

Protocol I8F-JE-GPGP (a)

A Phase 3, Long-Term Safety Study of Tirzepatide in Combination with Monotherapy of Oral Antihyperglycemic Medications in Patients with Type 2 Diabetes Mellitus (SURPASS J-combo)

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(SURPASS J-combo)**

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Tirzepatide (LY3298176)

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1. Synopsis

Title of Study:

A Phase 3, Long-Term Safety Study of Tirzepatide in Combination with Monotherapy of Oral Antihyperglycemic Medications in Patients with Type 2 Diabetes Mellitus (SURPASS J-combo).

Rationale:

Tirzepatide is a once-weekly dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon like peptide-1 (GLP-1) receptor agonist. It is a 39-amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors. The structure of tirzepatide is based on the GIP sequence and includes a C20 fatty di-acid moiety that **CCI**

Tirzepatide is administered by subcutaneous administration.

Study I8F-JE-GPGP (GPGP) is a multicenter, randomized, Phase 3, long-term, add-on treatment study designed to assess the safety and efficacy of once-weekly tirzepatide (5, 10, or 15 mg), administered subcutaneously in patients with type 2 diabetes mellitus (T2DM) taking therapeutic doses of various oral antihyperglycemic medications (OAMs): sulfonylureas (SUs), biguanides, alpha-glucosidase inhibitors (a-GIs), thiazolidinedione (TZD), glinides, or sodium-glucose cotransporter type 2 inhibitors (SGLT-2i's). The primary endpoint will be to assess the safety and tolerability of tirzepatide during 52 weeks of treatment as an add-on therapy to SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's in the treatment of T2DM, based on Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1. 2012).

Objective(s)/Endpoints:

Objectives	Endpoints
<p>Primary</p> <ul style="list-style-type: none"> To assess safety and tolerability of once-weekly tirzepatide during 52 weeks of treatment as an add-on therapy to SUs, biguanides, TZD, a-GIs, glinides or SGLT-2i's in the treatment of T2DM in terms of TEAEs. 	<ul style="list-style-type: none"> Incidence of TEAEs
<p>Secondary</p> <ul style="list-style-type: none"> To assess safety and tolerability of once-weekly tirzepatide during 52 weeks of treatment as an add-on therapy to SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's in the treatment of T2DM. 	<ul style="list-style-type: none"> Early discontinuations of investigational product due to AEs Adjudicated all deaths and nonfatal major CV events Adjudicated pancreatic AEs Serum calcitonin Incidence of allergic and hypersensitivity reactions Incidence of injection site reactions Incidence of treatment-emergent ADA to tirzepatide The change in systolic and diastolic blood

<ul style="list-style-type: none"> To assess the efficacy of once-weekly tirzepatide as an add-on therapy to SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's in the treatment of T2DM at 52 weeks. 	<p>pressure, and heart rate from baseline</p> <ul style="list-style-type: none"> Occurrence of hypoglycemic episodes Time to initiation of rescue therapy for severe persistent hyperglycemia <ul style="list-style-type: none"> Mean change in HbA1c Proportion of patients who achieve HbA1c <7%, ≤6.5%, and <5.7% Mean change in FSG Mean change in daily average 7-point SMBG profiles Mean change in body weight Proportion of patients who achieve weight loss of ≥5%, ≥10%, and ≥15% from baseline Mean change in fasting insulin Mean change in fasting C-peptide Mean change in HOMA-2
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Abbreviations: a-GIs = alpha-glucosidase inhibitors; ADA = anti-drug antibodies; AE = adverse event; FSG = fasting serum glucose; HOMA-2 = Updated Homeostasis Model Assessment; HbA1c = hemoglobin A1c; SGLT-2i's = sodium-glucose cotransporter type 2 inhibitors; SMBG = self-monitored blood glucose; SUs = sulfonylureas; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event; TZD = thiazolidinedione.

Summary of Study Design:

Study GPGP is a multicenter, randomized, Phase 3, long-term, add-on treatment study, which will assess the safety and efficacy of tirzepatide (5, 10, or 15 mg) in patients with T2DM taking therapeutic doses of various OAMs; SUs, biguanides, a-GIs, TZD, glinides, or SGLT-2i's. Approximately 441 patients who have been taking SUs (126 patients), or biguanides, TZD, a-GIs, glinides, or SGLT-2i (63 patients each) monotherapy will be randomized.

Treatment Arms and Duration:

Study GPGP will consist of 4 periods: a 2-week screening period, a 2-week lead-in period, a 52-week treatment period, and a 4-week safety follow-up period. Patients will be randomized in a 1:1:1 ratio (tirzepatide 5, 10, and 15 mg). Randomization will be stratified by OAM classes (SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's).

Number of Patients:

A total of approximately 441 patients (126 patients in combination with SUs and 63 patients each in combination with biguanides, TZD, a-GIs, glinides, or SGLT-2i's) will be randomized.

Statistical Analysis:

Sample size

Because the primary objective is to assess the safety of long-term treatment of tirzepatide and no formal hypothesis testing on the efficacy measures is planned, statistically derived power calculations were not considered for the determination of sample size. The sample size of the

study was based on the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1, 2012). The guideline requires long-term safety data of 1 year of treatment with combination therapy using other antihyperglycemic medications. At least 100 patients treated for 1 year in combination with SUs and at least 50 patients in combination with each of the other agents are required. By taking into account the overall drop-out rate of approximately 20%, 126 patients receiving combination treatment with SUs and 63 patients receiving combination treatment with other agents are planned to be randomized; therefore, a total of 441 patients are planned to be randomized.

General Consideration

Safety and efficacy will be assessed using the modified intention-to-treat (mITT) population, which consists of all randomly assigned participants who are exposed to at least 1 dose of investigational product. A statistical summary will be performed for each combination therapy, as well as overall.

Safety Analysis

Safety assessment will be based on all available data, irrespective of whether they were obtained while the participants had discontinued the investigational product or whether the participant had been given rescue medication. Summary statistics will be provided for incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and study discontinuation due to adverse events (AEs) or deaths from the first dose to the 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. A selected safety analysis (eg, hypoglycemia) will be conducted after excluding data while on rescue therapy or data after starting another permitted antihyperglycemic medication following permanent discontinuation of investigational drug.

Additional details, including analysis of AEs of special interest, will be provided in the statistical analysis plan (SAP).

Efficacy Analyses

The efficacy measure is mean change in glycated hemoglobin (HbA1c) from baseline to 52 week visit. The "efficacy" estimand, represents efficacy prior to discontinuation of investigational product without confounding effects of rescue therapy for persistent severe hyperglycemia.

The efficacy assessment, guided by the "efficacy" estimand, will use Efficacy Analysis Set (EAS), 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," and "treatment-by-visit interaction" as fixed effects, and "baseline HbA1c" as a covariate. An unstructured covariance structure will model the relationship of within-patient errors.

2. Schedule of Activities

Table GPGP.1. Schedule of Activities

Study Visit	Screening	Lead-in	Treatment											ET ^a	801 ^b
	1	2	3	4	5	6	7	8	9	10	11	12	13	—	56
Week of Treatment	-4	-2	0	4	8	12	16	20	24	32	40	48	52	—	56
Visit Window (days)	±7	±7	—	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	—	±7
Fasting Visit ^c	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Assessments															
Informed consent	X														
Medical history	X														
Demographics	X														
Previous diabetes therapy	X														
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundoscopic examination ^d		X													
Height	X														
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference			X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (2 sitting BP and HR) ^e	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG ^f	X		X			X					X		X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycemic events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests															
Pregnancy test (serum) ^g	X														
Pregnancy test (urine) ^h			X			X			X		X		X	X	
FSH test, estradiol ⁱ	X														
HbA1c	X		X	X		X			X		X		X	X	
Fasting Serum Glucose			X	X		X			X		X		X	X	
Insulin			X			X			X		X		X	X	
C-peptide			X			X			X		X		X	X	
Hematology	X		X			X			X		X		X	X	X
Chemistry panel	X		X			X			X		X		X	X	X
Lipid panel			X			X			X		X		X	X	X
Urinary albumin/creatinine ratio	X										X		X	X	X
eGFR (CKD-EPI)	X		X										X	X	
Lipase, pancreatic amylase	X		X			X			X		X		X	X	X
Calcitonin	X					X			X		X		X	X	X
Review screening lab test results		X													

Schedule of Activities

	Screening	Lead-in	Treatment											ET ^a	Follow-up
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	ET ^a	801 ^b
Week of Treatment	-4	-2	0	4	8	12	16	20	24	32	40	48	52	—	56
Visit Window (days)	±7	±7	—	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	—	±7
Fasting Visit ^c	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests															
Nonpharmacogenetic samples for storage			X			X			X		X		X	X	X
Pharmacogenetics sample ^l			X												
Immunogenicity (ADA) ^k			X	X		X			X		X		X	X	X
PK sample for immunogenicity ^l			X	X		X			X		X		X	X	X
Patient Education and Supplies															
Dispensing of SMBG meter/supplies		X	X	X	X	X	X	X	X	X	X	X			
SMBG meter training		X													
Weekly fasting SMBG measurement ^m			X	X	X	X	X	X	X	X	X	X	X	X	
7-point SMBG measurement ⁿ			X										X		
Dispensing of study diary and instruct in use		X	X	X	X	X	X	X	X	X	X	X			
Study diary review			X	X	X	X	X	X	X	X	X	X	X	X	X
Subcutaneous injection training/ injection site inspection/ review of technique		X													
Dispensing of investigational product and injection supplies			X	X	X	X	X	X	X	X	X	X			
Return of used investigational product containers, unused study medication, and study diary				X	X	X	X	X	X	X	X	X	X	X	X
Assessment of investigational product compliance				X	X	X	X	X	X	X	X	X	X	X	X
Patient-Reported Outcomes															
EQ-5D-5L			X										X	X	
DTSQs			X												
DTSQc													X	X	

Abbreviations: ADA = anti-drug antibodies; 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 Quality of Life – 5 Dimension – 5 Level; ET = early termination; FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HR = heart rate; OAM = oral antihyperglycemic medication; PK = pharmacokinetics; SMBG = self-monitored blood glucose.

