 7.4.2. 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 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. Antihyperglycemic medications other than study drugs are not allowed at any time during the study except as allowed for rescue therapy, after early study drug discontinuation, or short-term insulin use. Rescue therapy with other glucose-lowering agents may be medically indicated in certain situations after randomization due to severe, persistent hyperglycemia or early discontinuation of study treatment. Metformin will be the first choice of therapy unless contraindicated. Glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and pramlintide are prohibited medications and are not

allowed as rescue therapies. Short-term insulin use for up to 14 days is allowed for certain clinical situations (for example, elective surgery, during hospitalization, hyperosmolar states). If insulin is prescribed as a rescue therapy, it must be differentiated from short-term use of insulin therapy for medical emergencies when reported in the eCRF.

Patients who develop severe, persistent hyperglycemia based on prespecified thresholds (see Sections 7.8.2.3 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.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

A total of approximately 472 patients (118 patients per treatment group) will be randomized.

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 GPGK is designed to assess the efficacy, safety, and PK of tirzepatide QW (5 mg, 10 mg, and 15 mg) as monotherapy versus placebo in patients with T2DM who have inadequate glycemic control with diet and exercise alone and have not been treated with any OAM during the 3 months preceding to the start of the study. Patients must be naïve to antihyperglycemic injectable therapy.

Placebo was chosen as the comparator to meet the FDA requirement to compare the study drug versus a placebo in at least 1 study. 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.

The parallel-group design for treatment comparison was chosen to avoid any interaction between treatments that may interfere with the interpretation of the trial outcome. To minimize the potential confounding effect of changes to concomitant medications, 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 (see Section 7.7).

5.5. Justification for Dose

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 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-week would permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns.

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

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

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, are naïve of diabetes injectable therapies, and have not used any OAM during the 3 months preceding Visit 1

Patient Characteristics

[2] Have HbA1c ≥7.0% (≥53 mmol/mol) to ≤9.5% (≤80 mmol/mol) despite diet and exercise treatment, as determined by the central laboratory at Visit 1 (Note: HbA1c value as determined by the central lab at Visit 1)

[3] Are of stable weight (±5%) during the 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) ≥23 kg/m^2 at Visit 1

[5] 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,
  - 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,

  AND

  - not be breastfeeding

[6] 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, as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug)

(c) are willing and able to inject study drugs

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

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

Informed Consent

[7] 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

[8] Have type 1 diabetes mellitus (T1DM)

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

[10] Have history of

- 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)

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

[12] 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

[13] 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)

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

[15] 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

[16] Have an estimated glomerular filtration rate <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory at Visit 1

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

[18] Have family or personal history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia type 2 (MEN2)

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

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

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

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

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

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

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

Prior/Concomitant Therapy

[26] Use of any OAM during the 3 months preceding to Visit 1

[27] Have a history of use of any injectable therapy for T2DM treatment except for the use of insulin for treatment of gestational diabetes, or short-term use (≤14 days) for acute conditions such as acute illness, hospitalization, or elective surgery

[28] 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, alli®]) within 3 months prior to Visit 1 and/or between study entry (Visit 1) and randomization (Visit 3)

[29] 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

[30] 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

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

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

Other Exclusions

[33] 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

[34] Are Lilly employees

[35] 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 [4] (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 receive tirzepatide 5 mg, 10 mg, 15 mg, or placebo. Study drug will be administered QW as SC injection in patients with T2DM who are näive to injectable therapy, inadequately controlled with diet and exercise alone, and have not been treated with any oral antidiabetic medication during the 3 months preceding to the start of the study.

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

The starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW, for the duration of the study for the 5-mg group. For the 10-mg group, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study. For the 15-mg arm, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg to 12.5 mg to 15 mg) until the 15-mg dose is reached and maintained for the duration of the study.

Patients randomized to the placebo group will inject matched placebo subcutaneously QW for the entire treatment period.

It will not be possible for investigators and patients to know which treatment they are receiving.

Table GPGK.3. Treatment Regimens

Name of Drug	Dosage	Frequency	Drug Formulation	Route of Administration
Investigational Compound				
tirzepatide	5 mg	QW	Single-dose pen	SC
	10 mg	QW	Single-dose pen	SC
	15 mg	QW	Single-dose pen	SC
Comparators				
placebo		QW	Single-dose pen	SC

Abbreviations: QW = once weekly; SC = subcutaneous.

