Protocol I8F-MC-GPGI(b)

A Randomized, Phase 3, Double-blind Trial Comparing the Effect of the Addition of Tirzepatide Versus Placebo in Patients With Type 2 Diabetes Inadequately Controlled on Insulin Glargine With or Without Metformin

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Approval Date: 26-Jun-2020

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2019-000860-99

Confidential Information

Tirzepatide (LY3298176)

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1. Synopsis

Title of Study:
A Randomized, Phase 3, Double-blind Trial Comparing the Effect of the Addition of Tirzepatide versus Placebo in Patients with Type 2 Diabetes Inadequately Controlled on Insulin Glargine with or without Metformin (SURPASS-5).

Rationale:
Current incretin-based injectable treatment options for type 2 diabetes mellitus (T2DM) are directed at a single incretin molecular target (GLP-1 [glucagon-like peptide-1]) and therefore, could have therapeutic limitations. These treatment options offer improved glycemic control and a low risk of hypoglycemia, and have a potential for clinically relevant weight loss. However, a large proportion of patients still do not reach the treatment targets despite a high level of compliance with the treatment regimens. Therefore, it is important to provide additional treatment options for patients that allow for enhanced glucose control and weight loss while preserving an overall acceptable benefit/risk profile (Stark Casagrande 2013; Zaccardi et al. 2016).

Tirzepatide (LY3298176) is a once-weekly dual GIP (glucose-dependent insulinotropic polypeptide)/GLP-1 receptor agonist. It is a 39-amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety that CCI [redacted] It is administered subcutaneously.

Study I8F-MC-GPGI (GPGI) will compare tirzepatide (3 doses) to placebo, added to titrated once-daily basal insulin glargine in patients with T2DM previously treated with insulin glargine (with or without metformin). There are no available published reports on the effects of the combination of basal insulin and a long-acting, once-weekly (QW) dual GIP/GLP-1 receptor agonist on blood glucose (BG) to date. The combination of insulin glargine with tirzepatide is expected to provide improved glucose control and attenuate the weight gain and hypoglycemia risk associated with the more intensive titration and higher daily doses of insulin glargine.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To demonstrate superiority of QW tirzepatide 10 mg and/or 15 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, with respect to glycemic control at 40 weeks for:	• Mean change in HbA1c from baseline
Key Secondary (controlled for type 1 error) <u>Efficacy</u> • To demonstrate superiority of QW tirzepatide 5 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, with respect to glycemic control at 40 weeks for: • To demonstrate superiority of QW tirzepatide 5 mg, 10 mg, and/or 15 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, at 40 weeks for:	• Mean change in HbA1c from baseline • Mean change in body weight from baseline • Proportion of patients with HbA1c target values of <7.0% (53 mmol/mol) • Mean change in fasting serum glucose (central laboratory) from baseline
Additional Secondary (not controlled for type 1 error) <u>Efficacy</u> • To compare QW tirzepatide 5 mg, 10 mg, and 15 mg to placebo at 40 weeks for:	• Proportion of patients achieving HbA1c target ≤6.5% (48 mmol/mol), <5.7% (39 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% from baseline • Change from baseline in daily mean insulin glargine dose

Objectives	Endpoints
Safety • To compare QW tirzepatide 5 mg, 10 mg, and 15 mg to placebo to the end of safety follow-up 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 antidrug antibodies to tirzepatide • Mean change in systolic and diastolic blood pressure and heart rate from baseline • Occurrence of hypoglycemic episodes • Incidence of initiation of rescue therapy for severe, persistent hyperglycemia
Pharmacokinetics • To characterize the pharmacokinetics (PK) of QW tirzepatide 5 mg, 10 mg, and 15 mg and the relationships between tirzepatide exposure and safety, tolerability, and efficacy measures for:	• Population PK and pharmacodynamic parameters

Abbreviations: HbA1c = hemoglobin A1c; QW = once weekly.

Summary of Study Design:

Study GPGI is a multicenter, randomized, double-blind, parallel, multinational, placebo-controlled Phase 3 study which will assess the safety and efficacy of the addition of 5 mg, 10 mg, or 15 mg tirzepatide or placebo for change from baseline in hemoglobin A1c (HbA1c) in patients with T2DM receiving titrated basal insulin glargine (with or without metformin) over a 40-week treatment. Approximately, 472 patients with T2DM who have been treated with insulin glargine (U100), once daily with or without metformin ≥3 months prior to Visit 1, will be randomized.

Treatment Arms and Duration:

Study GPGI 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, tirzepatide 10 mg, tirzepatide 15 mg, and placebo). Patients will be stratified based on country, baseline HbA1c (≤8.0% or >8.0% [≤64, >64 mmol/mol]), and baseline metformin use (Yes or No).

Number of Patients:

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

Statistical Analysis:

Sample Size:

The trial is powered to evaluate superiority of tirzepatide 10 mg and tirzepatide 15 mg versus placebo in parallel relative to the primary endpoint (mean change from baseline in HbA1c at 40 weeks) under the following assumptions:

- use of 2-sample t-test to make statistical comparisons among treatment means,
- use of HbA1c data collected before initiation of any rescue medication or premature treatment discontinuation,
- no more than 28% patients in tirzepatide groups and placebo initiating any rescue medication or prematurely discontinue study drug,
- at least 0.60% (placebo adjusted) mean reduction in HbA1c from baseline to 40 weeks for the tirzepatide doses, and
- a common standard deviation (SD) of 1.1%.

Based on these assumptions, randomizing approximately 472 subjects using a 1:1:1:1 randomization ratio to 5 mg tirzepatide, 10 mg tirzepatide, 15 mg tirzepatide, and placebo is required to ensure at least 90% power to establish superiority of tirzepatide 10 mg and/or 15 mg doses versus placebo, each evaluated at a 2-sided significance level of 0.025. Furthermore, this sample size will ensure 90% power to establish superiority using an analysis of covariance (ANCOVA) utilizing all available HbA1c data at 40 weeks, irrespective of adherence to study drug or initiation of rescue therapy, and with missing data imputed with a conservative multiple

imputation method (as described in the Efficacy Analyses section below). It is assumed that efficacy (placebo adjusted) remains unchanged 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 imputation of missing data.

Efficacy:

Efficacy and safety will be assessed using the modified intention-to-treat population, which consists of all randomly assigned participants who are exposed to at least one dose of study drug. There will be 2 estimands of interest in comparing efficacy of tirzepatide doses with placebo relative to the primary measure of mean change in HbA1c 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, the primary efficacy assessment will be guided by the "treatment-regimen" estimand. This assessment will analyze change from baseline in HbA1c to 40-week visit using an ANCOVA with terms, treatment, country, metformin use (Yes or No), and baseline HbA1c as a covariate. The ANCOVA analysis will be conducted using 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 subjects with missing values will be imputed based on observed data in the same treatment arm from subjects 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 will be guided by the "efficacy" estimand. This assessment 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 from baseline in HbA1c assessed over time will be a mixed model for repeated measures (MMRM), with terms treatment, visit, treatment-by-visit interaction, country, metformin use (Yes or No), and baseline HbA1c as a covariate. An unstructured covariance matrix will model relationship of within-patient errors.

