Protocol I8F-MC-GPHG(d)

A Randomized, Placebo-Controlled, Crossover Study to Investigate the Effect of Once-Weekly Tirzepatide on the Counter-Regulatory Response to Hypoglycemia in Patients with Type 2 Diabetes Mellitus

NCT04050553

Approval Date: 17-Sep-2020

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EudraCT No. 2019-001360-29

Confidential Information

Tirzepatide (LY3298176)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly:
08 July 2019
Amendment (a) Electronically Signed and Approved by Lilly: 23 July 2019
Amendment (b) Electronically Signed and Approved by Lilly: 04 May 2020
Amendment (c) Electronically Signed and Approved by Lilly: 23 July 2020
Amendment (d) Electronically Signed and Approved by Lilly on approval date provided below

Approval Date: 17-Sep-2020 GMT

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1. Protocol Synopsis

Title of Study:
A Randomized, Placebo-Controlled, Crossover Study to Investigate the Effect of Once-Weekly Tirzepatide on the Counter-Regulatory Response to Hypoglycemia in Patients with Type 2 Diabetes Mellitus.

Rationale:
Study I8F-MC-GPHG (Study GPHG) is an approximately 38 to 42 week Phase 1 study designed to examine the effect of tirzepatide (LY3298176) on hypoglycemic counter-regulation in patients with type 2 diabetes mellitus (T2DM) when compared to placebo treatment. Tirzepatide is a long-acting, dual incretin mimetic (dual agonist) that binds to the glucose-dependent insulinotropic polypeptide receptor (GIPR) and the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R). Dual GIPR and GLP-1R agonism may provide improved glycemic control in patients with T2DM, engaging multiple physiologic pathways, including glucagon secretion by the pancreatic α cell. Since glucagon plays a key role in defense against hypoglycemia, it is important to assess the effects of tirzepatide on the physiologic response to hypoglycemia. Understanding the effect of tirzepatide on the counter-regulatory response to a hypoglycemic stimulus will provide important safety information for potential future clinical use.

Objectives/Endpoints:

Objectives	**Endpoints**
Primary To compare the effect of tirzepatide 15 mg once-weekly (QW) and placebo on glucagon response during hypoglycemia in T2DM patients following 12 weeks of treatment	Change in mean glucagon concentration during induced hypoglycemia from target plasma glucose (PG) concentration of 100 mg/dL to a nadir target of 45 mg/dL
Secondary To compare the effect of tirzepatide 15 mg QW and placebo in T2DM patients following 12 weeks of treatment on: • Other counter-regulatory hormone responses during hypoglycemia, insulin and C-peptide	• Change in mean glucagon concentration from target PG concentration of 100 mg/dL to 63 mg/dL and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Change in mean glucagon concentration from ambient PG to target PG concentrations of 100, 63, and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Change in mean insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations from target PG concentration of 100 mg/dL to 63 and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia
• Time to hypoglycemia recovery	• Time from termination of insulin infusion at PG concentration of 45 mg/dL to reach recovery PG concentration (72 mg/dL) ($t_{PG\_nadir\text{-}72\ mg/dL}$)

• Clinical hypoglycemia	• Hypoglycemic symptoms score at PG concentrations of 100, 63, and 45 mg/dL and after recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Hypoglycemic awareness at PG concentrations of 100, 63, and 45 mg/dL and after recovery (PG concentration 72 mg/dL) from induced hypoglycemia
• Vital signs during hypoglycemia	• Change in mean systolic and diastolic blood pressure and pulse rate from target PG concentration of 100 mg/dL to 63, and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia
• Additional safety and tolerability	• Adverse events (AEs) • Incidence of hypoglycemia outside of the hypoglycemic clamps

Plasma glucose concentrations: 100 mg/dL = 5.5 mmol/L; 72 mg/dL = 4.0 mmol/L; 63 mg/dL = 3.5 mmol/L; 45 mg/dL = 2.5 mmol/L; glucagon at ambient PG measured in the pre-prandial state prior to clamp initiation.

Summary of Study Design:

This is a Phase 1, single-center, 2-period, crossover, randomized, patient- and investigator-blind study in T2DM patients. This study is designed to compare tirzepatide 15 mg QW and placebo with respect to secretion of counter-regulatory hormones in response to a hypoglycemic stimulus and parameters of recovery from hypoglycemia.