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

- explaining the correct use of the investigational agent(s) to the patient. For SDP, a demonstration device will be used
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection

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

7.1.1. Packaging and Labelling

The sponsor will provide tirzepatide and placebo in SDPs. These will be dispensed via an interactive web-response system (IWRS). Single-dose 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 tirzepatide investigational SDP and placebo SDP.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized 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 randomized in a 1:1:1:1 ratio to receive tirzepatide 5 mg, 10 mg, 15 mg, or placebo.

7.2.1. Selection and Timing of Doses of Study Drugs

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

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. 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 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 subcutaneously in the abdomen or thigh using the injection supplies provided; a caregiver may administer the injection in the patient's upper arm. A new SDP will be used for each injection. If study drug is to always be injected in the same body region, patients should be advised to use a different injection site each week.

7.3. Blinding

This is a double-blind study. Investigators, site staff, clinical monitors, and patients will remain blinded to the treatment assignments until the study is complete.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

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

If an investigator, site personnel performing assessments, or patient is unblinded, 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. Details about dose administration of tirzepatide during the study are described in Sections 7.2.1 and 8.1.2.

7.4.2. 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 9.2.2.2.
- 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 14 [Week 40] or ET and Visit 801), only if the patient needs additional glycemic control as outlined in Section 5.1 under study Period III (safety follow-up period) discussion.

If a new antihyperglycemic medication is introduced, metformin will be the first choice of therapy unless contraindicated. Glucagon-like peptide-1 receptor agonists, DPP-4 inhibitors, and pramlintide are not allowed. Initiation of insulin as first rescue intervention for hyperglycemia should be reserved for patients with severe, persistent hyperglycemia with an average FSG ≥300 mg/dL (≥16.7 mmol/L) or in other clinical situations where the investigator believes more rapid glycemic control is warranted.

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 or administer 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 will 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 and reviewed by the investigator at each study visit.
- The patients will be instructed to return any unused study drug and/or empty cartons at the next visit to the study site for the purpose of performing drug accountability.

In the 3 tirzepatide treatment groups, as well as the placebo group, treatment compliance for each visit interval is defined as taking at least 75% of the required doses of study drug. Similarly, a patient will be considered significantly 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 treatments will be assessed at each visit based on the patient's adherence to the visit schedule, 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 complying with the protocol.

7.7. Concomitant Therapy

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.

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 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 (see Section 7.4.2). 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 randomized will not be reported to Lilly unless an SAE or AE occurs that the investigator believes may have been caused by a study procedure.

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

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 after conclusion of the study to patients.

7.8.2. 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 14; 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.

7.8.2.1. 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.

7.8.2.2. 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). If the patients fulfill the definition of increased risk of hypoglycemia, 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.

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

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

Investigators will be trained on the application of criteria for deciding when and how to intervene with patients who do not reach glycemic targets. If any of the FBG values within 1 week for 2 consecutive weeks exceed the limits outlined below and no intercurrent cause of the hyperglycemia could be identified (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), rescue medication will be prescribed as an add-on to randomized treatment. Patients will continue to follow the protocol-specified visit schedule as described in Section 7.4.2.

- >270 mg/dL (>15.0 mmol/L) from baseline to Week 6 (4 values/week)
- >240 mg/dL (>13.3 mmol/L) from Week 6 to Week 12 (4 values/week)
- >200 mg/dL (>11.1 mmol/L) from Week 12 to end of trial (4 values/week)
  OR
- HbA1c ≥8.5% (≥69 mmol/mol) by and after Week 24

7.8.2.4. 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 glucose-lowering intervention (Section 7.4.2). The new glucose-lowering intervention will be recorded on the eCRF specified for collecting antihyperglycemic 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 7.4.2) 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.

7.8.2.5. Management of Patients with Gastrointestinal Symptoms

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 intolerable 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.
- temporarily interrupt tirzepatide (omit 1 dose, the patient will take 3 of 4 doses at that dose level). After the interruption, restart at the same dose 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 drugs. De-escalation of study drugs will not be allowed. Patients who stop the study drug permanently will receive another glucose-lowering intervention (Section 7.4.2) 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 should take the above measures to keep the patient on study treatment before stopping the study drug permanently and initiate another glucose-lowering intervention.