Since they are intended for different purposes, each of the 2 primary efficacy assessments 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:

Safety assessment will be based on all available data, irrespective of whether they were obtained while the participants had discontinued the study drug or whether the participant had been given 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 subjects 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 GPGI. 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 GPGI.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**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**15**	**16**	**20**	**23**	**24**	**32**	**39**	**40**		**4 weeks post end of Tx**
Allowable Deviation (days)[c]	-	±3	±7	±3	±3	±3	±3	±3	±3	-	±3	±3	±3	±3	-	±3	±3	-	±3	±7	-	±7		±7
Fasting Visit[d]			X		X		X				X		X			X	X		X			X	X	X
PK only Visit										X					X			X			X			
Telephone Visit						X		X				X		X										
Informed consent	X																							
Randomization			X																					
Clinical Assessments																								
Medical history[e]	X																							
Physical Examination	X																					X	X	
Height	X																							
Weight	X		X				X				X		X			X	X		X	X		X	X	X
Waist circumference			X				X				X		X			X	X		X	X		X	X	
Electrocardiogram[f]			X																			X	X	X
Vital signs (2 sitting BP and HR)[g]	X		X	X	X		X		X	X	X		X		X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundoscopic examination[h]		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**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**15**	**16**	**20**	**23**	**24**	**32**	**39**	**40**		**4 weeks post end of Tx**
Allowable Deviation (days)[c]	-	±3	±7	±3	±3	±3	±3	±3	±3	-	±3	±3	±3	±3	-	±3	±3	-	±3	±7	-	±7		±7
Fasting Visit[d]			X		X		X				X		X			X	X		X			X	X	X
PK only Visit										X					X			X			X			
Telephone Visit						X		X				X		X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review hypoglycemic events collected in the diary			X	X	X	X	X	X	X		X	X	X	X		X	X		X	X		X	X	X
Patient Education																								
Diabetes education[i,j]		X																						
BG meter, SMBG training[j]		X																						
Dispense BG meter/supplies, as needed		X	X	X	X		X		X		X		X			X	X		X	X				
Study drug injection training[j]			X																					
Hand out diary, instruct in use[j]		X	X				X										X					X		
Remind patients about 7-point SMBG[k]		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**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**15**	**16**	**20**	**23**	**24**	**32**	**39**	**40**		**4 weeks post end of Tx**
Allowable Deviation (days)[c]	-	±3	±7	±3	±3	±3	±3	±3	±3	-	±3	±3	±3	±3	-	±3	±3	-	±3	±7	-	±7		±7
Fasting Visit[d]			X		X		X				X		X			X	X		X			X	X	X
PK only Visit										X					X			X			X			
Telephone Visit						X		X				X		X										
Review 7-point SMBG values collected in the diary			X																			X		
Dispense study drug			X	X	X		X		X		X		X			X	X		X	X				
Observe patient administer study drug[l]			X																					
Patient returns study drugs and injection supplies				X	X		X		X		X		X			X	X		X	X		X	X	
Assess study drug compliance				X	X	X	X	X	X		X	X	X	X		X	X		X	X		X	X	
Review insulin dose and adjustment per TTT algorithm			X	X	X	X	X	X	X		X	X	X	X		X	X		X	X				
Assess compliance with insulin dose adjustment TTT algorithm[m]				X	X		X		X		X		X			X	X		X	X		X	X	
Laboratory Tests																								
Serum pregnancy test[n]	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**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**15**	**16**	**20**	**23**	**24**	**32**	**39**	**40**		**4 weeks post end of Tx**
Allowable Deviation (days)[c]	-	±3	±7	±3	±3	±3	±3	±3	±3	-	±3	±3	±3	±3	-	±3	±3	-	±3	±7	-	±7		±7
Fasting Visit[d]			X		X		X				X		X			X	X		X			X	X	X
PK only Visit										X					X			X			X			
Telephone Visit						X		X				X		X										
Urine pregnancy test[o]			X										X						X			X		
Follicle-stimulating hormone test/Estradiol[p]	X																							
Chemistry panel	X[q]												X						X			X	X	X
Fasting serum glucose (central laboratory)			X		X		X				X		X			X	X		X			X	X	X
Lipid panel			X																			X	X	X
Urinary albumin/creatinine ratio	X[q]																					X	X	X
Serum creatinine, eGFR (CKD-EPI)[r]	X[q]												X						X			X	X	X
Calcitonin	X[q]												X						X			X	X	X
Hematology	X[q]												X						X			X	X	X
HbA1c	X		X				X				X		X			X	X		X			X	X	X
Pancreatic amylase, lipase	X[q]												X						X			X	X	X
Immunogenicity[s]			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	15	16	17	18	19	20	21	22	ET[b]	801
Week of Treatment	-3	-2	0	1	2	3	4	5	6	7	8	10	12	14	15	16	20	23	24	32	39	40		4 weeks post end of Tx
Allowable Deviation (days)[c]	-	±3	±7	±3	±3	±3	±3	±3	±3	-	±3	±3	±3	±3	-	±3	±3	-	±3	±7	-	±7		±7
Fasting Visit[d]			X		X		X				X		X			X	X		X			X	X	X
PK only Visit										X					X			X			X			
Telephone Visit						X		X				X		X										
PK sample for Immunogenicity[f]			X				X						X						X			X	X	X
Anti-GAD antibody			X																					
Tirzepatide PK[a]										X					X			X			X		X	
Stored samples																								
Pharmacogenetic stored sample			X																					
Nonpharmacogenetic stored sample			X										X						X			X	X	
Patient Reported Outcomes-to be completed by patient at site[y]																								
APPADL			X																			X	X	
IW-SP			X																			X	X	
DTSQs			X																					
DTSQc																						X	X	
EQ-5D-5L			X																			X	X	

Abbreviations: ADA = antidrug antibodies; APPADL = Ability to Perform Physical Activities of Daily Living; BG = blood glucose; BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; DTSQc = Diabetes Treatment Satisfaction Questionnaire change; DTSQs = Diabetes Treatment Satisfaction Questionnaire status; ECG = electrocardiogram; eCRF =electronic case report form; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Qualtiy of Life- 5 dimensions-5 levels; ET = early termination; F/U = follow-up; GAD = glutamic acid decarboxylase; HbA1c = hemoglobin A1c; HR = heart rate; IW-SP = Impact of Weight on Self-Perception; PK = pharmacokinetics; PRO = patient-reported outcome;; SMBG = self-monitored blood glucose; TTT = treat to target; 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, 5, 7, 11, 13, 16, 17, 19, 22, ET, and at follow-up, patients should be reminded to report to the site in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or any significant physical activity and before taking study drug(s), insulin glargine and metformin (if used).

[e] 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).

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

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

[h] Dilated fundoscopic exam 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 diabetic retinopathy and/or diabetic maculopathy (macular edema), or nonproliferative diabetic retinopathy that requires acute treatment. The results from this exam will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy. Follow up dilated fundoscopic exam should be performed when clinically indicated, and, the results recorded on the retinopathy eCRF.

[i] Includes counseling on diet and exercise, management of hypoglycemia, etc.

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

[k] 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 7-point SMBG is not performed, then data from the most recent nonconsecutive 4-point SMBG profiles can be used. If more than two 7-point SMBG profiles are available, the two most recent nonconsecutive profiles should be used. Patients will be required to collect a daily fasting BG and a 4-point SMBG once weekly between Visit 2 and 3, twice weekly from Visits 3-7 (Weeks 0-4) followed by weekly for the remainder of the study.

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

[m] Assessment of the patient's compliance to the TTT algorithm will be collected in the eCRF at Visits 7, 9, 11, 13, 16, 19, and 22 for the period since the previous clinic visit.

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

[o] A 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 13, 19, and 22. Pregnancy tests may be also 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.

[p] 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).

[q] Screening visit assessment will serve as baseline.

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

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

[t] Pharmacokinetic samples for immunogenicity must be taken prior to drug administration.

[u] Pharmacokinetic samples will be collected for all patients at these visits at time windows of 1 to 24 hours, 24 to 96 hours, OR 120 to 168 hours post dose, as assigned by IWRS for each PK sample. Dependent on the time-windows to which a patient gets assigned, they may be required to come to site for PK-specific visits.

[v] 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

Current incretin-based injectable treatment options for type 2 diabetes mellitus (T2DM) are directed at a single incretin molecular target (GLP-1 [glucagon-like peptide-1]) and therefore could have therapeutic limitations. These treatment options offer improved glycemic control and a low risk of hypoglycemia, and have a potential for clinically relevant weight loss. However, a large proportion of patients still do not reach the treatment targets despite a high level of compliance with the treatment regimens. Therefore, it is important to provide additional treatment options for patients that allow for enhanced glucose control and weight loss while preserving an overall acceptable benefit/risk profile (Stark Casagrande et al. 2013; Zaccardi et al. 2016).

Tirzepatide (LY3298176) is a once-weekly dual GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 receptor agonist. It is a 39-amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety that CCI It is administered subcutaneously.

Study I8F-MC-GPGI (GPGI) will compare tirzepatide (3 doses) to placebo, added to titrated once-daily basal insulin glargine in patients with T2DM previously treated with basal insulin (with or without metformin). Despite an inadequate glycemic control, insulin therapy is often not intensified in these patients, for multiple reasons, such as concern for hypoglycemia or weight gain (Khunti et al. 2016). Several studies have assessed the efficacy and safety of the addition of a once-weekly GLP-1 receptor agonist to basal insulin in this type of patients (Pozzilli et al. 2017; Guja et al. 2018; Rodbard et al. 2018). However, there is no available evidence on the effects of the combination of basal insulin and a long-acting, once-weekly dual GIP/GLP-1 receptor agonist on blood glucose (BG) to date. The combination of insulin glargine with tirzepatide is expected to provide improved glucose control and attenuate the weight gain and hypoglycemia risk associated with the more intensive titration and higher daily doses of insulin glargine.