Eligibility for this study for patients on metformin only will be assessed at the screening (Visit 1) up to 17 days prior to enrollment (Day -14 ±3) and confirmed at the beginning of the lead-in period (Visit 2).

Eligibility for patients on metformin and one other oral antidiabetic medication (OAM) will be assessed at the screening (Visit 1) up to 45 days prior to enrollment and confirmed at the beginning of the lead-in period (Visit 2), followed by discontinuation and a washout period for OAMs, other than metformin. The washout period for these patients will last at least 4 weeks between Visit 2 and Visit 3.

Eligible patients will undergo 2 treatment periods and will be randomized (Visit 3) to receive tirzepatide 15 mg QW in 1 period followed by placebo in the other, or vice versa, in a crossover fashion. Tirzepatide 15 mg will be attained via step-wise dose escalation to reduce the risk of gastrointestinal AEs.

There will also be a washout period of at least 8 weeks between the last dose of study drug in Period 1 and the first dose in Period 2.

At the end of each treatment period, patients will undergo a hypoglycemic clamp procedure.

Treatment Arms and Planned Duration for an Individual patient:
Each patient will receive tirzepatide 15 mg followed by placebo or vice versa in a crossover fashion. Tirzepatide dosing will start at a dose of 2.5 mg QW for 2 weeks, followed by step-wise escalation to 5 mg QW for the next 2 weeks, 10 mg QW for the next 4 weeks, and 15 mg QW for the final 4 weeks.

The planned study duration for an individual patient from screening through safety follow-up will be approximately 38 to 42 weeks.

Number of Patients:
Approximately 38 patients are planned to be enrolled so that 30 patients complete the study.

Statistical Analysis:

The primary pharmacodynamic (PD) parameter for analysis will be the change in mean glucagon concentration between the 100 mg/dL (5.5 mmol/L) clamp step and the nadir target 45 mg/dL (2.5 mmol/L) step. This will be evaluated using a linear mixed-effects model, with treatment, treatment period, and treatment sequence as fixed effects, and patient as a random effect. From the model, the difference between tirzepatide and placebo in least squares means estimates and the corresponding 95% confidence intervals for the difference will be calculated.

The secondary PD measures for statistical analysis are:

- Change in mean glucagon concentration from target PG concentration of 100 mg/dL (5.5 mmol/L) to 63 mg/dL (3.5 mmol/L) and to recovery (PG concentration 72 mg/dL [4.0 mmol/L]) from induced hypoglycemia
- Change in mean glucagon concentration from ambient PG to target PG concentrations of 100, 63, and 45 mg/dL (5.5, 3.5, and 2.5 mmol/L), and to recovery (PG concentration 72 mg/dL [4.0 mmol/L]) from induced hypoglycemia
- Change in mean insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations from target PG concentration of 100 mg/dL (5.5 mmol/L), to 63 and 45 mg/dL (3.5 and 2.5 mmol/L), and to recovery (PG concentration 72 mg/dL [4.0 mmol/L]) from induced hypoglycemia
- $t_{PG\_nadir\text{-}72\ mg/dL}$

These parameters will be analyzed using a similar model to that described for the primary endpoint. If the $t_{PG\_nadir\text{-}72\ mg/dL}$ is highly skewed, a log-transformation may be considered. If the assumptions of the model appear to be violated, a non-parametric analysis may be performed.

Change in mean systolic and diastolic blood pressure and pulse rate from target PG concentration of 100 mg/dL (5.5 mmol/L) to 63, 45, and 72 mg/dL (3.5, 2.5, and 4.0 mmol/L), and hypoglycemic symptom and awareness scores at target PG concentrations of 100, 63, and 45 mg/dL (5.5, 3.5, 2.5 mmol/L) and after recovery (PG concentration 72 mg/dL [4.0 mmol/L]) from induced hypoglycemia will be listed and summarized.