- ^a Early termination (ET) visit is conducted within 14 days after the decision of study discontinuation.
- ^b Visit 801 should be 4 weeks after Visit 13 or 4 weeks after early termination.
- ^c 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 investigational product.
- ^d Dilated fundoscopic examination will be performed by an eye-care professional (ophthalmologist or optometrist) for all patients between Visit 2 and Visit 3 to exclude patients with proliferative diabetic retinopathy and/or diabetic maculopathy or nonproliferative diabetic retinopathy that requires acute treatment. The results from this examination will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy. Follow-up dilated fundoscopic examination should be performed when clinically indicated, and the results recorded on the retinopathy eCRF (See exclusion criterion #11 Section 6.2).
- ^e 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 BP machine.
- ^f A single 12-lead ECG will be recorded, after the patient has been supine for 5 minutes. A local ECG will be performed at screening. The ECGs during the treatment period will be electronically transmitted via modem to the centralized ECG vendor designated by Lilly.
- ^g Serum pregnancy test to be performed by the central laboratory at Visit 1 for women of childbearing potential only.
- ^h Urine pregnancy tests can be performed as required at local laboratories. A urine pregnancy test must be performed at Visit 3 with the result available prior to randomization and first injection of investigational product(s) for women of childbearing potential only. Additional pregnancy tests will be performed at Visits 6, 9, 11, 13 and ET. Pregnancy tests may also be performed, at the investigator's discretion, during the study.
- ⁱ FSH test performed at Visit 1 for postmenopausal women at least 45 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months and estradiol levels consistent with a postmenopausal state (FSH \geq 40 mIU/mL and estradiol <30 pg/mL).
- ^j The blood sample should be collected at Visit 3 before any investigational product has been given to the patient.
- ^k In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional blood samples will be collected including ADA, PK, and exploratory immune safety sample.
- ^l PK samples for immunogenicity must be taken prior to drug administration.
- ^m The patients are required to measure their fasting (pre-breakfast) blood glucose (FBG) concentration at least once a week at approximately the same time of day before OAMs have been taken. By the investigator's decision, the frequency of measurement of FBG could be increased.
- ⁿ 7-point SMBG profiles (glucose measurements before breakfast, lunch, dinner, and at bedtime and 2-hours after breakfast, lunch, and dinner) should be performed on 2 days within the 2 weeks prior to Visit 3 (0 weeks), and Visit 13 (52 weeks).

3. Introduction

3.1. Study Rationale

Tirzepatide is a once-weekly dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon like peptide-1 (GLP-1) receptor agonist. It is a 39-amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors. The structure of tirzepatide is based on the GIP sequence and includes a C20 fatty di-acid moiety that **CCI** [REDACTED]. Tirzepatide is administered by subcutaneous (SC) administration.

Study I8F-JE-GPGP (GPGP) is a Phase 3 study designed to assess the safety and efficacy of once-weekly tirzepatide (5, 10, or 15 mg), administered SC in patients with type 2 diabetes mellitus (T2DM) taking therapeutic doses of various oral antihyperglycemic medications (OAMs): sulfonylureas (SUs), biguanides, alpha-glucosidase inhibitors (a-GIs), thiazolidinedione (TZD), glinides, or sodium-glucose cotransporter type 2 inhibitors (SGLT-2i's). The primary endpoint will be to assess safety and tolerability of tirzepatide during 52 weeks of treatment as an add-on therapy to SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's in the treatment of T2DM, based on Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1. 2012).

The data from this trial, together with the data from other Phase 3 trials, are expected to provide robust benefit/risk profiles of individual doses of tirzepatide, as required by regulatory agencies for regulatory submission and marketing approval.

3.2. Background

Tirzepatide is currently being investigated for its potential use in the treatment of hyperglycemia in T2DM. In normal physiology, the incretins GIP and GLP-1 are secreted from enteroendocrine cells in the gut following a meal, and these incretins enhance the physiological response to food, including sensation of satiety, insulin secretion, and nutrient disposal (Baggio and Drucker 2007). Patients with T2DM have impaired incretin responses (Baggio and Drucker 2007). Incretin-based treatments that are currently available fall within 2 classes: GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (Neumiller 2015). Most GLP-1 receptor agonists have a beneficial effect on glucose metabolism through the enhancement of glucose-dependent insulin secretion, reduction of inappropriately elevated glucagon levels, and a delay in gastric emptying. Dipeptidyl peptidase-4 inhibitors indirectly exert an incretin effect by preventing the proteolytic breakdown and inactivation of endogenous agonists of gastric inhibitory polypeptide receptor (GIPR) and GLP-1 receptor agonists. Each class has its therapeutic limitations. For example, dosing of GLP-1 receptor agonists may be limited by gastrointestinal (GI) adverse effects and DPP-4 inhibitors are limited in efficacy by the fact they inhibit degradation of endogenous incretins, but, even when protected from degradation, the endogenous incretins do not reach plasma levels similar to what is attained with exogenous incretin analog treatment. As a dual receptor agonist, tirzepatide binds both GIP and GLP-1 receptors and combines the signaling of each receptor for improved glycemic control. By virtue of being a GIP/GLP dual receptor agonist, tirzepatide has the potential of reaching higher

efficacy in target tissues such as the insulin-producing pancreatic β -cells that express both GIP and GLP-1 receptors before reaching its therapeutic limitation. Tirzepatide may, furthermore, attain additional efficacy by recruiting metabolically active tissues not targeted by classical GLP-1 analogs (for example, adipose tissue as indicated by the observation of increased energy utilization [Baggio and Drucker 2007]).

Three tirzepatide clinical trials have completed dosing and analysis: a Phase 1 study, Study I8F-MC-GPGA (GPGA), and 2 Phase 2 studies, Study I8F-MC-GPGB (GPGB) and I8F-MC-GPGF (GPGF). One Phase 1 study, Study I8F-JE-GPGC (GPGC) is ongoing in Japan.

The safety and tolerability and pharmacokinetic/pharmacodynamic (PK/PD) profiles of tirzepatide at doses and escalation regimens administered in Study GPGA supported further development of tirzepatide for once-weekly (QW) dosing in patients with T2DM.

Phase 2 studies have evaluated the efficacy, tolerability, and safety of tirzepatide in patients with T2DM with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy. Study GPGB, a 26-week Phase 2 study, compared the efficacy, tolerability, and safety of 4 doses (1, 5, and 10 mg [titrated]; and 15 mg [titrated]), of QW tirzepatide compared with QW dulaglutide 1.5 mg and QW placebo in 318 patients with T2DM, with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy. Tirzepatide 5mg, 10mg, and 15-mg significantly lowered glycated hemoglobin (HbA1c) and body weight in a dose-dependent manner, in comparison to placebo. In addition, reductions in HbA1c for the tirzepatide 5-, 10-, and 15-mg doses were greater than with dulaglutide 1.5 mg QW. Similar to adverse events (AEs) observed with the GLP-1 receptor agonist class and the Phase 1 Study GPGA, most of the tirzepatide AEs were gastrointestinal (GI)-related, consisting mainly of nausea, vomiting, and diarrhea, which were mild-to-moderate in intensity and dose-dependent. Serious AEs (SAEs) were balanced across the treatment groups, and none of the groups in the study reported severe hypoglycemia (Frias et al. 2018).

Study GPGF, a 3-month Phase 2 study, was designed to examine the efficacy, safety, and tolerability of QW tirzepatide administered in 3 different titration schemes (longer time intervals between dose escalations and different dose escalations), to reach the highest tirzepatide planned doses of 12 mg and 15 mg, compared with placebo, in patients with T2DM who have inadequate glycemic control with diet and exercise alone or with a stable dose of metformin monotherapy and was designed to support evaluation of optimized dosing regimen(s) in Phase 3.

In addition, the safety, tolerability, and PK/PD of tirzepatide are being evaluated in the ongoing Study GPGC; a Phase 1, 8-week multiple ascending dose (MAD) study in Japanese patients with T2DM. This study involves a comparison of 3 once-weekly SC dose levels of tirzepatide (2.5 mg to 10 mg titration regimen for Cohort 1; 5 mg to 15 mg titration regimen for Cohort 2; and 5 mg fixed dose for Cohort 3), or placebo. The interim safety and tolerability data of Study GPGC supports the use of doses up to 15 mg of tirzepatide in Japanese patients.

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 OAMs administered with tirzepatide may be found in each of their respective package inserts.