3.2. Background

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

Phase 1 Study GPGA was a combination of single ascending dose and multiple ascending dose study in 89 healthy subjects and a multiple dose proof-of-concept study in 53 patients with T2DM. Study GPGA investigated safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of tirzepatide administered as subcutaneous (SC) injections. The

results of this study supported further development of tirzepatide for once weekly (QW) dosing in patients with T2DM (Coskun et al. 2018).

Study GPGC was a Phase 1, multiple ascending dose study conducted in 48 Japanese patients with T2DM. Safety, tolerability, and PK/PD profiles of tirzepatide appeared comparable to previous studies in non-Japanese patients with T2DM, all of which supports the development of QW tirzepatide in this population.

A 26-week Phase 2 study (GPGB) assessed the efficacy, tolerability, and safety of QW administration of 4 doses (1 mg/5 mg/10 mg and 15 mg) of tirzepatide versus placebo and an active comparator (dulaglutide 1.5 mg QW) in 318 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, 10, 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 gastrointestinal (GI)-related, consisting mainly of nausea, vomiting, and diarrhea and were dose-dependent. The GI AEs were usually mild to moderate in intensity. Serious AEs (SAEs) were balanced across the treatment groups and none of the groups 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 clinical studies. This was a 12-week, placebo-controlled study to assess the efficacy and safety of 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).

In addition, detailed information about the known and expected benefits and risks of insulin glargine may be found in the marketed insulin glargine package insert.

4. Objectives and Endpoints

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

Table GPGI.2. Objectives and Endpoints

Objectives	Endpoints
Primary • To demonstrate superiority of QW tirzepatide 10 mg and/or 15 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, with respect to glycemic control at 40 weeks for:	• Mean change in HbA1c from baseline
Key Secondary (controlled for type 1 error) Efficacy • To demonstrate superiority of QW tirzepatide 5 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, with respect to glycemic control at 40 weeks for: • To demonstrate superiority of QW tirzepatide 5 mg, 10 mg, and/or 15 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, at 40 weeks for:	• Mean change in HbA1c from baseline • Mean change in body weight from baseline • Proportion of patients with HbA1c target values of <7.0% (53 mmol/mol) • Mean change in fasting serum glucose (central laboratory) from baseline
Additional Secondary (not controlled for type 1 error) Efficacy • To compare QW tirzepatide 5 mg, 10 mg, and 15 mg to placebo at 40 weeks for:	• Proportion of patients achieving HbA1c target ≤6.5% (48 mmol/mol), <5.7% (39 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% from baseline • Change from baseline in daily mean insulin glargine dose
Safety • To compare QW tirzepatide 5 mg, 10 mg, and 15 mg to placebo to the end of safety follow-up 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

Objectives	Endpoints
	• Incidence of treatment-emergent antidrug antibodies to tirzepatide • Mean change in systolic and diastolic blood pressure and heart rate from baseline • Occurrence of hypoglycemic episodes • Incidence of initiation of rescue therapy for severe, persistent hyperglycemia
Pharmacokinetics • To characterize the pharmacokinetics (PK) of QW tirzepatide 5 mg, 10 mg, and 15 mg doses and the relationships between tirzepatide exposure and safety, tolerability, and efficacy measures for:	• Population PK and PD parameters
Tertiary/Exploratory • To compare QW tirzepatide 5 mg, 10 mg, and 15 mg to placebo at 40 weeks for:	• 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 Impact of Weight on Self-Perception o Diabetes Treatment Satisfaction Questionnaire status/ Diabetes Treatment Satisfaction Questionnaire change o European Quality of Life-5 Dimensions-5 level

Abbreviations: HbA1c = hemoglobin A1c; HDL= high-density lipoprotein; LDL = low-density lipoprotein; PD = pharmacodynamics; PK=pharmacokinetics; QW = once weekly; TG = triglycerides; VLDL = very low-density lipoprotein.

5. Study Design

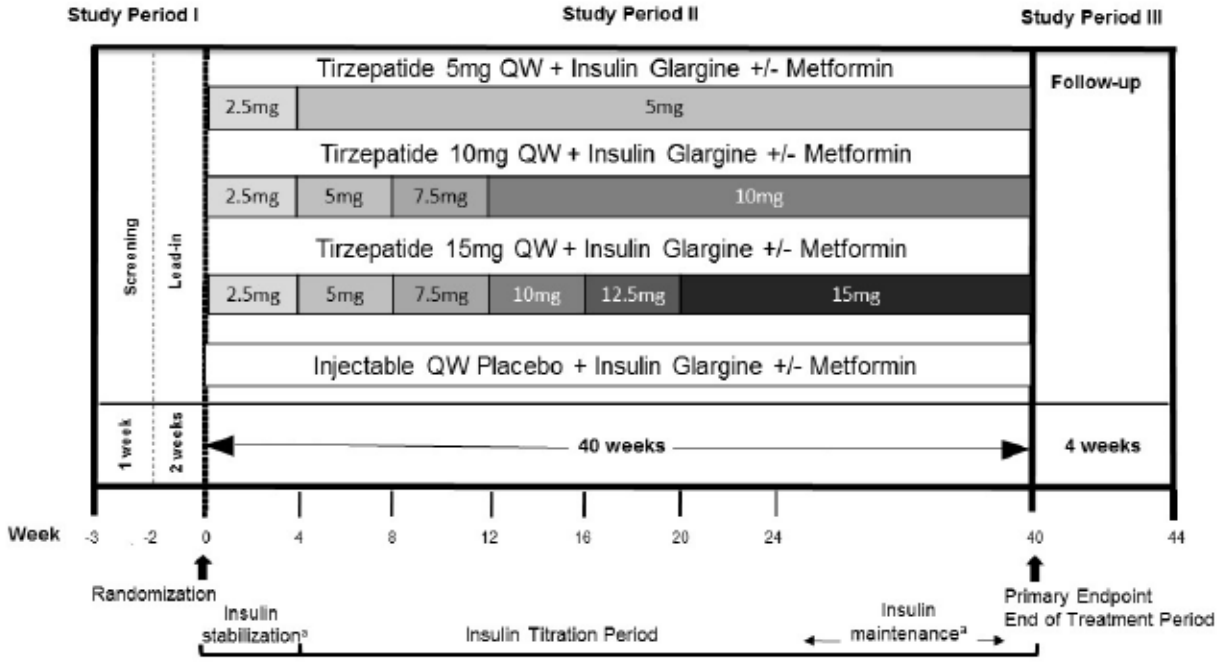
5.1. Overall Design

Study GPGI is a multicenter, randomized, double-blind, parallel, multinational, placebo-controlled Phase 3 study which will assess the safety and efficacy of the addition of 5 mg, 10 mg, or 15 mg tirzepatide, or placebo for change from baseline in HbA1c in patients with T2DM receiving titrated basal insulin glargine (with or without metformin) over a 40-week treatment. Approximately, 472 patients with T2DM who have been treated with insulin glargine (U100), once daily with or without metformin ≥3 months prior to Visit 1, will be randomized (see Section 2).

Study GPGI 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, tirzepatide 10 mg, tirzepatide 15 mg, and placebo). Patients will be stratified based on country, baseline HbA1c (≤8.0% or >8.0% [≤64, >64 mmol/mol]), and baseline metformin use (Yes or No).

Study governance considerations are described in detail in Appendix 3.

Figure GPGI.1 illustrates the study design.



[a] Stabilization Period = first 4 weeks after randomization, with restricted insulin dose adjustments. Insulin Glargine Titration Period Weeks 4 to 40 (end of treatment/end of study), with unrestricted insulin dose adjustments. Maintenance Period = Weeks 24 to 40 (end of treatment/end of study), the period when insulin glargine dose is expected to be stable.

Figure GPGI.1. Illustration of study design for Clinical Protocol I8R-MC-GPGI.

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 Study Schedule of Activities, Section 2.
- Patients who meet all applicable inclusion criteria and none of the applicable exclusion criteria (Section 6) at Visit 1 will continue on their prestudy therapy doses between Visits 1 and 2.