2. Schedule of Activities

Study Schedule Protocol I8F-MC-GPHG: Screening, Lead-in, Randomization/Dose 1 Period 1, and Dose 1 Period 2

Procedure	Screening	Lead-in (with or without washout)	Randomization and Dose 1, Treatment Period 1	Dose 1, Treatment Period 2	Comments
Visit	1	2	3	10	
Study Period Week	-6/-2[a]	-5/-1[a]	1	1	
Study Period Day	-14 ±3[a] or -42 ±3[a]	-7 ± 3[a] or -35 ±3[a] (prior to randomization)	1	1	Patients on metformin only should perform Visits 1 and 2 approximately 2 and 1 week prior to Visit 3. Patients on metformin and one additional OAM should perform Visit 1 about 6 weeks prior to Visit 3, in order to permit eligibility assessment at Visit 2. OAMs other than metformin will be discontinued immediately after Visit 2 followed by at least 4-weeks washout between Visit 2 and Visit 3.
Informed consent	X				
Medical history	X				
Drug and alcohol screen	X				May be repeated throughout the study as deemed necessary by the investigator.
Physical examination / medical assessments	X				Full physical examination at screening. After screening, medical assessments only performed to include medical review and targeted examination, as appropriate.
Height	X				
Weight	X		P	P	
Vital signs (BP/PR/body temperature)	X		P	P	Blood pressure and PR measurements will be taken after at least 5 minutes in the supine position.
ECGs	X		P	P	Single 12-lead ECGs will be collected. Electrocardiograms will be recorded using equipment available at the CRU. Patients must be supine for at least 5 minutes before ECG collection, and remain supine but awake during ECG collection.
AEs		X			

Procedure	Screening	Lead-in (with or without washout)	Randomization and Dose 1, Treatment Period 1	Dose 1, Treatment Period 2	Comments
Visit	1	2	3	10	
Study Period Week	-6/-2[a]	-5/-1[a]	1	1	
Study Period Day	-14 ±3[a] or -42 ±3[a]	-7 ± 3[a] or -35 ±3[a] (prior to randomization)	1	1	Patients on metformin only should perform Visits 1 and 2 approximately 2 and 1 week prior to Visit 3. Patients on metformin and one additional OAM should perform Visit 1 about 6 weeks prior to Visit 3, in order to permit eligibility assessment at Visit 2. OAMs other than metformin will be discontinued immediately after Visit 2 followed by at least 4-weeks washout between Visit 2 and Visit 3.
Concomitant medications	X	X			
Inclusion/exclusion criteria	X	X			For patients requiring OAM washout, eligibility must be confirmed prior to discontinuing the OAM.
Randomization			P		To occur after all other predose assessments are conducted.
Investigational Product					
Tirzepatide or placebo administration			X	X	
Clinical Procedures					
Outpatient visit	X	X	X	X	
Laboratory Tests					
Safety laboratory tests	X		P	P	See Appendix 2 for details. Patients will fast for at least 8 hours before each blood sample is collected (fasting). If not fasted prior to screening, patient may return for test within the screening window.
Serology	X				See Appendix 2 for details.
Pregnancy test (women of childbearing potential)	X	X[b]	P	P	Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at other times. Performed by local laboratory or on site.
Insulin, C-peptide			P	P	Fasting. Performed by central laboratory.

Procedure	Screening	Lead-in (with or without washout)	Randomization and Dose 1, Treatment Period 1	Dose 1, Treatment Period 2	Comments
Visit	1	2	3	10	
Study Period Week	-6/-2[a]	-5/-1[a]	1	1	
Study Period Day	-14 ±3[a] or -42 ±3[a]	-7 ± 3[a] or -35 ±3[a] (prior to randomization)	1	1	Patients on metformin only should perform Visits 1 and 2 approximately 2 and 1 week prior to Visit 3. Patients on metformin and one additional OAM should perform Visit 1 about 6 weeks prior to Visit 3, in order to permit eligibility assessment at Visit 2. OAMs other than metformin will be discontinued immediately after Visit 2 followed by at least 4-weeks washout between Visit 2 and Visit 3.
Glucagon			P	P	Fasting. Performed by central laboratory.
Calcitonin	X				Fasting. If not fasted prior to screening, patient may return for test within the screening window. Central laboratory.
Glucose Management					
Dispense blood glucose meters, test strips, study diaries, and disease management training		X			These SMPG-related procedures will be performed after eligibility is confirmed.
SMPG		X		X	For patients undergoing OAM washout, phone interviews will be conducted during lead-in to assess acceptability of glycemic control. Refer to Section 5.1.1 for further details
Review of study diary for SMPG			P	P	