4. Objectives and Endpoints

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

Table GPGP.2. Objectives and Endpoints

Objectives	Endpoints
<p>Primary</p> <ul style="list-style-type: none"> To assess safety and tolerability of once-weekly tirzepatide during 52 weeks of treatment as an add-on therapy to SUs, biguanides, TZD, a-GIs, glinides or SGLT-2i's in the treatment of T2DM in terms of incidence of TEAEs. 	<ul style="list-style-type: none"> Incidence of TEAEs
<p>Secondary</p> <ul style="list-style-type: none"> To assess safety and tolerability of once-weekly tirzepatide during 52 weeks of treatment as an add-on therapy to SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's in the treatment of T2DM. To assess the efficacy of once-weekly tirzepatide as an add-on therapy to SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's in the treatment of T2DM at 52 weeks. 	<ul style="list-style-type: none"> Early discontinuations of investigational product due to AEs Adjudicated all deaths and nonfatal major CV events Adjudicated pancreatic AEs Serum calcitonin Incidence of allergic and hypersensitivity reactions Incidence of injection site reactions Incidence of treatment-emergent ADA to tirzepatide The change in systolic and diastolic blood pressure, and heart rate from baseline Occurrence of hypoglycemic episodes Time to initiation of rescue therapy for severe persistent hyperglycemia Mean change in HbA1c Proportion of patients who achieve HbA1c <7%, ≤6.5%, and <5.7% Mean change in FSG Mean change in daily average 7-point SMBG profiles Mean change in body weight Proportion of patients who achieve weight loss of ≥5%, ≥10%, and ≥15% from baseline Mean change in fasting insulin Mean change in fasting C-peptide Mean change in HOMA-2

Objectives and Endpoints

Abbreviations: a-GIs = alpha-glucosidase inhibitors; ADA = anti-drug antibodies; AE = adverse event; CV = cardiovascular; FSG = fasting serum glucose; HbA1c = glycated hemoglobin; HOMA-2 = Updated Homeostasis Model Assessment; SGLT-2i's = sodium-glucose cotransporter type 2 inhibitors; SMBG = self-monitored blood glucose; SUs = sulfonylureas; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event; TZD = thiazolidinedione.

5. Study Design

5.1. Overall Design

Study GPGP is a multicenter, randomized, Phase 3, long-term, add-on treatment study which will assess the safety and efficacy of tirzepatide (5, 10, or 15 mg), in patients with T2DM taking therapeutic doses of various OAMs; SUs, biguanides, a-GIs, TZD, glinides, or SGLT-2i's. Approximately 441 patients who have been taking SUs (126 patients), or biguanides, TZD, a-GIs, glinides, or SGLT-2i (63 patients each) monotherapy will be randomized.

Study GPGP will consist of 4 periods (see [Figure GPGP.1](#)):

- 2-week screening period
- 2-week lead-in period
- 52-week treatment period
- 4-week safety follow-up period

Screening procedures and patient training (disease monitoring and management procedures, study diaries, and study procedures) will be performed at Visits 1 and 2 (screening and lead-in periods). 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.

At Visit 2, the screening laboratory results will be reviewed. For those patients meeting all other eligibility requirements, a dilated fundoscopic examination performed by an ophthalmologist or optometrist, must be completed between Visit 2 and Visit 3 to ensure patients with proliferative diabetic retinopathy, diabetic maculopathy, or non-proliferative diabetic retinopathy that requires acute treatment, are identified and excluded.

At Visit 3, patients will perform all required baseline study procedures (including the collection of all baseline laboratory measures) prior to randomization and prior to taking the first dose of investigational product. Patients will be randomized in a 1:1:1 ratio (tirzepatide 5 mg, 10 mg, and 15 mg). Following randomization, the patient will inject the first dose of investigational product at the study site, according to the dose escalation regimen. The date and time of the first dose of investigational product should be recorded on the electronic case report form (eCRF). Beginning at randomization, all patients will receive investigational product according to the randomized treatment arm for the duration of the 52-week treatment period. Patients should be maintained on stable doses of their OAM, unless dose modifications are required in the event of hypoglycemia (See Section [7.4.2.1](#)). A safety follow-up visit will occur approximately 4 weeks following the last dose of the investigational product.

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 tirzepatide 5-mg arm. For the 10-mg arm, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 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 arm, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 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.

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 (Section 7.7).

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

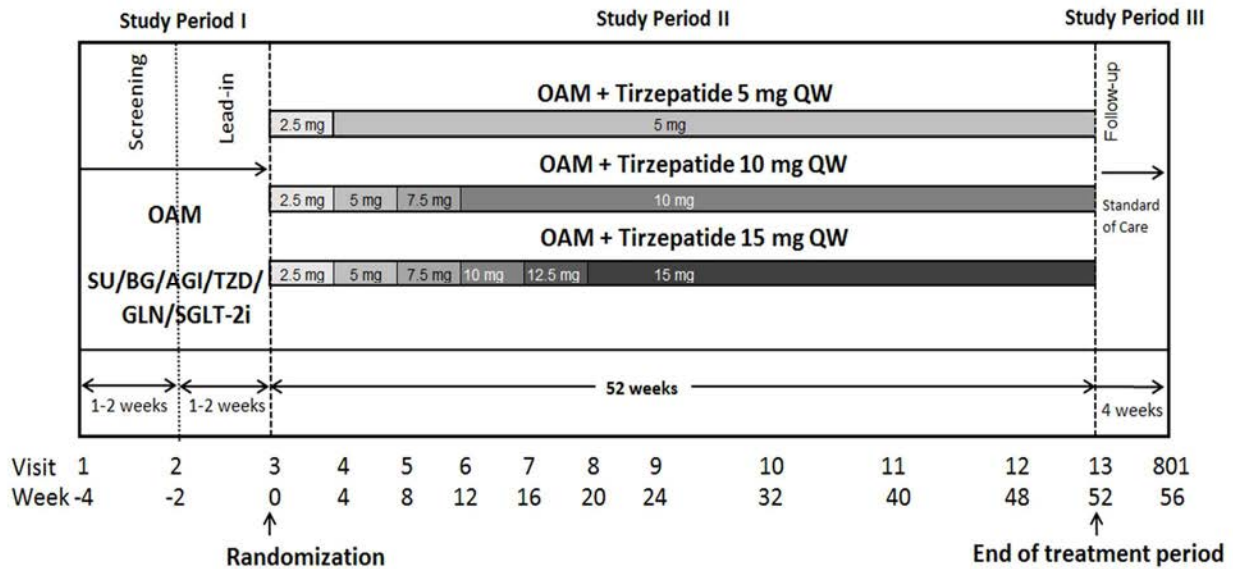
Antihyperglycemic medications other than investigational product are not allowed at any time during the study, except as allowed for rescue therapy, after early investigational product discontinuation or short term insulin use. No changes to background therapy can be made from Visit 1 to Visit 3 with the exception of rescue therapy. 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. Rescue therapy with antihyperglycemic medications, including insulins, will be allowed in certain situations after randomization due to severe, persistent hyperglycemia. In this case, GLP-1 receptor agonists and DPP-4 inhibitors are not allowed as rescue therapies.

After early discontinuation of study treatment, any antihyperglycemic medications, except for GLP-1 receptor agonists may be allowed. Short-term insulin use for up to 14 days is allowed for certain clinical situations (eg, 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.

Study governance considerations are described in detail in [Appendix 3](#).

[Figure GPGP.1](#) illustrates the study design.



Abbreviations: AGI = alpha-glucosidase inhibitor; BG = biguanide; GLN = glinide; OAM = oral antihyperglycemic medication; QW = once weekly; SGLT-2i = sodium-glucose cotransporter type 2 inhibitor, SU = sulfonylurea, TZD = thiazolidinedione.
 Note: All doses will be administered QW subcutaneously using single-use pens. Patients who have been taking each OAM monotherapy will be randomized to tirzepatide (5-, 10-, or 15-mg arm).

Figure GPGP.1. Illustration of study design for Clinical Protocol I8F-JE-GPGP.

5.2. Number of Participants

Because the primary objective is to assess the safety of long-term treatment of tirzepatide and no formal hypothesis testing on the efficacy measures are planned, statistically derived power calculations were not considered for the determination of sample size. The sample size of the study was based on the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1, 2012). The guideline requires long-term safety data of 1 year of treatment with combination therapy using other antihyperglycemic medications. At least 100 patients treated for 1 year in combination with SUs and at least 50 patients in combination with each of the other agents are required. By taking into account the overall drop-out rate of approximately 20%, 126 patients for the combination with SUs and 63 patients for the combination with each of the other agents are planned to be randomized; therefore, a total of 441 patients are planned to be randomized.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This study has been primarily designed to assess the safety of long-term treatment of QW tirzepatide as an add-on therapy for T2DM in patients who have inadequate glycemic control with monotherapy of OAM.

Study treatment will continue for up to 52 weeks to collect 1 year of safety data in combination with monotherapy of OAM. Sulfonylureas, biguanides, TZD, a-GIs, glinides, or SGLT-2i's have been chosen as combination therapy because they have a different mechanism of action from tirzepatide and are expected to be combined with tirzepatide in the clinical setting of T2DM in Japan. The investigators will be instructed to maintain patients on stable doses of their OAM (SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's) during the study. However, OAM dose modifications may be required in the event of hypoglycemia (refer to Section 7.4).

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 T2DM patients in Phase 1 and 2 studies. Dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5 mg increments every 4 weeks would permit adequate 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-, 10-, and 15-mg doses of tirzepatide.