Lead-in (Visit 2 to Visit 3)

At Visit 2:

- 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 not enrolled.
- 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 provided diaries and will be trained as appropriate to record;
    - BG values,
    - hypoglycemic events,
    - insulin dose assessments using the treat to target (TTT) algorithm,
    - medications, and
    - adverse events.
- Patients will be trained on disease management and study procedures; this training can be repeated at subsequent visits as deemed appropriate.
- Patients will be trained (if needed) to follow instructions for use of the insulin glargine prefilled pen that they are using.

After Visit 2:

- Patients will start insulin dose assessments once weekly for the remainder of the lead-in period (the use of the algorithm is restricted during the lead-in and stabilization periods, as described below).
- Patients will be requested to perform 4-point SMBG profiles at least once weekly, starting at Visit 2.
- Patients will need to perform two 7-point SMBG profiles done on 2 nonconsecutive days in the 2-week period prior to Visit 3 (randomization) and Visit 22 (Week 40).
- During the lead-in period, patients should continue their prestudy therapy and should not change the dose, in order to allow reliable assessment of HbA1c at baseline (Visit 3).
- Insulin doses should be adjusted only for the safety of the study participants (occurrence of hypoglycemia due to inadequate insulin dose or severe hyperglycemia, defined as mean daily BG from 4-point SMBG profile >270 mg/dL [>15 mmol/L]. In these situations, the patient should contact the site in order to adjust the dose per the TTT algorithm (see Section 7.2, Table GPGI.2).
- Patients who are taking concomitant metformin and develop any condition that is a contraindication for its use will be considered ineligible and will be discontinued from the trial before randomization.

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 ECG) prior to randomization and prior to taking the first dose of study drug.
- Patients should arrive to the clinic in the fasting state; the fasting state should have lasted at least 8 hours without having taken any doses of study drug, insulin glargine and metformin (if used).
- Responsible study-site personnel will review the diary and assess the need to adjust the insulin glargine dose per the TTT algorithm criteria (Table GPGI.3). Only patients who require further insulin glargine dose increase, as indicated by FBG above the target concentration per the TTT algorithm (see Section 7.1) during the week prior to the visit, will be eligible for further participation in the study.
- The questionnaires (European Quality of Life [EQ-5D-5L], Ability to Perform Physical Activities of Daily Living [APPADL], Impact of Weight on Self-Perception [IW-SP], and Diabetes Treatment Satisfaction Questionnaire status [DTSQs]) 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) with a demonstration pen.

Treatment period: General Considerations

The treatment period will last 40 weeks, starting with a 4-week stabilization period immediately after randomization and followed by a 36-week glargine titration period. The maintenance period is defined as a part of the titration period when insulin glargine dose is expected to be stable and optimized (Weeks 24 to 40 [Visits 19 to 22]). Patients should inject their first dose of study drug under the supervision of the staff at Visit 3 (baseline) while still at the study site. The date and time of the first dose of study drug should be recorded on the electronic case report form (eCRF).

Patients will:

- perform daily BG measurements per their weekly SMBG plan as outlined in this section and in Section 2.
- perform insulin glargine dose assessments once or twice per week, depending on the study period, as described in the sections below.
- discuss other relevant clinical information, for example, AEs and concomitant medications at each visit. Patients who are taking concomitant metformin during the lead-in period will be required to continue using the same dose of metformin throughout

the treatment period. Discontinuation of metformin or changes in its dose will not be permitted, except in the cases of development of contraindications (per country-specific label) for its use or in the case of increased risk of hypoglycemia (see Section 7.4.2 for details).

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

Post randomization period (end of Visit 3 to Visit 22):

Stabilization Period (End of Visit 3 through Visit 7 [Weeks 0 through 4])

The main purposes of this period are to introduce randomized study drugs (QW tirzepatide or QW placebo) in a safe manner, to assure regular and correct use of the self-monitoring and insulin dose adjustment procedures, and to study diaries during the entire study. Patients will be required to perform 4-point SMBG profiles and insulin dose assessment per the TTT algorithm twice weekly during this period. In an effort to allow appropriate time for tirzepatide to reach steady state, insulin glargine dose adjustments during the 4-week stabilization period should be restricted to those needed in the case of significant safety risks due to inadequate insulin dose:

- occurrence of hypoglycemia; (see Sections 7.4.2 and 9.2.2.1); in this case, the insulin glargine dose will be decreased per the TTT algorithm; or
- development of severe hyperglycemia, defined as mean daily PG from 4-point SMBG profile >270 mg/dL (>15 mmol/L); in this case, insulin dose will be increased per the TTT algorithm.

Patients should be instructed to contact the sites if any of the above situations occurred, in order to adjust the insulin glargine dose per the TTT algorithm. In addition, for patients with baseline HbA1c ≤8.0%, the insulin glargine dose will be decreased by 20% immediately after randomization, not later than 7 days after the first dose of study drug, and will then remain unchanged during the stabilization period to decrease the risk of hypoglycemia. The insulin glargine dose will remain unchanged if baseline HbA1c is >8.0%. If the baseline HbA1c value for a patient is not available within the first 7 days after randomization, the study site should immediately consult the responsible Lilly physician (not later than the date of Visit 4) to discuss if an adjustment in insulin dose would be appropriate based on the available clinical data for the patient.

In addition to the clinic visits, one telephone visit will be scheduled during this period (Visit 6, Week 3). At this visit, procedures will include

- assessments of SMBG,
- adjustment of insulin dose for safety reasons (hypoglycemia and/or severe hyperglycemia),
- study drug compliance (will be re-assessed at the office visit),
- hypoglycemic events,
- concomitant medications, and
- AEs.

The data obtained at these telephone visits will be entered into the case report forms (CRFs) at the next office visit.

Titration Period (End of Visit 7 through Visit 22 [Weeks 5 through 40])

Throughout the treatment period, patients will collect the following data in the patient diary to be reviewed at the next office visit:

- SMBG,
- insulin dose assessments,
- insulin doses administered,
- dates when study drug was administered, and
- hypoglycemic events.

For that purpose, at each visit, study diaries for the period after the previous office visit, will be collected, and instructions will be reviewed at each visit. Study drug and injection supplies will be returned per the Schedule of Activities (Section 2) and according to local requirements. New supplies will be dispensed as needed.

In addition to the clinic visits, 3 telephone visits will be scheduled during this period. At each of these visits, procedures will include

- assessments of SMBG,
- compliance with insulin titration algorithm,
- insulin dose,
- study drug compliance (will be re-assessed at the office visit),
- hypoglycemic events,
- concomitant medications, and
- AEs.

The data obtained at these telephone visits will be entered into the CRFs at the next office visit.

At the beginning of the titration period, the patient will be instructed to start using the TTT algorithm without restrictions in order to reach the optimal dose of insulin glargine as soon as possible. The patient will be requested to perform insulin dose assessment once weekly during this period. Results of SMBG and hypoglycemic events will be used by the patient to assess insulin glargine doses per the titration algorithm. Additional assessments may be requested by

the investigator based on his or her clinical judgment. Outcome of the assessment will be recorded in patient diaries.

Compliance with study drug administration schedule and compliance with the insulin glargine titration algorithm will be assessed at every office visit and collected in the eCRF at prespecified visits (Section 2). Based on the outcome of these reviews, the site staff should discuss additional insulin glargine dose adjustments while the patient is still at the site and provide retraining, if needed.

Patients should be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties administering their study drugs or with the titration algorithm at any time during the study. Patients should also be advised about the appropriate course of action in the event that study drug is not taken as instructed (for example; missing doses).

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 visit.
- Patients discontinuing the study early and performing an early termination (ET) visit will also be asked to perform the safety follow-up visit, so that the safety follow-up visit will be their final visit.
- During the safety follow-up period, patients will not receive study drug.
- Patients will be treated with another glucose-lowering intervention decided upon by the investigator. Initiation of new antihyperglycemic therapy for the safety follow-up period 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 and/or after early study drug discontinuation. Rescue therapy with other glucose-lowering agents, including prandial insulin, may be medically indicated in certain situations after randomization due to severe, persistent hyperglycemia or early discontinuation of study treatment. Glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase (DPP-4) inhibitors, and pramlintide are prohibited medications and are not allowed as rescue therapies. No other basal insulins are allowed during the course of the study.