Procedure	Screening	Lead-in (with or without washout)	Randomization and Dose 1, Treatment Period 1	Dose 1, Treatment Period 2	Comments
Visit	1	2	3	10	
Study Period Week	-6/-2[a]	-5/-1[a]	1	1	
Study Period Day	-14 ±3[a] or -42 ±3[a]	-7 ± 3[a] or -35 ±3[a] (prior to randomization)	1	1	Patients on metformin only should perform Visits 1 and 2 approximately 2 and 1 week prior to Visit 3. Patients on metformin and one additional OAM should perform Visit 1 about 6 weeks prior to Visit 3, in order to permit eligibility assessment at Visit 2. OAMs other than metformin will be discontinued immediately after Visit 2 followed by at least 4-weeks washout between Visit 2 and Visit 3.
Diagnostics					
PK sample			P	P	PK and immunogenicity to be time-matched as much as possible.
Immunogenicity			P	P	
Pharmacogenetic sample			P		Single sample taken predose on Day 1 Period 1.
Nonpharmacogenetic stored samples			P	P	Fasting sample.

Abbreviations: AE = adverse event; BP = blood pressure; ECG = electrocardiogram; FSH = follicle-stimulating hormone; P = predose; PK = pharmacokinetic; PR = pulse rate; SMPG = self-monitoring of blood glucose.

[a] Visit windows are relative to randomization (Period 1, Day 1).

[b] A serum pregnancy test will be taken during Visit 2 if the FSH ≤40mIU/mL at Visit 1.

Note: If multiple procedures take place at the same time point, the following order may be consulted for prioritization: ECG, vital signs, counter-regulatory hormone samples, safety laboratory tests, PK samples, immunogenicity samples, storage samples.

Study Schedule Protocol I8F-MC-GPHG: Treatment Periods 1 and 2

Procedure	**Treatment Periods 1 and 2**													**Comments**
Visit Period 1 **Visit Period 2**	4 11	5 12		6 13				7 14			8 15	9 16	9 16	
Study Period Week	2	3	4	5	6	7	8	9	10	11	12	12	12	
Study Period Day	8 ±1	15 ±1	22	29 ±1	36	43	50	57 ±1	64	71	78 ±2	79 ±2	80 ±2	Patients should attend on stated day. When the patient is unable to attend CRU on the stated day, visit windows should be used for dosing only. **Days 78, 79, and 80 should occur consecutively, without interruption.**
Weight				P				P			P			
Vital signs (BP/PR/body temperature)	P	P		P				P			P	X See Appendix 6		Refer to screening table.
ECGs				P							P	X See Appendix 6		Refer to screening table.
Concomitant medications	X													
AEs	X													
Physical examination / medical assessments	X										X			Refer to screening table.
Alcohol breath test												X		
CRU admission												X		
CRU discharge													X	
Outpatient visit	X	X		X				X			X			
Dispense study treatment		X		X				X						For outpatient use.
Telephone visit			X			X			X					May be more frequent if there is evidence of missed doses.
Investigational Product														
Tirzepatide or placebo administration	X	X	X	X	X	X	X	X	X	X	X			Patients will self-administer study drug when not in CRU.

Procedure	Treatment Periods 1 and 2													Comments
Visit Period 1 **Visit Period 2**	4 11	5 12		6 13				7 14			8 15	9 16	9 16	
Study Period Week	2	3	4	5	6	7	8	9	10	11	12	12	12	
Study Period Day	8 ±1	15 ±1	22	29 ±1	36	43	50	57 ±1	64	71	78 ±2	79 ±2	80 ±2	Patients should attend on stated day. When the patient is unable to attend CRU on the stated day, visit windows should be used for dosing only. **Days 78, 79, and 80 should occur consecutively, without interruption.**
Glucose Management														
SMPG	X													
Fasting blood glucose	P	P												The central laboratory will test fasting blood glucose.
Review of study diary for SMPG	X	X		X				X			X			
Laboratory Tests														
Safety laboratory tests				X							X			Refer to screening table.
Pregnancy test (women of childbearing potential)				X				X			X			Refer to screening table.
Insulin, C-peptide												X See Appendix 6		Fasting. Performed by central laboratory.
Growth hormone, cortisol														Fasting. Performed by central laboratory.
Adrenaline, noradrenaline														Fasting. Performed by central laboratory.
Glucagon														Fasting. Performed by central laboratory.