Based on interim data in Study GPGC, there were no clinically meaningful difference in the PK, PD, and safety profile between Japanese patients and non-Japanese patients. Hence, the doses and associated escalation schemes chosen for this Phase 3 study GPGP are the same as that chosen for global studies.

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. Subjects who do not qualify based upon Visit 1 laboratory measurements will have an opportunity to have 1 additional screening visit with repeat screening laboratory tests.

Type of Patient and Disease Characteristics

- [1] Have been diagnosed with T2DM based on the World Health Organization classification before the screening visit (Visit 1)

Patient Characteristics

- [2] Have body mass index (BMI) of ≥ 23 kg/m² at Visit 1
- [3] Have been taking SUs (glibenclamide, gliclazide, glimepiride), biguanides, TZD, a-GIs, glinides, or SGLT-2i monotherapy for at least 3 months before Visit 1 and have been on the following dose for at least 8 weeks before Visit 1 (OAM daily doses are provided in [Appendix 4](#))
- [4] Have HbA1c $\geq 7.0\%$ to $< 11.0\%$, as determined by the central laboratory at Visit 1
- [5] Are of stable weight ($\pm 5\%$) during 3 months preceding Visit 1; and agree to not initiate an intensive diet and/or exercise program during the study with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment
- [6] 20 years or older at the time of signing informed consent
- [6a] Male patients (see [Appendix 7](#) for more details):

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

- [6b] Female patients:

Female patients not of childbearing potential due to surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation) congenital anomaly (ie, Müllerian 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 of amenorrhea with follicle-stimulating hormone (FSH) and estradiol levels consistent with a postmenopausal state (FSH \geq 40 mIU/mL and estradiol <30 pg/mL).

Female patients of child-bearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must:

- test negative for pregnancy at Visit 1 based on a serum pregnancy test

AND

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

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

- a) perform 7-point self-monitored blood glucose (SMBG) testing
- b) learn how to self-inject treatment, 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 investigational product; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the investigational product)
- c) are willing and able to inject investigational product QW
- d) maintain a study diary, as required, for this protocol
- e) Have a sufficient understanding of the primary language of the country such that they will be able to complete the patient questionnaires

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

6.2. Exclusion Criteria

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

Medical Conditions

[9] Have type 1 diabetes mellitus

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

[11] Have a history of

- proliferative diabetic retinopathy

or

- diabetic maculopathy

or

- nonproliferative diabetic retinopathy that requires acute treatment

(a dilated fundoscopic exam, performed by an ophthalmologist or optometrist between Visit 2 and Visit 3, is required to confirm eligibility)

- [12] Have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1
- [13] Have had 1 or more episodes of ketoacidosis or hyperosmolar state/coma requiring hospitalization within the 6 months prior to Visit 1
- [14] Have a known clinically significant gastric emptying abnormality (eg, severe diabetic gastroparesis or gastric outlet obstruction), have undergone or plan to have during the course of the study: gastric bypass (bariatric) surgery, or restrictive bariatric surgery (eg, Lap-Band[®]), or chronically take drugs that directly affect GI motility
- [15] Have any of the following cardiovascular conditions within 2 months prior to Visit 1: acute myocardial infarction, cerebrovascular accident (stroke), or hospitalization due to heart failure
- [16] Have a history of New York Heart Association Functional Classification IV congestive heart failure
- [17] 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 to participate only if their ALT level is ≤3.0 times the upper limit of normal (ULN) for the reference range
- [18] Have an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² (<45 mL/min/1.73 m² for patients who take biguanides and SGLT-2i's), calculated by Chronic Kidney Disease-Epidemiology (CKD-EPI) as determined by central laboratory at Visit 1
- [19] Have evidence of a significant, uncontrolled endocrine abnormality (eg, thyrotoxicosis or adrenal crises), in the opinion of the investigator
- [20] Have family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN-2)
- [21] Have a serum calcitonin level of ≥35 ng/L at Visit 1
- [22] Have evidence of a significant, active autoimmune abnormality (eg, 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

- [23] Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant
- [24] 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
- [25] Have a history of any other condition (such as known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, may preclude the patient from following and completing the protocol
- [26] Have any hematological condition that may interfere with HbA1c measurement (eg, hemolytic anemias, sickle-cell disease)

Prior/Concomitant Therapy

- [27] Have history of use of any injectable therapy for T2DM treatment (GLP-1 receptor agonists and insulin) within 3 months prior to Visit 1
- [28] Are receiving chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, or inhaled preparations) or have received such therapy within 1 month prior to Visit 1 and/or between study entry (Visits 1) and randomization (Visit 3)
- [29] Have been treated with drugs that promote weight loss (eg, Sanorex[®] [mazindol]) within 3 months prior to Visit 1 and/or between study entry (Visit 1) and randomization (Visit 3)

Prior/Concurrent Clinical Trial Experience

- [30] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational drug or device or off-label use of a drug or device (other than the investigational product/device used in this study), or are concurrently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- [31] Have participated, within the last 30 days, in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 30 days or 5 half-lives (whichever is longer) should have passed
- [32] Have previously completed or withdrawn from this study or any other study investigating tirzepatide

Other Exclusions

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

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 6.1), 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

Subjects who do not qualify, based upon Visit 1 laboratory measurements, will have an opportunity to have 1 additional screening visit with repeat screening laboratory tests.

7. Treatments

7.1. Treatments Administered

In this study, patients will receive treatment with 1 of the 3 doses of tirzepatide (5, 10, 15 mg), each administered QW as SC injection(s) in patients with T2DM. Patients should continue taking their usual OAM (SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's) dose and regimen throughout the active treatment period, unless dose modifications are required in the event of hypoglycemia (refer to Section 7.4).

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

Table GPGP.3. Tirzepatide Treatment Regimens

Name of Drug	Dosage	Frequency	Drug Formulation	Route of Administration
Investigational Compound				
Tirzepatide	5 mg ^a	QW	Single-use pen	SC
	10 mg ^a	QW	Single-use pen	SC
	15 mg ^a	QW	Single-use pen	SC

Abbreviations: QW = once weekly; SC = subcutaneous.

^a 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 tirzepatide 5-mg arm. For the 10-mg arm, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 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 arm, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 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.

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

- explaining the correct use of the investigational product to the patient
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection, as well as records of interruptions in investigational product administration
- instructing the patient to discard all used single-use pens for tirzepatide in a closeable, puncture-resistant container and dispose according to local regulations

7.1.1. Packaging and Labeling

Tirzepatide will be supplied by Lilly in single-use pens which will be packaged in cartons to be dispensed. Clinical study materials will be labeled according to the country's regulatory requirements.

7.1.2. Medical Devices

The manufactured medical device provided for use in the study is the tirzepatide single-use pen.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to 1 of the study treatment arms at Visit 3. Assignment to treatment arms will be determined by a computer-generated random sequence using an interactive web response system (IWRS). Patients will be randomized in a 1:1:1 ratio to receive 5 mg tirzepatide, 10 mg tirzepatide, or 15 mg tirzepatide.

7.2.1. Selection and Timing of Doses

Assignment to 1 of the 3 tirzepatide doses will occur at randomization. There are no restrictions on the time of day each weekly dose is given, but it is advisable to administer SC injections on the same day and same time each week. The actual date and time of all dose administrations will be recorded in the subject's eCRF. If a dose of investigational product, including tirzepatide is missed, the patient should take it as soon as possible, unless it is within 72 hours of the next dose, in which case that dose should be skipped and the next dose taken at the appropriate time.

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

7.4.1. Tirzepatide

Tirzepatide will be increased based on the schedule (refer to [Figure GPGP.1](#)) De-escalation will be allowed ONLY ONCE, IF patients experience intolerable GI AEs which persist after all the measures mentioned in Section 7.4.1.1 have been implemented (refer to Section 7.4.1.1 for details).

7.4.1.1. Management of Patients with Gastrointestinal Symptoms

In the Phase 2 program, the most commonly reported treatment-emergent adverse events (TEAEs) for patients receiving tirzepatide were nausea, vomiting, and diarrhea. The tirzepatide dose escalation scheme has been designed to improve GI tolerability. The escalation period is considered to be 24 weeks, which allows 20 weeks to escalate to 15 mg and an additional 4 weeks to reach steady state. During the dose-escalation period, every effort should be made by the investigator to be able to escalate and maintain patients on the corresponding investigational product dosage.

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

- Advise patients to eat smaller meals (eg, splitting 3 daily meals into 4 or more smaller meals) and to stop eating when they feel full.
- Prescribe symptomatic medication (eg, anti-emetic or anti-diarrheal 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. The data related to temporary interruption of study treatment should be documented in source documents and entered into the eCRF.

- After the interruption, restart at the same dose with the patient taking medication to alleviate his/her GI symptoms (Section 8.1.2).

If intolerable GI symptoms or events persist despite the above measures, the investigator may decide to continue treatment at a lower, tolerated maintenance dose of tirzepatide (5 mg or 10 mg).

- Patients at 5 mg or lower will be discontinued from tirzepatide.
- Patients at 7.5 mg or 10 mg will decrease the dose to 5 mg.
- Patients at 12.5 mg or 15 mg will decrease the dose to 10 mg.

If de-escalation of the tirzepatide dose is necessary, the investigator will use the IWRS to receive the appropriate tirzepatide dispensing information. If de-escalation is needed between scheduled visits, the IWRS will have unscheduled visits (eg, Visit 13a) dedicated to provide dispensing information for patients whose dose has been de-escalated. Those patients who have their doses de-escalated, will not be escalated again. The dose can be de-escalated only once. After that, the patients will have to discontinue tirzepatide if intolerable GI AEs persist.