Patients who develop severe, persistent hyperglycemia based on prespecified thresholds (see Section 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 study 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 or placebo) 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 GPGI is designed to determine the comparative benefits and risks of QW tirzepatide (5 mg, 10 mg, or 15 mg) versus placebo in patients with T2DM who have inadequate glycemic control on stable doses of insulin glargine with or without metformin.

Placebo was chosen as the comparator to meet the FDA requirement to compare the study drug versus a placebo in at least one 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. Moreover, the duration of the study is considered sufficient and appropriate for patients to optimize dosing of insulin glargine in the placebo group for comparison with the tirzepatide treatment groups with respect to change in HbA1c.

The parallel-group design for treatment comparison was chosen to avoid any interaction between treatments that may interfere with the interpretation of the study outcome. 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). Metformin was chosen as allowed concomitant antihyperglycemic medication as it is commonly used in combination with basal insulin in clinical practice.

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 Phases 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 and have been treated with insulin glargine (U100), once daily with or without metformin ≥3 months prior to Visit 1

Patient Characteristics

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

[3] Have been on stable doses of once-daily insulin glargine (>0.25 U/kg/day or >20 U/day) and metformin (if taken) during the 3-month period prior to Visit 1. Insulin glargine dose is considered stable when all doses during this period are within the range defined by ±20% of the most commonly used insulin dose during this same period. Doses of metformin are considered stable if all prescribed doses during this period are in the range between the minimum required dose (≥1500 mg/day) and the maximum approved dose per the locally approved label

[4] Require further insulin glargine dose increase at Visit 3 per the TTT algorithm based on the SMBG data collected during the prior week

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

[6] Have body mass index (BMI) ≥23 kg/m^2 at Visit 1

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

(a) Male patients:

- Male patients should be willing to use reliable contraceptive methods throughout the study and for at least 3 months after last injection (Appendix 6)

(b) Female patients:

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

          OR

        - have had at least 6 months and less than 12 months of spontaneous amenorrhea with follicle-stimulating hormone (FSH) and estradiol levels consistent with a postmenopausal state (FSH ≥40 mIU/mL and estradiol <30 pg/mL).
    - Female patients of childbearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must:
        - test negative for pregnancy at Visit 1 based on a serum pregnancy test

          AND

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

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

(a) perform fingerstick 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 a study diary, 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

[9] 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

[10] Have type 1 diabetes mellitus (T1DM)

[11] Had chronic or acute pancreatitis any time prior to study entry (Visit 1)

[12] 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)

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

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

[15] 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: a gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or chronically take drugs that directly affect GI motility

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

[17] Have New York Heart Association Functional Classification III and IV CHF

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

[19] Have an estimated glomerular filtration rate <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory at Visit 1; for patients on metformin, estimated glomerular filtration rate <45 mL/min/1.73 m^2 (or lower than the country-specific threshold for using the protocol-required dose of metformin per local label)

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

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

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

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

[24] 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

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

[26] 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

[27] 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

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

Prior/Concomitant Therapy

[29] Treatment with any glucose-lowering agent(s) other than stated in the inclusion criteria [4] in a period of 3 months prior to Visit 1 and between Visit 1 and Visit 3

[30] 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], Apidex® [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)

[31] 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

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

medically compatible with this study

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

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

Other Exclusions

[35] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

[36] Are Lilly employees

[37] Are unwilling or unable to comply with the use of a paper diary to directly record data from the subject

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 [5] (Section 6), patients should not initiate during the study an organized diet and/or exercise weight reduction program 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

Eligibility for this study will be determined at the initial screening visit (Visit 1). Screening procedures and patient training will be performed at Visits 1 and 2 (screening and lead-in periods). Patient training will include disease monitoring and management procedures, study diaries, and study procedures. At Visit 3, patients will perform all required baseline study procedures (including the collection of all baseline laboratory measures and ECG) prior to randomization and prior to taking the first dose of study drug. Following randomization, the patient will inject the first dose of study drug/placebo at the study site. The date and time of all doses of study drug should be recorded on the electronic case report form (eCRF). Beginning at randomization, all patients will receive study drug according to the randomized treatment group for the duration of the 40-week treatment period. A safety follow-up visit will occur approximately 4 weeks following the last dose of the study drug.

7.1.1. Tirzepatide Dosing

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

7.1.2. Placebo Dosing

Patients randomized to the placebo group will inject matched placebo subcutaneously QW for the entire treatment period. This is a double-blind study, and therefore it will not be possible for investigators and patients to know which treatment they are receiving.

7.1.3. Insulin Glargine Dosing

Insulin glargine will be injected once daily, as a single SC injection, always at the same time of day, ideally at bedtime. Patients will be instructed to adjust insulin glargine doses to a target FBG of <100 mg/dL (5.5 mmol/L) according to the schedule below (Table GPGI.3). For this purpose, patients will be required to measure their FBG each morning and to collect 4-point SMBG profiles at least once a week. The 4-point SMBG profile will consist of fasting, pre-midday meal, pre-evening meal, and bedtime measures. Patients will collect the 4-point SMBG profiles once weekly between Visit 2 and Visit 3, twice weekly from Visits 3-7 (Weeks 0-4) followed by once weekly for the remainder of the study.

Table GPGI.3. Treat-to-Target Algorithm

Median Fasting Blood Glucose[a]		Adjustment of Insulin Glargine if Dose is <20 Units	Adjustment of Insulin Glargine if Dose is ≥20 Units
mg/dL	mmol/L		
≤70	≤3.9	−1 or −2 units[b,c]	−2 to 4 units[b,c]
71 to 100	4.0 to 5.5	No adjustment	No adjustment
101 to 119	5.6 to 6.6	+1 units	+2 units
120 to 139	6.7 to 7.7	+2 units	+4 units
140 to 179	7.8 to 9.9	+3 units	+6 units
≥180	≥10.0	+4 units	+8 units

Abbreviation: SMBG = self-monitored blood glucose.

[a] Based on the last 3 SMBG values.

[b] Dose should also be decreased by 1 to 2 units or 2 to 4 units in the following situations:
If multiple episodes of nonsevere hypoglycemia were recorded during the assessment period at any time during the day; and/or
If at least 1 episode that met the criteria for severe hypoglycemia (events requiring assistance of a third person to administer therapy) or was associated with SMBG value <54 mg/dL (<3.0 mmol/L) was recorded during the assessment period.

[c] If only 1 hypoglycemic episode with SMBG value ≥54 mg/dL (≥3.0 mmol/L) and ≤70 mg/dL (≤3.9 mmol/L) was recorded, insulin dose should not be changed.

Source: Adapted from Riddle et al. 2003.

The site personnel will instruct the patient, with the patient insulin dose adjustment from the patient diary and study-specific training materials provided to the study sites, when and how to assess whether an insulin dose adjustment is needed using the algorithm. The investigator or his or her designee is responsible to ensure that the insulin dose titration regimen used by study participants follows the same requirements defined in the TTT plan throughout the study. The patient is responsible for completing the insulin dose assessments and making the required dose adjustments (self-adjustment). Assessment of insulin doses per the TTT algorithm and administered insulin doses will be recorded by the patient in study period-specific diaries. Patients should be instructed to contact the study site if they are unable to decide on the appropriate dose adjustment at any time during the trial. Site personnel will verify at each office or telephone visit that the assessment(s) has been made and that the insulin adjustment was appropriate. If needed, they will propose further adjustments based upon their review of data collected since the previous visit. If assessments were not made or the algorithm was not correctly followed, patients will receive additional training and instructions.

During the lead-in period (Visits 2 and 3 [baseline]), insulin doses should be adjusted per TTT algorithm (Table GPGI.3) only when needed to protect the safety of patients (occurrence of hypoglycemia or severe persistent hyperglycemia). See Section 5.1 for more details. Insulin dose assessments during this period will occur once per week.