Procedure	Treatment Periods 1 and 2													Comments
Visit Period 1 **Visit Period 2**	4 11	5 12		6 13				7 14			8 15	9 16	9 16	
Study Period Week	2	3	4	5	6	7	8	9	10	11	12	12	12	
Study Period Day	8 ±1	15 ±1	22	29 ±1	36	43	50	57 ±1	64	71	78 ±2	79 ±2	80 ±2	Patients should attend on stated day. When the patient is unable to attend CRU on the stated day, visit windows should be used for dosing only. **Days 78, 79, and 80 should occur consecutively, without interruption.**
Investigative Tests														
Hypoglycemic clamp												X See Appendix 6		
Diagnostics														
PK sample				P							P			PK and immunogenicity to be time-matched as much as possible.
Immunogenicity				P							P			
Nonpharmacogenetic stored samples											P			Fasting sample.
Cognitive Assessments														
Hypoglycemic symptom awareness												X See Appendix 6		
Hypoglycemic symptoms score														

Abbreviations: AEs = adverse events; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; P = predose; PK = pharmacokinetics; PR = pulse rate; SMPG = self-monitoring of plasma glucose.

Note: If multiple procedures take place at the same time point, the following order may be consulted for prioritization: ECG, vital signs, glucose sampling, counter-regulatory hormone samples, safety laboratory tests, PK samples, immunogenicity samples, cognitive assessments, storage samples.

Study Schedule Protocol I8F-MC-GPHG: Washout Period

Procedure	Washout Period
Visit	
Study Week[a]	12-20 (12-22)
Study Day[a]	81-135 (81-149)
Clinical Procedures	
Washout / crossover	X
Concomitant medications	X[b]
AEs	X[b]
Glucose Management	
SMPG	X[b]

Abbreviations: AEs = adverse events; SMPG = self-monitoring of plasma glucose.

[a] Washout period is at least 8 weeks and up to 10 weeks, if necessary.

[b] Data will be reviewed and recorded in the electronic case report form at the dose 1 Period 2 visit.

Study Schedule Protocol I8F-MC-GPHG: Follow-up / Early Termination

Procedure	ET	Final FU	Comments
Visit	-	17	
Study Week	-	36	
Study Day	As soon as possible after discontinuation decision	Within 4 weeks from last dose/ET	
Clinical Procedures			
Weight	X	X	
Vital signs (BP/PR/body temperature)	X	X	Refer to screening table.
ECGs	X	X	Refer to screening table.
Concomitant medications	X	X	
AEs	X	X	
Physical examination / medical assessments	X	X	Refer to screening table.
Outpatient visit	X	X	
Glucose Management			
Review of study diary for SMPG[a]	X	X	
Study diary collection		X	
Laboratory Tests			
Pregnancy test (women of childbearing potential)	X	X	Refer to screening table.
Diagnostics			
PK sample	X	X	Samples for immunogenicity and PK to be time-matched as far as possible.
Immunogenicity	X	X	

Abbreviations: AEs = adverse events; BP = blood pressure; ECG = electrocardiogram; ET = early termination; FU = follow-up; PK = pharmacokinetics; PR = pulse rate; SMPG = self-monitoring of plasma glucose;

[a] SMPG will continue until Follow-up visit.

Note: If multiple procedures take place at the same time point, the following order may be consulted for prioritization: ECG, vital signs, PK samples, immunogenicity samples.

3. Introduction

3.1. Study Rationale

Study I8F-MC-GPHG (Study GPHG) is an approximately 38-42 week Phase 1 study designed to evaluate the effect of tirzepatide (LY3298176) on hypoglycemic counter-regulation in patients with type 2 diabetes mellitus (T2DM) when compared to placebo treatment. Tirzepatide is a long-acting, dual incretin mimetic (dual agonist) that binds to the glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) and the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R). Dual GIPR and GLP-1R agonism (GIPRA/GLP-1RA) may provide improved glycemic control in patients with T2DM, engaging multiple physiologic pathways, including glucagon secretion by the pancreatic α cell. Since glucagon plays a key role in defense against hypoglycemia, it is important to assess the effects of tirzepatide on the physiologic response to hypoglycemia. Understanding the effect of tirzepatide on the counter-regulatory response to a hypoglycemic stimulus will provide important safety information for potential future clinical use.