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 7.8.2.2 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 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, 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 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, AE). 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.

- If the number of consecutive missed doses is ≤2, the treatment 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 the treatment should be restarted at 5 mg or matched placebo irrespective of the dose the patient was receiving before the interruption and subsequently escalated as required by protocol.
- 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.
- The investigator will use the IWRS to receive the appropriate study drug dispensing information to preserve blinding of the study drug

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 7.8.2.5.

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 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

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

- 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 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 not initiate any new glucose-lowering therapy. 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 Assessments

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

- Mean change in body weight
- Proportion of patients achieving a target HbA1c <7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol), and <5.7% (39 mmol/mol)
- Mean change in FSG values measured in the central laboratory
- Mean change in daily average 7-point SMBG profiles
- Proportion of patients who achieved weight loss ≥5%, ≥10%, and ≥15%

9.1.3. Exploratory Assessments and Procedures

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

- Mean change in waist circumference
- Changes from baseline in mean BMI
- Mean change in lipids (total cholesterol, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein, and triglycerides)
- Biomarkers
- APPADL scores
- EQ-5D-5L scores
- IW-SP scores

9.1.4. Body Weight, Height, Waist Circumference and Body Mass Index

Body weight and waist circumference will be measured at prespecified time points (see 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. Waist circumference should be measured at midpoint, between lower margin of least palpable rib and top of iliac crest (approximately 1 inch (2.54 cm) above the navel), (Appendix 7).

Body mass index will be computed from the patient's weight and height. Body mass index 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 and 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.

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 Event 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 2017, ADA 2018):

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 7.8.2.2 for guidance on management of increased hypoglycemia risks.

9.2.2.2. Severe, Persistent Hyperglycemia

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

Investigators will be trained on the application of criteria for deciding when and how to intervene with 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 7.8.2.3.

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 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/AE form. For detailed information concerning the management of GI AEs, please refer to Section 7.8.2.5.

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 2017). 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, to 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.

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).

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

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via 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 10.3.6.

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 the 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 discontinued from treatment due to a hepatic event or abnormality of liver tests

- Hepatic event considered to be an SAE

9.5. Pharmacokinetics

Pharmacokinetic samples will be collected from all patients. Plasma tirzepatide concentrations will be determined from blood samples obtained from patients receiving tirzepatide treatment. Blood samples for PK assessment will be collected at Week 0, 7, 15, 23, and 40 of study drug treatment per the Study Schedule or at ET (see Section 2).

All patients will have a single PK sample collected following the first dose at Week 0. This PK sample can be collected any time after this first dose on the day of drug administration. Additionally, each patient will be assigned via IWRS to one of the sampling PK time windows of 1 to 24 hours, 24 to 96 hours, or 120 to 168 hours post dose at Weeks 7, 15, and 23 of study drug treatment per the Study Schedule or at ET (see Section 2). The PK sample after the last dose of study drug administered at Week 39 will be collected at Visit 14 (Week 40).

The date and time of the most recent SC injection administered prior to collecting the sample must be recorded on the eCRF from the study diaries. The actual date and time at which each sample was drawn must be recorded on the laboratory requisition form. Instructions for the collection and handling of blood samples will be provided by the sponsor.

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 following last patient visit for the study.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel (until the study has been unblinded).

9.6. Pharmacodynamics

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

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 whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

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

9.9.2. 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.

9.9.3. 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 120 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).

10. Statistical Considerations

10.1. Sample Size Determination

Patients will be randomized in a 1:1:1:1 ratio to tirzepatide 5 mg, 10 mg, 15 mg, or placebo.

The trial is powered to assess superiority of tirzepatide 5 mg, 10 mg, or 15 mg versus placebo in parallel relative to mean change from baseline in HbA1c at 40 weeks under the following assumptions:

- use of 2-sample t-test to compare treatment means utilizing HbA1c data collected before initiation of any rescue medication and premature treatment discontinuation;
- up to 25% patients in tirzepatide arms and up to 35% patients in placebo arm initiating any rescue medication or premature treatment discontinuation;
- at least 0.65% (placebo adjusted) mean reduction in HbA1c for the tirzepatide doses; and
- a common standard deviation (SD) of 1.1%.