During the treatment period, office visits will occur weekly or every other week during the first 2 months, and thereafter every 4 to 8 weeks to enable the site to properly monitor patients' usage of the TTT algorithm. After randomization, during the 4-week stabilization period, the insulin

glargine dose will remain unchanged if the patient's baseline (Visit 3) HbA1c is >8.0%. For patients with baseline HbA1c ≤8.0%, the insulin glargine dose will be decreased by 20% immediately (within 7 days) after randomization and will then remain unchanged during the stabilization period. Additional insulin dose adjustments during the stabilization period will only be allowed using the TTT algorithm (Table GPGI.3) in case of the occurrence of hypoglycemia or the development of severe hyperglycemia. See Section 5.1 for more details. Patients will be requested to perform insulin dose assessments twice per week during the stabilization period for safety purposes. Following stabilization, patients will be treated for an additional 36 weeks, and they will be required to assess their insulin glargine dose once weekly, using the FBG values for that week. During this period, the insulin dose will be adjusted per the TTT algorithm as described in Section 5.1 with no restriction. The decision to adjust insulin glargine doses will be based upon the median of the last 3 daily FBG (SMBG) values collected after the previous dose assessment. If only 2 values are available for assessment, then the average value will be calculated and used to adjust the dose. If only one value is available, the patient should contact the investigator site for instructions on adjusting insulin dose. In case of recorded hypoglycemic episodes any time during the period included in the assessment, the criteria provided in Table GPGI.3 should be followed.

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, and after early study drug discontinuation. Rescue therapy with other glucose-lowering agents, including prandial insulin, may be medically indicated in certain situations after randomization due to severe, persistent hyperglycemia or early discontinuation of study treatment. Rescue treatment with GLP-1 receptor agonists, pramlintide, DPP-4 inhibitors or other basal insulins will not be allowed. Short-term treatment with a nonstudy insulin for less than 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.

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

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

7.1.4. 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.

7.1.5. Medical Devices

The combination products used in the study are tirzepatide investigational SDP and a marketed insulin glargine prefilled pen.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to one 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 Drug

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. 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 scheduled dose, in which case, that dose should be skipped and the next dose should be taken at the appropriate time.

All patients will inject study drug subcutaneously in the abdomen or thigh using the SDP; 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.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency codes, generated by a computer drug-labeling system, will be available to the investigator. These codes, which reveal the patient's treatment group when opened, may be opened during the study ONLY if the patient's well-being requires knowledge of the patient's treatment assignment.

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 calls resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) for the patient to continue in the study.

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 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.

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 Section 7.1.

7.4.2. Reduction and/or Discontinuation of Concomitant Antihyperglycemic Medications

1) If increased risk of hypoglycemia during the period between 2 insulin dose assessments is judged to be related to the treatment regimen, the following changes should be made:
    - Decrease the insulin glargine dose by 2 to 4 U, per the TTT algorithm, in the following cases:
        - If the median FPG value for the assessment period is ≤70 mg/dL (≤3.9 mmol/L); and/or
        - If multiple episodes of nonsevere hypoglycemia were recorded at any time during the day for the assessment period; and/or
        - If at least 1 episode that met the criteria for severe hypoglycemia (events requiring assistance to administer therapy) or was associated with SMBG value <54 mg/dL (<3.0 mmol/L) was recorded during the assessment period;
    - In the case of repeated hypoglycemic events, even with a very low glargine dose and despite glargine dose decreases per the TTT algorithm, administration of insulin glargine may be temporarily or permanently discontinued;
    - If increased risk of hypoglycemia persists despite discontinuation of insulin glargine, then dose reduction or discontinuation of metformin (for patients who are taking it) should be considered.

2) In certain situations short-term discontinuation will be required in line with the product(s) labeling for each respective country (for example, for metformin: severe dehydration, elective surgery, or need for radiologic examination involving IV iodinated contrast dye). Once the situation that led to temporary discontinuation of the drug resolved, treatment should be restarted at investigator discretion.

3) If a patient develops contraindications to metformin (if used), such that the use of the drug is contraindicated according to the country-specific label, the drug should be discontinued; in this case, the insulin glargine dose may need to be further adjusted.

A patient will be considered noncompliant with the protocol (protocol deviation) if he or she changes the dose or discontinues metformin (if used) for reasons other than those described here. In the case of noncompliance that lasts >14 days during the treatment period, the patient will not be included in the per-protocol analyses.

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. Patients will be considered to be noncompliant with their insulin glargine treatment if they miss their daily dose of insulin glargine for more than 7 consecutive days or for more than 7 days within a month (that is, a patient is considered to be compliant if they are ≥75% compliant with their required

insulin glargine therapy). Similarly, a patient will be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

In addition to the assessment of a patient's compliance with the study drug administration, other aspects of compliance with the study 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 not to be 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. Glucagon-like peptide-1 receptor agonists, DPP-4 inhibitors, pramlintide, and other basal insulins are prohibited medications and are not allowed as rescue therapies.

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.

7.7.1. 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 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 (Weeks 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, anti-emetic 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 8.1.1) and will continue participating in the study according to the protocol to collect all planned efficacy and safety measurements. The new glucose-lowering intervention will be recorded on the eCRF specified for collecting antihyperglycemic medications.

In the event of intolerable persistent GI symptoms that occur after the escalation period (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.

7.8. Treatment after the End of the Study

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

Tirzepatide will not be made available after conclusion of the study to patients.

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 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 electronic case report form.

  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 (INR) >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
- Acute or chronic pancreatitis
- If a patient is diagnosed with MTC after randomization, or has 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.

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. 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 doses missed is ≤2, the treatment can be restarted at the same dose, if the drug was well tolerated prior to discontinuation.
- If the number of missed doses is ≥3, then the IWRS will dispense 5 mg/matched placebo irrespective of the dose the patient was receiving before the interruption and subsequently escalated as required by protocol.

If study drug interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 9.2 of this protocol. If the study drug interruption is due to intolerable persistent GI AE (for example, nausea, vomiting, or diarrhea), the patients should be treated as suggested in Section 7.7.1.

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 identify 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 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 is 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 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 (GCP),
- 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 be prescribed an appropriate glucose-lowering regimen and glucose self-monitoring plan. 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% (53 mmol/mol), ≤6.5% (48 mmol/mol), or <5.7% (39 mmol/mol)
- Mean change in fasting serum glucose (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%
- Change in daily mean insulin glargine dose

9.1.3. Exploratory Assessments and Procedures

The following secondary efficacy measures will be assessed 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
- IW-SP scores
- DTSQs/DTSQc
- EQ-5D-5L scores

9.1.4. 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 to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, 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 informed consent form (ICF) is signed, study site personnel will record via electronic case report form (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. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via eCRF.

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 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 adverse event 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 subjects once they have discontinued and/or completed the study (the patient disposition case report form (CRF) has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he or she considers that the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

9.2.2.1. Hypoglycemia

Patients will collect information on episodes of hypoglycemia starting from Visit 2 until the last study visit (Follow-up Visit or Early Termination 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. 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/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 a 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.

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 at the discretion of investigator in accordance with American Diabetes Association/European Association for the Study of Diabetes guidance (Inzucchi et al. 2015). Rescue medication will be prescribed as add-on to randomized treatment, and patients will continue to follow the protocol-specified visit schedule.

Because insulin glargine dose adjustments without restrictions will be initiated at the end of the stabilization period (see Section 5.1), decision on the presence of severe, persistent hyperglycemia can be first considered 12 weeks after the initiation of this period (approximately 16 weeks after randomization)..

Add-on glycemic rescue therapy will be allowed for patients who met any one of the following prespecified criteria for severe, persistent hyperglycemia 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 the patient does not have an acute condition causing severe hyperglycemia):

(a) average daily BG from the once-weekly 4-point SMBG profile >270 mg/dL (>15.0 mmol/L) over at least a consecutive 2-week period at any time 16 to 24 weeks post randomization;
OR
(b) average daily BG from the once-weekly 4-point SMBG profile >240 mg/dL (>13.3 mmol/L) over a consecutive 2-week period at any time 25 to 32 weeks post randomization;
OR
(c) average daily BG from the once-weekly 4-point SMBG profile >200 mg/dL (>11.1 mmol/L) over a consecutive 2-week period at any time beyond the first 32 weeks post randomization.
OR
(d) HbA1c ≥8.5% at 24 weeks, with inadequate response to the existing regimen defined as improvement in HbA1c over the last 3 months (Week 12 to Week 24) that is, <0.3%

Rescue therapy option:

The criteria described above for severe, persistent hyperglycemia will only be applicable after Week 16. The first choice before initiating any rescue therapy for those patients during the initial 16 weeks will be to follow the TTT algorithm to increase the dose of insulin glargine.

Rescue treatment with pramlintide, DPP-4 inhibitors, or GLP-1 receptor agonists will not be allowed. Additionally, use of other basal insulins will not be allowed.