3.2. Background

GLP-1 is synthesized and secreted from enteroendocrine L cells in the small and large intestine and is a well-characterized incretin hormone that potentiates insulin and reduces glucagon secretion, in a glucose-dependent manner, after meal ingestion. GLP-1 exerts its insulinotropic action through distinct G-protein-coupled receptors highly expressed on islet β cells and also in some non-islet cells. For example, GLP-1Rs are expressed throughout the brain, in regions that control glucose homeostasis, gut motility, food intake, aversive signaling, and cardiovascular function (Campbell and Drucker 2013). Currently, there are several regulatory approved GLP-1 receptor agonists (GLP-1 RAs) for the treatment of diabetes and obesity. The dosing of GLP-1RAs in man is limited by gastrointestinal (GI) adverse effects, such as nausea and vomiting.

GIP, also known as gastric inhibitory polypeptide, is synthesized and secreted by enteroendocrine K cells in the proximal intestine. GIPR is widely expressed in islets, gut, adipose tissue, and brain. GIP secretion is primarily regulated by nutrients, especially fats. GIP is responsible for the majority of the insulinotropic incretin effect in man and has important additional functions that are distinct from GLP-1. GIP promotes glucagon secretion at low blood glucose (BG) levels to augment endogenous glucose production. It stimulates lipolysis and inhibits insulin-induced lipogenesis in human adipocytes. In preclinical models, the effect of selective GIP signaling on body weight regulation was neutral. However, recent preclinical reports have demonstrated that GIPR agonism complements GLP-1R agonism to improve energy homeostasis, in addition to glucose-lowering effects. Co-administration of individual mono-agonists as well as unimolecular co-agonists have shown profound weight-lowering benefits that exceed that of either agent alone (Finan et al. 2016). Despite the observed effects of GIP, currently, no pharmaceutical agents that are based on its structure and function have been developed for treatment of metabolic conditions.

Tirzepatide, a dual GIPRA/GLP-1RA, is a 39-amino acid synthetic peptide. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety which facilitates albumin binding and thus prolongs the duration of action. It has a chemical structure and pharmacologic profile that is distinct from the GLP-1RA due to the addition of GIP, which is unique among the marketed incretin mimetics. It is administered once-weekly (QW) by subcutaneous (SC) injection.

Tirzepatide is being developed as a therapy to improve glycemic control in adults with T2DM, as an adjunct to diet and exercise. Phase 3 studies are also planned for chronic weight management in obese/overweight adults and a Phase 2 study is planned for non-alcoholic steatohepatitis.

In a Phase 1 study (Coskun et al. 2018) that included single and multiple ascending dose (SAD, MAD) parts, tirzepatide has been administered as single SC doses up to 8 mg in healthy subjects. In the MAD part, higher doses up to 10 mg were attained in healthy subjects via dose escalation. Doses up to 15 mg were achieved in patients with T2DM via dose escalation. In this study, GI adverse events (AEs) (nausea, vomiting, diarrhea, and abdominal distension) and decreased appetite were the most frequently reported events by both healthy subjects and patients with T2DM and were dose related. Most AEs were mild in severity, a few were moderate, and none were reported as severe. During the SAD part of the study, the high incidence of GI AEs, notably vomiting, were considered to be dose limiting at the 8-mg dose; therefore, the 5-mg dose was considered the maximum tolerated dose. A dose-dependent increase in heart rate was detected for both healthy subjects and patients with T2DM who received tirzepatide, similar to what was observed with selective GLP-1 RAs. A few subjects experienced transient elevations in lipase and/or amylase levels, but these episodes were not associated with any relevant clinical outcomes.

Once-weekly doses of 1, 5, 10, and 15 mg have been further investigated in a Phase 2 study (Frias et al, 2018). An additional dose level of 12 mg and alternate dose escalation schemes were investigated in a 12-week Phase 2 study. Doses above 5 mg of tirzepatide were attained via step-wise dose escalation. Results from the two Phase 2 studies demonstrated that tirzepatide at doses between 5 and 15 mg provided clinically meaningful efficacy in both glucose- and body weight-lowering. Gastrointestinal-related AEs (nausea, diarrhea, and vomiting) were the most frequently reported AEs in Phase 2 studies. The majority of the treatment-emergent adverse events (TEAEs) were mild or moderate in severity. There were no other clinically relevant safety observations in the Phase 1 and 2 studies.