7.4.2. Oral Antihyperglycemic Medications

7.4.2.1. Dose Adjustments in the Event of Hypoglycemia

Throughout the study, the investigator should maintain patients on stable doses of their OAM (SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's). However, only if a patient requires a reduction of the dosage of his/her OAM due to occurrence of hypoglycemia without interrupting study treatment, the dose of OAMs may be reduced by the investigator's decision.

In this case, the reason and details of the dose reduction will be recorded on source documents and will be entered in the appropriate section of the eCRF.

7.4.2.2. Dose Adjustments in the Event of Severe, Persistent Hyperglycemia

Throughout the study, the investigator should maintain patients on stable doses of their OAM (SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's). Therefore, increasing the dose of the concomitant OAM is not permitted. When a patient experiences hyperglycemia, rescue therapy with basal or rapid acting insulins, may be medically indicated (see [Appendix 8](#)). The investigator should first determine whether there are any possible causes for the patient's hyperglycemia (eg, excess food consumption, a change in dietary habits, illness, pharmacological treatments, or poor compliance with OAMs or study treatment). If any possible causes are identified, the investigator should address these issues first and encourage the patient to comply with any necessary behavioral changes to prevent hyperglycemia before prescribing a rescue therapy.

Patients on allowed rescue therapy for hyperglycemia will remain in the study (unless a discontinuation criterion of study was met) and will continue to administer investigational product.

7.5. Preparation/Handling/Storage/Accountability

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

- Confirming that 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.
- Ensuring that 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 investigational product in a locked and secure environment. Please refer to the investigational product label for specific storage conditions. Patients will receive insulated bags with cooling gel packs for use in transporting the investigational product from the site to home.

Temperature logs must be maintained to verify correct storage conditions at the investigator site, throughout the study. Patients should be instructed to store the investigational product in their refrigerators, but are not required to maintain temperature logs.

Study site staff must regularly assess whether the patient is correctly administering the assigned investigational product and storing the investigational product according to the provided instructions.

7.6. Treatment Compliance

Investigational product compliance will be determined by the following:

- Investigational product 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 investigational product and/or empty cartons at the next visit to the study site for the purpose of performing drug accountability.

In the 3 tirzepatide treatment arms, treatment compliance overall is defined as taking at least 75% of the total required doses of investigational product. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

In addition to the assessment of a patient's compliance with the investigational product 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, compliance with the concomitant

antihyperglycemic medication regimen, completion of study diaries, the results of home blood glucose (BG) monitoring, and any other parameters the investigator considers necessary.

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

7.7. Concomitant Therapy

Patients will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments. Prohibited medications include following;

- Any antihyperglycemic medications, except for concomitant OAMs
- Any medications that promote weight loss (eg, Sanorex[®] [mazindol])
- Any chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, or inhaled preparations)

Short-term insulin use is allowed for certain clinical situations (eg, elective surgery, during hospitalization, hyperosmolar states). Rescue therapy with antihyperglycemic medications including insulins will be allowed in certain situations after randomization due to severe, persistent hyperglycemia (see [Appendix 8](#)). In this case, GLP-1 receptor agonists and DPP-4 inhibitors are not allowed as rescue therapies. After early discontinuation of study treatment, any antihyperglycemic medications, except for GLP-1 receptor agonists may be allowed. 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.

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) must be documented, and the name of the drug and the date(s) of administration must be recorded in the patient's diary and on the "Concomitant Medications" section of the eCRF.

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

Nonstudy medications taken by patients who are screened, but not randomized, will not be reported to Lilly, unless an SAE occurs.

7.8. Treatment after the End of the Study

7.8.1. *Treatment after Study Completion*

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

7.8.2. *Special Treatment Considerations*

An additional therapeutic intervention should be considered for patients with persistent hyperglycemia, as described in [Appendix 8](#).

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 the eCRF.

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

- ALT or aspartate aminotransferase (AST) >8X ULN
 - ALT or AST >5X ULN for more than 2 weeks
 - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio (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 investigational product would not be medically appropriate (see Section 8.1.3)
 - Acute or chronic pancreatitis
 - If a patient is diagnosed with medullary thyroid cancer (MTC) after randomization
 - 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 investigational product-related hypersensitivity reaction

- Any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent investigational product discontinuation is the appropriate measure to be taken
- If female patient becomes pregnant
- If a patient is diagnosed with type 1 diabetes mellitus (T1DM)
- Temporary discontinuation of concomitant OAM ≥ 14 days

Patients who stop the investigational product permanently may receive another antihyperglycemic medication, except for GLP-1 receptor agonists, and will continue participating in the trial, according to the protocol, to collect all planned safety and efficacy measurements.

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

8.1.2. Temporary Interruption of Study Treatment

Temporary discontinuation of concomitant antihyperglycemic medications <14 consecutive days is allowed for certain clinical situations (eg, severe dehydration, elective surgery, or need for radiologic exam involving intravenous [IV] iodinated contrast dye). In certain situations after randomization, the investigator may need to temporarily interrupt investigational product. Every effort should be made by the investigator to maintain patients on investigational product and to restart investigational product after any temporary interruption, as soon as it is safe to do so.

- If the number of consecutive 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 consecutive doses missed is ≥ 3 , then the treatment should be restarted at 5 mg, irrespective of the dose the patient was receiving before the interruption and subsequently escalated as required by protocol (See Manual of Operations for further details).

If investigational product 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 investigational product interruption is due to intolerable persistent GI AE (eg, nausea, vomiting, or diarrhea), the patients should be treated, as suggested in Section 7.4.1.1. The data related to temporary interruption of study treatment will be 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 clinical research physician (CRP)/clinical research scientist (CRS) agree it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor CRP/CRS 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 investigational product
- adherence to visit schedule
- missing assessments
- investigational product discontinuation due to AE (Section 8.1.1)
- development of comorbidities
- 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
- investigator decision
 - the investigator decides that the patient should be discontinued from the study
- patient decision
 - the patient requests to be withdrawn from the study

Patients who agree to provide information relevant to any trial 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 will discontinue investigational product and will have end-of-study procedures (early termination [ET] visit) performed as shown in the Schedule of Activities (Section 2). During the ET visit, the patient will be prescribed an appropriate antihyperglycemic medication 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 AE 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. Efficacy Assessments

The following efficacy parameters at Week 52 will be assessed in this study

- Mean change in HbA1c
- Proportion of patients who achieve HbA1c <7%, ≤6.5%, and <5.7%
- Mean change in fasting serum glucose (FSG)
- Mean change in daily average 7-point SMBG profiles
- Mean change in body weight
- Proportion of patients who achieve weight loss of ≥5%, ≥10%, and ≥15% from baseline
- Mean change in fasting insulin
- Mean change in fasting C-peptide
- Mean change in Updated Homeostasis Model Assessment (HOMA-2)

9.1.1.1. 7-Point Self-Monitored Blood Glucose Profiles

Patients will be asked to perform a 7-point SMBG profile on 2 days during the 2 weeks before Visits 3 and 13 (refer to the Schedule of Activities in Section 2). Patients will test and record SMBG concentrations in their study diaries before each meal (breakfast, lunch, and dinner) and approximately 2 hours after the start of each meal, and at bedtime. The 7-point SMBG profiles will be entered into eCRF and analyzed.

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

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

After the informed consent form (ICF) is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study procedure, investigational product via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to investigational product 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 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 AE should have additional data collected using the eCRF (Section 9.4.5.1).

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product(s) 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 in the study diary regarding episodes of hypoglycemia, starting from Visit 1 until the last study visit. For that purpose, patients will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate

information for each episode of hypoglycemia in the study according to the Schedule of Activities (Section 2).

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia: (the BG values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips) in accordance with the 2017 American Diabetes Association position statement on glycemic targets (American Diabetes Association 2017):

Glucose Alert Value (Level 1):

- **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 BG 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 BG ≤ 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 BG ≤ 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 BG level of < 54 mg/dL (< 3.0 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG < 54 mg/dL (< 3.0 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured BG < 54 mg/dL (< 3.0 mmol/L).

Severe hypoglycemia (Level 3):

- **Severe hypoglycemia** is defined as an 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. Plasma 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.

Nocturnal hypoglycemia:

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

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

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

9.2.2.2. Severe, Persistent Hyperglycemia

Add-on glycemic rescue therapy will be allowed for patients who meet any of the following prespecified criteria for severe, persistent hyperglycemia. In this case, the investigator determines if a new intervention is warranted, after noncompliance with the assigned therapeutic regimen is ruled out as the reason for hyperglycemia. Patients should continue administering assigned investigational products. The criteria are as follows:

- a) Blood glucose concentration measured by weekly 1-point SMBG before breakfast >270 mg/dL (>15.0 mmol/L) over at least a consecutive 2-week period any time during the first 8 weeks post-randomization;

OR

- b) Blood glucose concentration measured by weekly 1-point SMBG before breakfast >240 mg/dL (>13.3 mmol/L) over at least a consecutive 2-week period at any time 9-16 weeks post-randomization;

OR

- c) Blood glucose concentration measured by weekly 1-point SMBG before breakfast >200 mg/dL (>11.1 mmol/L) over a consecutive 2-week period at any time beyond the first 16 weeks post-randomization.