On the basis of these assumptions, randomizing 472 patients using a 1:1:1:1 randomization ratio to tirzepatide 5 mg (118 patients), tirzepatide 10 mg (118 patients), tirzepatide 15 mg (118 patients), and placebo (118 patients) will provide at least 90% power to establish superiority for a tirzepatide dose compared to placebo at a 2-sided significance level of 0.017. Furthermore, this sample size will ensure at least 90% power for the HbA1c superiority evaluation utilizing all available HbA1c data at 40 weeks with missing data imputed with a conservative multiple imputation method (as described in the Efficacy Analyses [Section 10.3.3] below), provided that the mean reduction in HbA1c for the tirzepatide doses is at least 0.65% (placebo adjusted) and SD increases to no more than 1.3% due to the inclusion of data on rescue medications, inclusion of data after premature treatment discontinuation, and missing data imputation.

10.2. Populations for Analyses

For purposes of analysis, the following analysis sets are defined in Table GPGK.4.

Table GPGK.4. Description of Analysis Population and Data Sets

Analysis Set	Description
Screened patients	All participants who sign informed consent
Randomized patients	All patients who are randomly assigned a treatment arm
modified intent-to-treat (mITT) population	All randomly assigned participants who are exposed to at least 1 dose of study drug. In the event of a treatment error, participants will be analyzed according to the treatment they were randomized.
Efficacy analysis set (EAS)	Data obtained during Study Period II from the mITT population, excluding 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 will be calculated at 95%, 2-sided. In statistical summaries and analyses, patients will be analyzed as randomized.

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

The primary efficacy assessment, 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. As they are intended for different purposes, no multiplicity adjustments will be made for conducting 2 primary efficacy assessments relative to efficacy and treatment-regimen estimands.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses with placebo irrespective of adherence to study drug or initiation of antihyperglycemic rescue therapy. Thus, 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 model for repeated measures (MMRM) with terms:

- treatment,
- visit,
- treatment-by-visit interaction,
- country,
- any past prior use (yes or no) of any oral antidiabetic medication,
- baseline HbA1c category [≤8.5% (≤69 mmol/mol) 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, randomized, and receiving at least 1 dose of study drug will be presented by treatment groups. A listing of randomized 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 time to initiation of rescue therapy for severe, persistent hyperglycemia will be analyzed and 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. Frequency counts and percentages of patients compliant to study drug will be summarized by treatment arms 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 superiority of tirzepatide 5 mg, and/or 10 mg, and/or 15 mg to placebo 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. This assessment will analyze change in HbA1c values from baseline obtained at the 40-week visit using analysis of covariance with terms:

- treatment,
- country,
- any past prior use (yes or no) of any oral antidiabetic medication, and
- baseline HbA1c as a covariate.

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

For the Pharmaceuticals and Medical Devices Agency (PMDA), the primary efficacy assessment will be guided by the "efficacy" estimand, with controlling overall family-wise type 1 error rate at a 2-sided alpha of 0.05 only for primary endpoint evaluation that tirzepatide QW is superior to placebo in HbA1c change from baseline to 40 weeks. Additional details will be provided in the SAP.

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 EAS. The primary analysis model for HbA1c measurements over time will be a 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, and treatment-by-visit interaction, country, any past prior use (yes or no) of any oral antidiabetic medication 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 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:

- Superiority of tirzepatide dose(s) to placebo relative to mean change in body weight from baseline to the 40-week visit
- Superiority of tirzepatide dose(s) to placebo relative to proportion of patients achieving the target value of HbA1c <7% (<53 mmol/mol) at the 40-week visit
- Superiority of tirzepatide dose(s) to placebo relative to mean change in FSG (central laboratory) at the 40-week visit
- Superiority of tirzepatide dose(s) to placebo relative to proportion of patients achieving the target value of HbA1c <5.7% (<39 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 I error-controlled secondary efficacy analyses will be conducted relative to both estimands, the "efficacy" estimand and the "treatment-regimen" estimand separately.

Analysis of change from baseline in body weight and FSG at the 40-week visit will be conducted in a manner similar to the primary efficacy analyses with baseline HbA1C category [≤8.5% (≤69 mmol/mol) or >8.5% (>69 mmol/mol)] added in the model, and baseline of the corresponding variable as a covariate. The MMRM analyses were 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) and <5.7% (<39 mmol/mol) at the 40-week visit will be conducted using a logistic regression analysis with terms: 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 placebo irrespective of adherence to study drug or initiation of rescue therapy. Thus, safety analyses will be conducted using the SS. Selected safety analyses may be conducted after excluding data on rescue therapy or data after starting another antihyperglycemic medication.