Investigators must use clinical judgment in the interest of safety of the patient at all times. In any situation that, in the investigator's opinion, may require an intervention that is not consistent with the requirements provided in this section, he or she should also consult the Lilly physician before such intervention is implemented, except when an immediate adjustment of the treatment regimen is medically required.

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 pancreatic amylase 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 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 AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or pancreatic amylase) 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; Steinberg et al. 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic amylase ≥3X ULN) is not mandated, but may be performed based on the investigator's clinical judgment and assessment of the patient's overall clinical condition. 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 multiple endocrine neoplasia type 2 (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), and
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

9.2.2.6. Supraventricular arrythmias 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 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, as SAEs. Additional data, such as type of reaction and treatment received, will be collected on any AEs or SAEs that the investigator deems related to study drug(s) via a CRF created for this purpose. Additional samples should also be collected as outlined in Section 9.5. Study drug(s) should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug(s). Study drug(s) may be restarted when/if it is safe to do so, in the opinion of the investigator. 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.

9.2.2.8. Injection Site Reactions

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

9.2.2.9. Anti-Drug Antibodies

The occurrence of ADA formation will be assessed as outlined in Section 10.3.6.

9.2.2.10. 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.

9.2.2.11. Hepatobiliary Disorders

All events of treatment emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 9.4.5 and Appendix 4.

9.2.2.12. Severe Gastrointestinal Adverse Events

Tirzepatide may cause severe GI AEs, such as; nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the eCRF/AE form. For detailed information concerning the management of GI AEs, please refer to Section 7.7.1.

9.2.2.13. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute or worsening of chronic renal failure. Gastrointestinal AEs have been reported with tirzepatide, including nausea, diarrhea, and vomiting. These are consistent with other GLP-1 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.

9.2.2.14. 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. If ketoacidosis is suspected, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

Lactic acidosis has been reported rarely in patients with T2DM associated with use of metformin, excessive alcohol intake and decrease renal function. Routine bicarbonate assessment will be performed during the course of the study. If lactic acidosis is suspected, metformin should be temporarily discontinued until the resolution of the event.

9.2.2.15. Amputation/Peripheral Revascularization

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

9.2.2.16. Major Depressive Disorder/Suicidal Ideation

The prevalence of depressive symptoms and disorders is increased in patients with T1DM or T2DM (ADA Guideline, 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, 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 and/or Product Label for insulin glargine.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, electrocardiograms (ECGs) should be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study-specific recommendations included in Manual of Operations for the study.

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 subject management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the 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

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from vital signs measurement 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 CRF.

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 predose 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 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 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, respectively.

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

9.4.5. Safety Monitoring

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

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
- elevated 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 a 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 after Week 7, 15, 23, and 39 of treatment per the Study Schedule or at ET (Section 2). 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, 23, and 39. 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 date and time at which each sample was drawn must be recorded on the laboratory accession page.

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry (LC/MS) method. Bioanalytical samples collected to measure tirzepatide concentrations will be retained for a maximum of 1 year following last 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 Samples 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 diabetes. 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/investigational review boards) 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 deoxyribonucleic acid (DNA), ribonucleic acid (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 development of tirzepatide or after tirzepatide become(s) commercially available.

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. 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. 2011; 2012). Items are scored on a 5-point numeric rating scale, where 5 = "not at all difficult" and 1 = "unable to do." A raw overall score is calculated by simply summing the scores of the 7 items, and 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.

9.9.2. Impact of Weight on Self-Perception Questionnaire

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

9.9.3. Diabetes Treatment Satisfaction Questionnaire

The status (s) and change (c) versions of the DTSQ will be used during the study to assess the patient's satisfaction with their diabetes treatment and the perceived frequency of hyperglycemia

and hypoglycemia. The questionnaire contains 8 items (Bradley 1994). Each item is rated on a 7-point Likert scale. Six items (1 and 4 through 8) are summed to produce a measure of treatment satisfaction ranging from 0 "very dissatisfied" to 6 "very satisfied." The remaining 2 items (2 and 3) are treated individually. Item 2 measures the perceived frequency of hyperglycemia on a scale ranging from 0 "none of the time" to 6 "most of the time," and Item 3 measures the perceived frequency of hypoglycemia on the same scale. The change version has the same 8 items as the status version with a small alteration of the wording of Item 7. The DTSQ change response options differ from those of the DTSQ status to produce measures of relative change rather than absolute satisfaction (3 "much more satisfied now" to -3 "much less satisfied now").

9.9.4. European Quality of Life

Generic health-related quality of life will be assessed using the EQ-5D-5L (EuroQoL Group 2015). The EQ-5D-5L is a standardized 5-item instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems), for a total of 3125 possible health states. In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). In addition, the EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analog scale. In conjunction with the health state data, it provides a composite picture of the respondent's health status.

The EQ-5D-5L is used worldwide and is available in more than 130 different languages. Details on the instrument, and scoring, organizing, and presenting the data collected can be found in the EQ-5D-5L User Guide (EuroQoL Group 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 10 mg and 15 mg, each tested in parallel, against placebo at a 2-sided significance level of 0.025, relative to the primary endpoint (mean change in HbA1c from baseline to 40 weeks), under the following assumptions: use of a 2-sample t-test utilizing HbA1c data collected before initiation of any rescue medication or premature treatment discontinuation with no more than 28% of subjects initiating rescue medication or prematurely discontinuing treatment in each treatment group; 0.6% greater mean reduction in HbA1c from baseline for 10 and 15 mg tirzepatide compared with placebo; 1:1:1:1 randomization; and a common standard deviation (SD) of 1.1%. On the basis of these assumptions, a sample size of 472 subjects is required to ensure at least 90% power to demonstrate that tirzepatide 10 mg and/or 15 mg are superior to placebo relative to the primary endpoint.

Furthermore, this sample size will ensure 90% power for the superiority evaluation conducted using an analysis of covariance (ANCOVA) utilizing all available HbA1c data at 40 weeks with missing data imputed with a conservative multiple imputation method (as described in Section 10.3.3 below), provided a 0.6% greater mean reduction in HbA1c from baseline for 10 and 15 mg tirzepatide compared with placebo and SD increases to no more than 1.3% due to the inclusion of data on rescue medications and after premature treatment discontinuation and imputation of missing data.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined as follows:

Population	Description
Screened patients	All participants who sign informed consent
Randomized patients	All patients who are randomly assigned a treatment group.
modified intention-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 then 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	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 Periods 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 clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval (CI) 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. The first estimand, the "efficacy" estimand, represents efficacy prior to discontinuation of study drug without the confounding effects of antihyperglycemic rescue therapy. The 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 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.

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, the safety analysis will be conducted using the SS. Selected safety analysis (for example, hypoglycemia) may be conducted excluding data after introducing another antihyperglycemic therapy.

Summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time will be a mixed model for repeated measures (MMRM), with terms: treatment, visit, and treatment-by-visit interaction, country, metformin use (Yes or No), and baseline measurement as a covariate. An unstructured covariance matrix will model the relationship of within-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. Summary statistics for discrete count measures will include sample size, mean, SD, median, minimum, and maximum. The negative binomial regression model will be used for the treatment comparison of discrete count measures.

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

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 population, frequency, counts and percentages of patients completing the study, prematurely discontinuing the study, including the reason for premature discontinuation, will be presented by treatment group. A Kaplan-Meier analysis of time from randomization to premature discontinuation from study by treatment group will be provided.

10.3.2.2. Patient Characteristics

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

10.3.2.3. Concomitant Therapy

Concomitant medications, including previous therapy for diabetes, will be summarized by anatomical therapeutic chemical classification and treatment group using the mITT population. In particular, the incidence of rescue therapy for severe, persistent hyperglycemia will be

analyzed as an exploratory safety endpoint. Dose modifications of oral antihyperglycemic therapy will also be compared between treatment groups.

10.3.2.4. Treatment Compliance

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

Treatment compliance is defined as taking at least 75% of required injections of study drug. Frequency counts and percentages of patients compliant to study drug will be summarized by treatment arm 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 10 mg and 15 mg of tirzepatide to placebo relative to mean change in HbA1c from baseline to the 40-week visit.