OR

- d) HbA1c $\geq 8.5\%$ (69 mmol/mol) 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 $<0.3\%$.

Investigators should first confirm that the patient is fully compliant with the assigned therapeutic regimen and that he/she does not have an acute condition that is raising his/her BG. For patients who meet criteria for severe persistent hyperglycemia, the investigator will decide, in consultation with the patient, on an appropriate antihyperglycemic medication (rescue therapy). Investigators should follow national standards of care for diabetes management in respective participating countries or the American Diabetes Association/European Association for the Study of Diabetes guidance (Inzucchi et al. 2015). Antihyperglycemic medications including insulins will be allowed as the rescue intervention. In this case, GLP-1 receptor agonists and DPP-4 inhibitors are not allowed as rescue therapies. Patients who receive a new intervention should also continue administering investigational products for the remaining period in the trial.

9.2.2.3. Pancreatitis

Acute pancreatitis is defined as an AE of interest in all trials with tirzepatide, including this trial. Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve

peripancreatic tissues and/or remote organ systems (Banks and Freeman 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half the cases [Banks and Freeman 2006; Koizumi et al. 2006]; the pain is often associated with nausea and vomiting)
- serum amylase (total and/or pancreatic) and/or lipase $\geq 3X$ 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 tirzepatide, but will continue in the study on another antihyperglycemic medication. 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 AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to investigational products.

Each patient will have measurements of pancreatic amylase and lipase (assessed at the central laboratory) as shown on the Schedule of Activities (Section 2) to assess the effects of the investigational doses of tirzepatide on pancreatic enzyme levels. Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck et al. 2017; Steinberg et al. 2017a; Steinberg et al. 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic lipase $\geq 3X$ 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 Events Classification (CEC) committee. In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from patients with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed eCRF page by study site. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

9.2.2.4. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or MEN-2 will be excluded from the study. The assessment of thyroid safety during the trial 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/mL 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/mL and increases by $\geq 50\%$, 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/mL, tirzepatide should be restarted when it is safe to do so.

9.2.2.5. Major Adverse Cardiovascular Events

Deaths and nonfatal cardiovascular (CV) AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. The nonfatal CV AEs to be adjudicated include: myocardial infarction (MI); 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. Relevant data from patients who experienced death or nonfatal CV AEs will be entered into a specifically designed eCRF page by study site.

9.2.2.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders

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

9.2.2.7. Hypersensitivity Events

All allergic or hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, 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 investigational product(s) via an eCRF created for this purpose. Additional samples should also be collected, as outlined in Section 9.4.4. Investigational product(s) should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to investigational product. Investigational product may be restarted when/if it is safe to do so, in the opinion of the investigator. If the investigational product is permanently discontinued, the patient will receive another antihyperglycemic medication, judged by the investigator to be

appropriate, based on the patient's clinical status, and will continue in the trial to collect all planned efficacy and safety measurements.

9.2.2.7.1. Injection Site Reactions

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

9.2.2.7.2. Anti-Drug Antibodies

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

9.2.2.8. Diabetic Retinopathy Complications

Dilated retinal fundoscopic examination will be performed by an 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 exam will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy.

A follow-up, dilated fundoscopic examination should be performed, when clinically indicated by any AE suspected of worsening retinopathy, and the findings should be recorded on the retinopathy eCRF.

9.2.2.9. Hepatobiliary Disorders

All events of 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 9.4.5.1 and Appendix 5.

9.2.2.10. Severe Gastrointestinal Adverse Events

Tirzepatide may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs, as well as antiemetic/antidiarrheal use, will be collected in the eCRF. For detailed information concerning the management of GI AEs, please refer to Section 7.4.1.1.

9.2.2.11. Acute Renal Events

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

9.2.2.12. Metabolic Acidosis, Including Diabetic Ketoacidosis

Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been reported rarely in patients with T2DM. Patients who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis, regardless of presenting blood glucose levels, as ketoacidosis may be present even if blood glucose levels are <250 mg/dL. If ketoacidosis is suspected, SGLT-2i's should be discontinued (if used), patients 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 decreased renal function. Routine bicarbonate assessment will be performed during the course of the study. If lactic acidosis is suspected, metformin should temporarily be discontinued (if used) until the resolution of the event.

9.2.2.13. Amputation/Peripheral Revascularization

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

9.2.2.14. Major Depressive Disorder/Suicidal Ideation

The prevalence of depressive symptoms and disorders is increased in patients with T1DM or T2DM (American Diabetes Association 2017). Any AE of major depressive disorder or suicidal ideation should be reported.

9.2.2.15. Individual Clinical Events Adjudication

- All AEs of acute or chronic pancreatitis, as well as cases of pancreatic hyperenzymemia only that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis will be adjudicated by an independent committee of expert physicians.
- 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: MI; 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.

9.2.3. *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 or drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

Investigational product overdose (more than the specified number of injections) will be reported as an AE. In the event of overdose, refer to the IB for tirzepatide.

9.4. Safety

9.4.1. *Electrocardiograms*

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study-specific recommendations included in the 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, except for the screening ECG, which will be performed locally. 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 (systolic blood pressure, diastolic blood pressure, and heart rate), height, weight, and waist circumference should be conducted according to the Schedule of Activities (Section 2) and following the study-specific recommendations included in the Manual of Operations for the study.

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 the 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).

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

9.4.4. Immunogenicity Assessments

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

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against tirzepatide. To interpret the results of immunogenicity, a PK sample will be collected at the same time points as the immunogenicity sample. All samples for immunogenicity should be taken predose, when applicable and possible. In the event of drug hypersensitivity reactions (immediate or nonimmediate), additional samples will be collected (including ADAs, PK, and, exploratory immune safety samples), as close to the onset of the event as possible, at the resolution of the event, and 30 days following the onset of the event. Instructions for the collection and handling of blood samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of the tirzepatide at a laboratory approved by the Sponsor. Samples collected at Visit 801 will assess immunogenicity at washout of tirzepatide (5 half-lives post-end of treatment).

Treatment-emergent ADAs are defined in Section 10.3.5.

Samples with tirzepatide ADAs 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.

9.4.5.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT $\geq 3X$ ULN, ALP $\geq 2X$ ULN, or elevated TBL $\geq 2X$ ULN, liver testing (Appendix 5) 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 $\geq 5X$ ULN on 2 or more consecutive blood tests
- elevated serum TBL to $\geq 2X$ ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to $\geq 2X$ 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

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

The date and time of SC injection 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 requisition form.

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.

9.6. Pharmacodynamics

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

Samples collected to measure PD will be identified by the patient number (coded) and retained at a facility selected by Lilly or its designee for a maximum of 15 years following last patient visit for the study at a facility selected by Lilly or its designee.

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 T2DM. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards (IRBs) impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of tirzepatide or after tirzepatide becomes 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 nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2), where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to investigational products, pathways associated with T2DM, mechanism of action of investigational products, 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 becomes commercially available. Any samples remaining after 15 years will be destroyed.

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 his/her 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 his/her fasting condition.

9.9.1. *European Quality of Life – 5 Dimension – 5 Level (EQ-5D-5L)*

Generic HR-QoL will be assessed using the EQ-5D-5L (EuroQoL 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 healthcare, 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 170 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 2015).

9.9.2. *Diabetes Treatment Satisfaction Questionnaire (DTSQ)*

The status (s) and change (c) versions of the Diabetes Treatment Satisfaction Questionnaire (DTSQ) will be used during the study to assess the patients' satisfaction with his/her 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 DTSQc response options differ from those of the DTSQs to produce measures of relative change rather than absolute satisfaction.

10. Statistical Considerations

10.1. Sample Size Determination

Because the primary objective is to assess the safety of long-term treatment of tirzepatide and no formal hypothesis testing on the efficacy measures is planned, statistically derived power calculations were not considered for the determination of sample size. The sample size of the study was based on the requirement of the Japanese guideline for oral hypoglycemic agents; Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1. 2012). The guideline requires long-term safety data of 1 year of treatment with combination therapy using other antihyperglycemic medications. At least 100 patients treated for 1 year in combination with an SU, and at least 50 patients in combination with each of the other agents (SUs, biguanides, TZD, a-GIs, glinides, or SGLT-2i's) is required. By taking into account the overall drop-out rate of approximately 20%, 126 patients receiving combination treatment with an SU and 63 patients receiving combination treatment with other agents are planned to be randomized, resulting in a total of 441 patients that are planned to be randomized.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
Randomized	All patients who are randomly assigned a treatment arm
Modified intention-to-treat (mITT)	All randomly assigned participants who are exposed to at least 1 dose of investigational product
Efficacy analysis set (EAS)	Data obtained during Study Period II from mITT, excluding data after initiating rescue antihyperglycemic medication or stopping investigational product (last dose date + 7 days). In the event of a treatment error, participants will be analyzed according to the treatment to which they were randomized.
Safety analysis set (SAS)	Data obtained during both Study Period II and III from mITT, regardless of adherence to investigational product 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 SAP or the clinical study report (CSR). Additional exploratory data analyses may be conducted, as deemed appropriate.

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

The efficacy measure is mean change in HbA1c from baseline to 52 week visit. The “efficacy” estimand represents efficacy prior to discontinuation of investigational product without confounding effects of rescue therapy for persistent severe hyperglycemia.