Tirzepatide terminal half-life was estimated to be approximately 5 days, thus supporting a QW dosing regimen, with maximum observed drug concentration (C_{max}) occurring 24 to 72 hours postdose. Tirzepatide QW dosing at 5, 10, and 15 mg is currently being investigated in Phase 3 safety and efficacy studies in patients with T2DM.

Hypoglycemia is a common side effect of diabetes therapy, resulting in a lack of adequate cerebral glucose supply, leading to a range of neurogenic and neuroglycopenic symptoms, which in turn can lead to death if not treated in time (Balijepalli et al. 2017). It is defined as the decrease of BG level below 70 mg/dL (3.9 mmol/L) with or without symptoms of autonomic

nervous system activation and neuroglycopenia (EMA 2012, Seaquist et al 2013). Hypoglycemia is common in T2DM patients using a combination of oral glucose-lowering medications, in subgroups of T2DM patients with renal insufficiency, and in elderly patients (Morales and Schneider 2014). Additionally, the counter-regulatory systems against hypoglycemia are also affected in diabetic patients. The responsiveness of counter-regulatory hormones, especially glucagon, recovery from hypoglycemia, and awareness of symptoms of hypoglycemia is essential for a patient with diabetes in particular if treated with medications with known risk of causing hypoglycemia.

The effect of dual agonist tirzepatide on secretion of counter-regulatory hormones like glucagon and on hypoglycemia symptoms is currently unknown. Study GPHG aims to characterize the counter-regulatory hormone response throughout hypoglycemia while ensuring that safety is not compromised during a controlled hypoglycemic stimulus in patients with T2DM during treatment with tirzepatide compared to placebo.

3.3. Benefit/Risk Assessment

The most common safety issue with administration of tirzepatide was related to frequent reporting of decreased appetite and GI side effects, most commonly nausea, vomiting, and diarrhea. These GI events were generally mild in severity, with few moderate, and no severe events reported in a Phase 1 study. No other clinically relevant safety concerns were identified in the dose range up to 15 mg, the highest dose investigated in Phase 1 and in Phase 2 studies in T2DM patients, administered QW up to 26 weeks. The data indicate that the safety profile for a dual GIPRA/GLP-1RA is similar to the safety profile of the selective GLP-1RAs. Potential risks, such as GI effects, acute pancreatitis, increases in heart rate, and hypoglycemic events are consistent with the risks associated with currently available long-acting GLP-1RAs. These risks are clinically detectable and manageable, and will be monitored during the study.

During the hypoglycemic clamp procedures, plasma glucose (PG) levels will be closely monitored and glucose infused, if necessary, to prevent PG dropping below the target values. Should the symptoms of hypoglycemia become unacceptable, glucose will be infused to increase PG. Vital signs and continuous electrocardiogram (ECG) will be monitored during the clamp procedures and the clamp will be terminated should the patient experience symptoms of cardiovascular stress (tachycardia, bradycardia, or other relevant changes in ECG), or neurological symptoms related to neuroglycopenia.

In addition to the comprehensive safety monitoring plan for all patients included in this study, PG levels will also be regularly monitored outside of the hypoglycemic clamps to reduce risks related to acute diabetic complications. Section 9.2.2.2 (Hypoglycemia) and Section 9.2.2.3 (Severe, Persistent Hyperglycemia) describe definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia or hyperglycemia. If a patient fulfills any of the rescue medication criteria, the patient will be offered rescue medication at the discretion of the investigator (Section 7.4.1.2 Management of Hyperglycemia). Section 7.7.1 (Management of Patients with Gastrointestinal Symptoms) provides detailed information concerning the management of GI AEs.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated AEs of tirzepatide are to be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the investigational product (IP) can be found in Section 6 (Development Core Safety Information) of the IB. Information on SAEs that are expected in the study population independent of drug exposure will be assessed by the sponsor in aggregate, periodically during the course of the study, and can be found in Section 5 (Effects in Humans) of the IB.

4. Objectives and Endpoints

Table GPHG.1 shows the objectives and endpoints of the study.