For the FDA, 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 obtained at the 40-week visit using an ANCOVA with terms, treatment, stratification factors, and baseline HbA1c as a covariate. Missing change in HbA1c 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 arm 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, the primary efficacy assessment will be guided by the "efficacy" estimand, controlling the overall family-wise type 1 error rate at a 2-sided alpha of 0.05 only for the primary endpoint evaluation that QW tirzepatide is superior to placebo in HbA1c change from baseline to 40 weeks. Additional details will be provided in the SAP.

The ANCOVA analysis will report LSMean and standard error (SE) values for each dosing arm as well as the difference in mean change in HbA1c from baseline to the 40-week visit. Comparisons will be made between 10 mg tirzepatide and placebo as well as between 15 mg tirzepatide and placebo. The 97.5% CIs and between treatment p-values will also be included for the differences. If the difference between either tirzepatide dose and placebo is directionally superior, and the 2-sided p-value is <0.025, the tirzepatide dose will be declared superior to placebo.

For all other purposes, the primary efficacy analysis will be guided by the "efficacy" estimand defined in Section 10.3.1. This assessment will be conducted using the EAS. The primary analysis model for HbA1c measurements over time will be an MMRM. The response variable of MMRM will be change in HbA1c from baseline values obtained at each scheduled postbaseline visit. The independent variables of the MMRM model are treatment group (10 mg tirzepatide, 15 mg tirzepatide, and placebo), visit, and treatment-by-visit interaction, country, metformin use (Yes or No), and baseline HbA1c as a covariate. An unstructured covariance structure will model the relationship of within-patient errors. If the analysis fails to converge, the following variance-covariance matrix will be used (in order) until convergence is achieved: heterogeneous compound symmetry, compound symmetry, and first-order autoregressive. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The MMRM analysis will report LSMean and standard error (SE) values for each dosing arm as well as the difference in mean change in HbA1c from baseline to the 40-week visit. Comparisons will be made between 10 mg tirzepatide and placebo as well as between 15 mg tirzepatide and placebo. The 97.5% CIs and between treatment p-values will also be included for the differences. If the difference between either tirzepatide dose and placebo is directionally superior, and the 2-sided p-value is <0.025, the tirzepatide dose will be declared superior to placebo.

10.3.3.2. Secondary Analyses

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

- superiority of the 5 mg tirzepatide dose to placebo relative to mean change in HbA1c from baseline to the 40-week visit
- superiority of each tirzepatide dose to placebo relative to mean change in body weight from baseline to the 40-week visit
- superiority of each tirzepatide dose to placebo relative to the proportion of patients achieving the target value of HbA1c <7% at the 40-week visit
- superiority of each tirzepatide dose to placebo relative to mean change in FSG from baseline to the 40-week visit

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

Analysis of change from baseline in HbA1c for the 5 mg tirzepatide dose at the 40-week visit will be conducted in a manner similar to the primary efficacy analyses as discussed in Section 10.3.3.1.

Analysis of change from baseline in body weight as well as FSG at the 40-week visit will be conducted in a manner similar to the primary efficacy analyses with, respectively, change in weight from baseline and change in FSG from baseline as the response variables and baseline body weight and baseline FSG as covariates.

Comparisons among treatments relative to the proportion of patients achieving the HbA1c target value of <7.0% (53 mmol/mol) at the 40-week visit will be conducted using a logistic regression analysis with terms of treatment, country, metformin use (Yes or No), and baseline HbA1c as a covariate. In the analysis of patients achieving the HbA1c target value relative to the "efficacy" estimand, subjects 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 without imputation of missing data 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 excluding data after the introduction of another antihyperglycemic therapy.

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 subjects 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 in each category (either total or nocturnal) will be compared between tirzepatide doses and placebo using negative binomial regression analysis. Selected safety analyses may be conducted excluding data after introduction of another antihyperglycemic therapy (for example, rescue 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 dates of randomization, event, first dose and last dose of study drug, and time from randomization to the event will be listed.

10.3.4.4. Central Laboratory Measures, Vital Signs, and Electrocardiograms

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

The percentages of patients with TE abnormal, high, or low laboratory measures at any time will be summarized and compared between treatment groups by using Fisher's exact test. A TE abnormal value is defined as a change from normal value at baseline to a value greater than the high limit at any time during Periods II and III. A TE low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time during Periods II and III. High and low laboratory limits will be determined by the central laboratory reference ranges.

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 (MRD) if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). The MRD of the ADA assay is 1:10. For TE ADA patients, 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 from baseline to Visit 18 will be provided by age, race, ethnicity, gender, duration of diabetes, baseline HbA1c (≤8.0% or >8.0% [≤64, >64 mmol/mol], and baseline metformin use.

10.3.8. Interim Analyses

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

Unblinding details are specified in the unblinding plan section of the statistical analysis plan (SAP) or a separate unblinding plan document.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APPADL	Ability to Perform Physical Activities of Daily Living
AST	aspartate aminotransferase
BG	Blood glucose
blinding/masking	A double-blind study is one in which neither the patient/subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects 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
CRF	case report form
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.
CSR	Clinical Study Report

CV	cardiovascular
DPP-4	dipeptidyl peptidase-4
DTSQs	Diabetes Treatment Satisfaction Questionnaire status
EAS	efficacy analysis set
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture system
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
FDA	Food and Drug Administration
FSG	fasting serum glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
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.
ICH	International Council for Harmonisation

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	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
IW-SP	Impact of Weight on Self-Perception
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NAFLD	nonalcoholic fatty liver disease
OTC	over the counter
p-amylase	pancreatic amylase
PK/PD	pharmacokinetics/pharmacodynamics
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QW	once weekly
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.
TTT	treat to target
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology	**Clinical Chemistry**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
	Bicarbonate
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose, fasting
Urinalysis[a,b]	
Albumin	**Pregnancy Test** (females only)[b]
Creatinine	
	Follicle-stimulating hormone (FSH)[c]
	Estradiol
HbA1c	**eGFR** (calculated by CKD-EPI equation)[d]
Endocrine	**Pancreas** (exocrine)
Calcitonin	Serum pancreatic amylase
	Serum lipase
Immunogenicity	
Tirzepatide anti-drug antibody	
Anti-GAD antibodies	
Nonpharmacogenetic Stored Samples	**Lipid Panel**
EDTA plasma	Total cholesterol
Serum	LDL
P800 plasma	HDL
	VLDL
	Triglycerides
Samples for PK Analysis	

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; GAD = glutamic acid decarboxylase; 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] 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 13, 19 and 22. Pregnancy tests may be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period.

[c] 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).

[d] 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 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 type 2 diabetes mellitus (T2DM) and clinical research in T2DM will participate as investigators in this clinical study.

Appendix 3.1.6. Protocol Signatures

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

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

Appendix 3.1.7. Final Report Signature

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

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

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

Appendix 3.2. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate

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

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

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

Appendix 3.2.1. Data Capture System

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

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

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

Data collected via the sponsor-provided data capture system(s) will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

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

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study I8F-MC-GPGI 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 normalised 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 GPGI Standardized Protocols for the Measurement of Height, Weight and Waist Circumference

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2017) (Available at: https://www.who.int/ncds/surveillance/steps/Section%204%20Step%202%20Physical%20Measurements.pdf)) Accessed January 17, 2019.

Measuring Height

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

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

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

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

Measuring Weight

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

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

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

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

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

Measuring Waist Circumference

- Waist circumference should be measured at midpoint, between lower margin of least palpable rib and top of iliac crest (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 22) 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 22, minimize missing data, and preserve the intended conduct of the study, the visit window for Visit 22 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 22.

2) For patients requiring an extension for Visit 22 up to Week 44, additional investigational product (tirzepatide or placebo) 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 will be obtained per local regulations for those patients who will be dispensed additional investigational product (tirzepatide or placebo) 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 the COVID-19 pandemic restrictions.

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

Appendix 9. Protocol Amendment I8F-MG-GPGI(b) A Randomized, Phase 3, Double-blind Trial Comparing the Effect of the Addition of Tirzepatide versus Placebo in Patients with Type 2 Diabetes Inadequately Controlled on Insulin Glargine with or without Metformin (SURPASS-5)

Overview

Protocol I8F-MC-GPGI titled "A Randomized, Phase 3, Double-Blind Trial Comparing the Effect of the Addition of Tirzepatide versus Placebo in Patients with Type 2 Diabetes Inadequately Controlled on Insulin Glargine with or without Metformin (SURPASS-5)" 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-GPGI Amendment (b)

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

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