The efficacy assessment, guided by the “treatment-regimen” estimand will be conducted as supplemental analyses. The “treatment-regimen” estimand represents the efficacy irrespective of adherence to investigational product or initiation of rescue antihyperglycemic medications, which will be conducted using mITT set. Because no formal hypothesis testing on the efficacy measures is planned, no multiplicity adjustments will be made for conducting 2 efficacy assessments. Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses, irrespective of adherence to investigational product or initiation of antihyperglycemic rescue medication. Thus, safety analysis will be conducted using safety analysis set (SAS). A selected safety analyses (eg, hypoglycemia) will be conducted after excluding data while on rescue therapy or data after starting another permitted antihyperglycemic medication following permanent discontinuation of investigational product. Unless specified otherwise, summary statistics will be presented by treatment groups (3 different tirzepatide doses) and overall within each of the combination therapies.

Summary statistics for continuous measures will include sample size, mean, standard deviation [SD], median, minimum, and maximum. Dose-response relationship will be assessed, if appropriate.

The Kaplan-Meier method will be used for estimation of cumulative event-free survival rates over time for each treatment.

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. Summary statistics for discrete count measures will include sample size, mean, SD, median, minimum, and maximum. Dose response relationship will be assessed if appropriate.

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

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

Frequency counts and percentages of all patients screened, randomized, and receiving at least 1 dose of investigational product will be presented by treatment groups. A listing of randomized patients not receiving investigational product will be provided. Of the patients in the mITT set, frequency counts and percentages of patients completing the study or prematurely discontinuing the study (including reason for premature discontinuation) will be presented by treatment groups.

A Kaplan-Meier analysis of time from randomization to premature discontinuation from study by treatment group will be provided. Patients with important protocol deviations will be listed.

A detailed description of patient disposition will be provided at the end of the study.

10.3.2.2. Patient Characteristics

Demographic, medical history, and preexisting conditions will be descriptively summarized by treatment groups, using the mITT set.

10.3.2.3. Concomitant Therapy

Concomitant medications, including previous therapy for diabetes, will be summarized by Anatomical Therapeutic Chemical classification and treatment groups, using the mITT set. In particular, the time to initiation of rescue therapy for severe, persistent hyperglycemia will be analyzed as an exploratory safety endpoint. Dose modifications of oral antihyperglycemic medications will also be described by treatment groups.

The frequencies and percentages of patients taking concomitant medications before and after allocation (Visit 3) will be summarized. Patient listings for the use of concomitant medications will be provided.

10.3.2.4. Treatment Compliance

Treatment compliance, overall, is defined as taking at least 75% of the total required injections of investigational product. Frequency counts and percentages of patients compliant to investigational product will be summarized by treatment groups and visits using the mITT set.

10.3.3. Efficacy Analyses

The efficacy assessment, guided by the “efficacy” estimand, will use Efficacy Analysis Set (EAS) 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 an MMRM with the following terms: “treatment”, “visit”, and “treatment-by-visit interaction” as fixed effects; and “baseline HbA1c” as a covariate. An unstructured covariance structure will model the relationship of within-patient errors.

The following efficacy measures will be summarized through 52 weeks.

- Mean change in HbA1c
- Proportion of patients who achieve HbA1c <7%, ≤6.5%, and <5.7%
- Mean change in FSG
- Mean change in daily average 7-point SMBG profiles
- Mean change in body weight
- Proportion of patients who achieve weight loss of ≥5%, ≥10%, and ≥15% from baseline
- Mean change in fasting insulin
- Mean change in fasting C-peptide
- Mean change in HOMA-2

The efficacy assessment for selected efficacy measures, guided by the “treatment regimen” estimand, will be based on the mITT population and data irrespective of adherence to

investigational product, initiation of rescue therapy and premature treatment discontinuation. 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, irrespective of adherence to investigational product or initiation of rescue therapy. Thus, safety analysis will be conducted using the SAS. A selected safety analyses (eg, hypoglycemia) will be conducted after excluding data while on rescue therapy or data after starting another permitted antihyperglycemic medication following permanent discontinuation of investigational product.

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, investigational product 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 along with assessment of dose-response relationship.

10.3.4.1. Hypoglycemic Events

Incidence of documented symptomatic hypoglycemia events and severe hypoglycemia in each category (either total or nocturnal) will be summarized by each treatment which will be repeated excluding data following initiation of rescue antihyperglycemic medication.

10.3.4.2. Gastrointestinal Events

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

10.3.4.3. Adjudicated Cardiovascular Events

Listing 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 investigational product, and time from randomization to 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 percentages of patients with treatment-emergent abnormal, high, or low laboratory measures at any time will be summarized. A treatment-emergent abnormal value is defined as a change from normal value at baseline to an abnormal value at any time during the follow-up.

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

A treatment-emergent low result is defined as a change from a value greater than or equal to the

low limit at baseline to a value less than the low limit at any time during Periods II and III. High limit and low limit will be provided in the SAP.

10.3.5. Evaluation of Immunogenicity

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

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

10.3.6. Other Analyses

10.3.6.1. Health Economics

Analyses of actual and change from baseline in 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.

10.3.6.2. Subgroup Analyses

Subgroup analyses of mean change in HbA1c, mean change in body weight, AEs, and hypoglycemic events will be provided by age, gender, baseline BMI group (<25 or ≥ 25 kg/m²), duration of diabetes, and baseline HbA1c ($\leq 8.5\%$, $>8.5\%$) for each of the combination therapies. Additional details will be provided in the SAP.

10.3.7. Interim Analyses

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

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibodies
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.
a-GI	alpha-glucosidase inhibitor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
CEC	Clinical Events Classification
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease-Epidemiology
COA	clinical outcome assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
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.
CRS	clinical research scientist
CSR	clinical study report
CT	computed tomography
CV	cardiovascular
DNA	deoxyribonucleic acid

Term	Definition
DPP-4	dipeptidyl-peptidase-4
DTSQc	Diabetes Treatment Satisfaction Questionnaire change
DTSQs	Diabetes Treatment Satisfaction Questionnaire status
EAS	efficacy analysis set
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture system
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	European Quality of Life – 5 Dimension – 5 Level Questionnaire
ERB	ethical review board
ET	early termination
FBG	fasting blood glucose
FSG	fasting serum glucose
FSH	follicle-stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIPR	gastric inhibitory polypeptide receptor
GLP-1	glucagon like peptide-1
HbA1c	glycated hemoglobin
HOMA-2	Updated Homeostasis Model Assessment
IB	Investigator’s Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
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.
INR	International Normalized Ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

Term	Definition
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group, irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
LC/MS	liquid chromatography/mass spectrometry
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia syndrome type 2
MI	myocardial infarction
mITT	modified intention-to-treat (population)
MMRM	mixed-model for repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
NAFLD	nonalcoholic fatty liver disease
OAM	oral antihyperglycemic medication
OTC	over the counter (medication)
PD	pharmacodynamics
PK	pharmacokinetics
PRO	patient-reported outcome
QW	once weekly administration
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SC	subcutaneous

Term	Definition
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
SGLT-2i	sodium-glucose cotransporter type 2 inhibitor
SMBG	self-monitored blood glucose
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TZD	thiazolidinedione
ULN	upper limit of normal

Appendix 2. Protocol GPGP Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology^a

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

Urinalysis^{a,b}

Albumin
 Creatinine

Nonpharmacogenetic Stored Samples^a

Serum
 EDTA plasma
 P800 plasma

Immunogenicity^j

Anti-tirzepatide antibody

Hepatitis Testing^{a,c}

Endocrine^a

Calcitonin

Pharmacokinetics^j

Tirzepatide plasma levels

Clinical Chemistry^a

Sodium
 Potassium
 Chloride
 Bicarbonate
 Total bilirubin
 Direct bilirubin
 Alkaline phosphatase
 Alanine aminotransferase (ALT/SGPT)
 Aspartate aminotransferase (AST/SGOT)
 Gamma-glutamyl transferase (GGT)
 Blood urea nitrogen (BUN)
 Creatinine
 Creatine kinase (creatinine phosphokinase)^d
 Uric acid
 Calcium
 Albumin

Lipid Panel (fasting)^a

Total cholesterol
 High-density lipoprotein-cholesterol (HDL-C)
 Low-density lipoprotein-cholesterol (LDL-C)^e
 Very-low-density lipoprotein-cholesterol (VLDL-C)
 Triglycerides

Pharmacogenetics Sample^a

Pregnancy test (females only)^{a,f}

Follicle-stimulating hormone (FSH)^g
 Estradiol^g

HbA1c^a

Glucose, fasting^{a,h}

Pancreas (exocrine)^a

Pancreatic-amylase
 Lipase

C-peptide^a

Insulin, fasting^h

eGFR (calculated by CKD-EPI equation)ⁱ

Clinical Laboratory Tests

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; LDL = low-density lipoprotein; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvate transaminase; WBC = white blood cell.