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized MedDRA Queries. Summary statistics will be provided for incidence of TEAEs, SAEs, study discontinuation due to AEs, study drug discontinuation due to AEs, deaths, and other CV endpoints. Counts and proportions of 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 placebo. 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 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 by using Fisher's exact test. A TE abnormal value is defined as a change from normal value at baseline to a value greater than the

high limit at any time during 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. Pharmacokinetic/Pharmacodynamic Analyses

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

10.3.6. 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). 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.

10.3.7. Other Analyses

10.3.7.1. Health Economics

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

10.3.7.2. Subgroup Analyses

Subgroup analyses of mean change in HbA1c values from baseline to Visit 14 will be provided by

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

10.3.8. Interim Analyses

No interim analyses of efficacy 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 (only for unplanned efficacy review).

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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/masking	A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BMI	body mass index
CEC	clinical endpoint committee
CHF	congestive heart failure
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
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-Dimensions
ERB	ethical review board
ET	early termination
FBG	fasting blood glucose
FSG	fasting serum glucose
FSH	follicle-stimulating hormone
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
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.

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 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
SDP	single-dose pen
SMBG	self-monitoring of 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

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

Urinalysis
Albumin
Creatinine

HbA1c

Endocrine
Fasting plasma glucagon
Fasting serum Insulin
Calcitonin
Fasting C-peptide

Immunogenicity
Tirzepatide anti-drug antibody
PK sample for immunogenicity

Nonpharmacogenetic Stored Samples
EDTA plasma
Serum
P800 plasma

Pharmacogenetic Stored Samples

Samples for Pharmacokinetic Analysis

Clinical Chemistry
Serum Concentrations of
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[b]

Pregnancy Test (females only)[c]
Follicle-stimulating hormone (FSH)[d]
Estradiol[c]

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

Pancreas (exocrine)
Serum pancreatic amylase
Serum 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; 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] Glucose as part of the chemistry panel at Visit 1 can be collected irrespective of the fasting status of the patient.

[c] 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 7, 12, and 14. 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

[d] Follicle-stimulating hormone 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).

[e] 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 I8R-MC-GPGK 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 GPGK 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 2008) (Available at: http://www.who.int/chp/steps/Part3_Section3.pdf) Accessed November 05, 2018.

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 (approximately 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 14) 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 14, minimize missing data, and preserve the intended conduct of the study, the visit window for Visit 14 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 14.
2) For patients requiring an extension for Visit 14 up to Week 44, additional IP 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 IP 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.

Appendix 9. Protocol Amendment I8F-MC-GPGK(b) A Randomized, Double-blind, Placebo Controlled Trial Comparing the Efficacy and Safety of Three Tirzepatide Doses versus Placebo in Patients with Type 2 Diabetes, Inadequately Controlled with Diet and Exercise Alone (SURPASS-1)

Overview

Protocol I8F-MC-GPGK titled "A Randomized, Double-blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Three Tirzepatide Doses versus Placebo in Patients with Type 2 Diabetes, Inadequately Controlled with Diet and Exercise Alone (SURPASS-1)" 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-GPGK Amendment (b)

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities	Added language to direct readers to Appendix 8 in case of patients whose participation in this study is affected by restrictions due to the COVID-19 pandemic.	This enables patients and investigators to adjust the Visit 14 window and to ensure patient safety and trial integrity.
Appendix 8. Changes to Study Procedures due to the COVID-19 Pandemic	An appendix was added to provide guidance for Visit 14 on: 1) Adjusting the Visit 14 window to be brought forward no sooner than 14 days (Week 38) or extended up to 28 days (Week 44), 2) Additional IP dispensed for Visit 14, and 3) Consent from the patients for the additional IP needed for Visit 14.	This enables patients and investigators to adjust the timing of Visit 14 (primary endpoint) and to ensure patient safety and trial integrity.

Leo Document ID = 8833f24f-6da0-48ff-bc64-cc8d12cc1bb3

Approver: PPD

Approval Date & Time: 15-Apr-2020 20:16:00 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 15-Apr-2020 22:04:01 GMT

Signature meaning: Approved