- ^a All tests will be performed or sample stored by the Lilly-designated central laboratory.
- ^b Urinary albumin and creatinine are measured at a central laboratory and the ratio is calculated.
- ^c As needed per hepatic monitoring criteria (refer to [Appendix 5](#)).
- ^d Creatine kinase MB (CK-MB) is to be assayed if creatine kinase result >1000 IU/L.
- ^e LDL is calculated using the Friedwald equation.
- ^f A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only and will be analyzed at a central laboratory. Pregnancy tests may be repeated at any time during the study and analyzed locally at the investigator's discretion. Urine pregnancy tests will be performed by a local laboratory.
- ^g Follicle-stimulating hormone (FSH) test performed at Visit 1 for postmenopausal women at least 45 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months and estradiol levels consistent with a postmenopausal state (FSH \geq 40 mIU/mL and estradiol <30 pg/mL).
- ^h Fasting serum glucose and insulin values will be used to calculate beta-cell function and insulin sensitivity using the Updated Homeostasis Model Assessment (HOMA-2). Fasting serum glucose samples must be obtained after 8 hours or more without eating, drinking (other than water) or performing any significant physical activity.
- ⁱ Estimated glomerular filtration rate will be calculated by the central laboratory at required visits and included in laboratory result reports.
- ^j Assayed by Lilly-designated laboratory.

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/patient's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that his/her 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/patient's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the patients/patient's legal representative's willingness to continue his/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 Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

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

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form

- other relevant documents (eg, 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, cardiology, nephrology, internal medicine, family medicine, general medicine, or any other specialty physician who has experience treating T2DM and clinical research experience in T2DM will participate as investigators in this clinical trial.

Appendix 3.1.6. Protocol Signatures

The Sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his/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 to the best of his/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 their 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.

- Sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (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 evaluate CRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

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 the eCRF 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 eCRF.

Additionally, clinical outcome assessment (COA) data (questionnaires, scales, self-reported diary data, rating scales, etc.) 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 party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive 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-JE-GPGP is described in the Letter of Agreement.

Appendix 4. Protocol GPGP Oral Antihyperglycemic Medication (OAM) Daily Dose

Eligible patients must have been taking monotherapy of sulfonylureas (SUs) (glibenclamide, gliclazide, glimepiride, biguanides, thiazolidinedione [TZD], alpha-glucosidase inhibitors [a-GIs], glinides, or sodium-glucose cotransporter type 2 inhibitor [SGLT-2i's]) monotherapy for at least 3 months before Visit 1 and must have been on the dose for at least 8 weeks before Visit 1 and have an inadequate glycemic control.

OAM	Generic Name	Minimum Maintenance Dose (mg/day)
SUs	glibenclamide	1.25
	gliclazide	40
	glimepiride	1
Biguanides	buformin	100
	metformin	750
a-GIs	acarbose	300
	voglibose	0.6
	miglitol	150
Glinides	nateglinide	270
	mitiglinide	30
	repaglinide	1.5
TZD	pioglitazone	15
SGLT-2i's	ipragliflozin	50
	dapagliflozin	5
	luseogliflozin	2.5
	tofogliflozin	20
	canagliflozin	100
	empagliflozin	10

Abbreviations; a-GIs = alpha-glucosidase inhibitors; SGLT-2i's = sodium glucose transporter 2 inhibitors; SUs = sulfonylureas; TZD = thiazolidinedione.

Appendix 5. 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

Hemoglobin
 Hematocrit
 RBC
 WBC
 Neutrophils, segmented
 Lymphocytes
 Monocytes
 Eosinophils
 Basophils
 Platelets

Hepatic Chemistry^a

Total bilirubin
 Direct bilirubin
 Alkaline phosphatase
 ALT
 AST
 GGT
 CPK

Haptoglobin^a

Hepatic Coagulation^a

Prothrombin Time
 Prothrombin Time, INR

Hepatic Serologies^{a,b}

Hepatitis A antibody, total
 Hepatitis A antibody, IgM
 Hepatitis B surface antigen
 Hepatitis B surface antibody
 Hepatitis B Core antibody
 Hepatitis C antibody
 Hepatitis E antibody, IgG^c
 Hepatitis E antibody, IgM^c

Anti-nuclear antibody

Alkaline Phosphatase Isoenzymes^a

Anti-smooth muscle antibody (or anti-actin antibody)^a

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

^a Assayed by Lilly-designated or local laboratory.

^b Reflex/confirmation tests may be performed depending on regulatory requirements and/or testing availability.

^c Hepatitis E virus testing in endemic areas only.

Appendix 6. World Health Organization Classification of Diabetes and Diagnostic Criteria

CCI [REDACTED]

[REDACTED]

Appendix 7. 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 the preferred and usual lifestyle) or in a same-sex relationship with no sexual relationship with males (as part of the preferred and usual lifestyle). Note: periodic abstinence (eg, 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 trials

Effective Methods of Contraception:

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

Men, regardless of their fertility status, with non-pregnant women of child bearing potential partners must agree to use 2 forms of effective contraception, where at least 1 form is highly effective 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 8. Management of Patients with Severe, Persistent Hyperglycemia during the Treatment Period

Below are 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 the investigator in accordance with American Diabetes Association/European Association for the Study of Diabetes guidance (Inzucchi et al. 2015). Rescue treatment with antihyperglycemic medications, including insulins, will be allowed. In this case, GLP-1 receptor agonists and DPP-4 inhibitors are not allowed as rescue therapies. Rescue medication will be prescribed as add-on to randomized treatment and patients will continue to follow the protocol-specified visit schedule.

Add-on glycemic rescue therapy will be allowed for patients based on the following criteria:

- 1) The patient is fully compliant with the assigned therapeutic regimen

AND

- 2) has no acute condition that raises blood glucose

AND

- a) Blood glucose concentration measured by weekly 1-point self-monitored BG (SMBG) before breakfast >270 mg/dL (>15.0 mmol/L) over at least a consecutive 2-week period any time during the first 8 weeks postrandomization;

OR

- b) Blood glucose concentration measured by weekly 1-point SMBG before breakfast >240 mg/dL (>13.3 mmol/L) over at least a consecutive 2-week period at any time 9-16 weeks postrandomization;

OR

- c) Blood glucose concentration measured by weekly 1-point SMBG before breakfast >200 mg/dL (>11.1 mmol/L) over at least a consecutive 2-week period at any time beyond the first 16 weeks postrandomization.

OR

- d) Glycated hemoglobin (HbA1c) $\geq 8.5\%$ (69 mmol/mol) 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 $<0.3\%$.

Appendix 9. Protocol Amendment I8F-JE-GPGP(a) Summary A Phase 3, Long-Term Safety Study of Tirzepatide in Combination with Monotherapy of Oral Antihyperglycemic Medications in Patients with Type 2 Diabetes Mellitus (SURPASS J-combo)

Overview

Protocol I8F-JE-GPGP A Phase 3, Long-Term Safety Study of Tirzepatide in Combination with Monotherapy of Oral Antihyperglycemic Medications in Patients with Type 2 Diabetes Mellitus (SURPASS J-combo) has been amended. The new protocol is indicated by amendment (a) 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 as follows:

- A change to section 3.2 to clarify the description of Phase 2 studies
- A change to section 5.1 to correct the duration of short-term insulin use
- A change to section 7.4.1.1 to delete the description of the Manual of Operations
- Changes to section 7.7 to add the description of prohibited concomitant therapy
- Changes to section 9.2.2.2 for consistency with Appendix 8
- A change to section 9.9.1 to correct the number of health states used in EQ-5D-5L
- Changes to section 10.3.1 and 10.3.4 for consistency with synopsis
- Changes to Appendix 7 for consistency with inclusion criterion [6b]

Revised Protocol Sections

Note: Deletions have been identified by ~~strikethroughs~~.
Additions have been identified by the use of underline.

3.2. Background

.....

Serious AEs (SAEs) were balanced across the treatment groups, and none of the groups in the ~~either~~ study reported severe hypoglycemia (Frias et al. 2018).

.....

5.1. Overall Design

.....

Short-term insulin use for up to ~~less than~~ 14 days is allowed for certain clinical situations (eg, elective surgery, during hospitalization, hyperosmolar states).

.....

7.4.1.1. Management of Patients with Gastrointestinal Symptoms

.....

The dose can be de-escalated only once. After that, the patients will have to discontinue tirzepatide if intolerable GI AEs persist. ~~Please see the Manual of Operations for more detailed instructions.~~

.....

7.7. Concomitant Therapy

.....

Prohibited medications include following: ~~any antihyperglycemic medications, except for concomitant OAMs.~~

- Any antihyperglycemic medications, except for concomitant OAMs
- Any medications that promote weight loss (eg, Sanorex[®] [mazindol])
- Any chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, or inhaled preparations)

.....

9.2.2.2. Severe, Persistent Hyperglycemia

.....

- b) Blood glucose concentration measured by weekly 1-point SMBG before breakfast >240 mg/dL (>13.3 mmol/L) over at least a consecutive 2-week period at any time 9-16 ~~8 to 16~~ weeks post-randomization;

.....

9.9.1. European Quality of Life – 5 Dimension – 5 Level (EQ-5D-5L)

.....

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 ~~3254~~ possible health states.

.....

10.3.1. General Statistical Considerations

.....

A ~~S~~selected safety analyses (eg, hypoglycemia) will ~~may~~ be conducted after excluding data while on rescue therapy or data after starting another permitted antihyperglycemic medication following ~~of data after the~~ permanent discontinuation of investigational product.

.....

10.3.4. Safety Analyses

.....

A ~~S~~selected safety analyses (eg, hypoglycemia) will be conducted after excluding data while on rescue therapy or data after starting another permitted antihyperglycemic medication following ~~or data after the~~ permanent discontinuation of investigational product.

.....

Appendix 7. Classification of Contraceptive Methods**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 non-pregnant women of child bearing potential partners must agree to use 2 forms of effective contraception, where at least 1 form is highly effective ~~either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus 1 additional highly effective (<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.

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