Table GPHG.1. Objectives and Endpoints

Objectives	Endpoints
Primary To compare the effect of tirzepatide 15 mg QW and placebo on glucagon response during hypoglycemia in T2DM patients following 12 weeks of treatment	Change in mean glucagon concentration during induced hypoglycemia from target PG concentration of 100 mg/dL to a nadir target of 45 mg/dL
Secondary To compare the effect of tirzepatide 15 mg QW and placebo in T2DM patients following 12 weeks of treatment on: • Other counter-regulatory hormone responses during hypoglycemia, insulin and C-peptide	• Change in mean glucagon concentration from target PG concentration of 100 mg/dL to 63 mg/dL and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Change in mean glucagon concentration from ambient PG to target PG concentrations of 100, 63, and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Change in mean insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations from target PG concentration of 100 mg/dL to 63 and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia
• Time to hypoglycemia recovery	• Time from termination of insulin infusion at PG concentration of 45 mg/dL to reach recovery PG concentration (72 mg/dL) ($t_{PG\_nadir\text{-}72\ mg/dL}$)
• Clinical hypoglycemia	• Hypoglycemic symptoms score at PG concentrations of 100, 63, and 45 mg/dL and after recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Hypoglycemic awareness at PG concentrations of 100, 63, and 45 mg/dL and after recovery (PG concentration 72 mg/dL) from induced hypoglycemia
• Vital signs during hypoglycemia	• Change in mean systolic and diastolic blood pressure and pulse rate from target PG concentration of 100 mg/dL, to 63, and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia
• Additional safety and tolerability	• AEs • Incidence of hypoglycemia outside of the hypoglycemic clamps

Exploratory To compare the effect of tirzepatide 15 mg QW and placebo in T2DM patients following 12 weeks of treatment on: • Other hypoglycemic clamp and recovery parameters	• Amount of insulin required to reach PG concentrations of 63 and 45 mg/dL from 100 mg/dL. • $AUC_{GIR,PG\_nadir\text{-}72\ mg/dL}$ • Proportions of patients who require glucose infusion to attain recovery (PG concentration 72 mg/dL) and associated G_{tot} • PG achieved at the end of spontaneous recovery
• Other safety parameters	• Frequency of treatment-emergent anti-tirzepatide antibodies

Abbreviations: AE = adverse event; $AUC_{GIR,PG\_nadir\text{-}72\ mg/dL}$ = area under the glucose infusion rate curve from time of termination of insulin infusion until recovery (PG concentration of 72 mg/dL); G_{tot} = total amount of glucose infused; PG = plasma glucose; QW = once-weekly; T2DM = type 2 diabetes mellitus.

Plasma glucose concentrations: 100 mg/dL = 5.5 mmol/L; 72 mg/dL = 4.0 mmol/L; 63 mg/dL = 3.5 mmol/L; 45 mg/dL = 2.5 mmol/L; glucagon at ambient PG measured in the pre-prandial state prior to clamp initiation.

5. Study Design

5.1. Overall Design

This is a Phase 1, single-center, 2-period, crossover, randomized, patient- and investigator-blind study in T2DM patients. This study is designed to compare tirzepatide 15 mg QW and placebo with respect to secretion of counter-regulatory hormones in response to a hypoglycemic stimulus and parameters of recovery from hypoglycemia.

Eligibility for this study will be assessed at screening (Visit 1) and confirmed at the beginning of the lead-in period (Visit 2). After eligibility is confirmed at Visit 2, patients will receive training and information on how to subsequently monitor their own diabetes condition. Where applicable, patients will be required to undergo a washout of OAMs other than metformin between Visit 2 and Visit 3 (refer to Section 5.1.1 for details)

Following baseline assessments, eligible patients will be randomized (Visit 3) to treatment sequence. All patients will undergo 2 treatment periods, receiving tirzepatide in 1 period and placebo in the other, in a crossover fashion.

Tirzepatide 15 mg will be attained via step-wise dose escalation to reduce the risk of GI AEs as described in Section 5.1.2 (Treatment).

There will be a washout period of at least 8 weeks between the last dose of study drug in Period 1 and the first dose in Period 2. The washout period will ensure sufficient washout of the study drug based on tirzepatide's elimination half-life of approximately 5 days.

At the end of each treatment period, patients will undergo a hypoglycemic clamp procedure (see Appendix 6 for details).

Study governance considerations are described in detail in Appendix 3.

Figure GPHG.1 illustrates the study design.

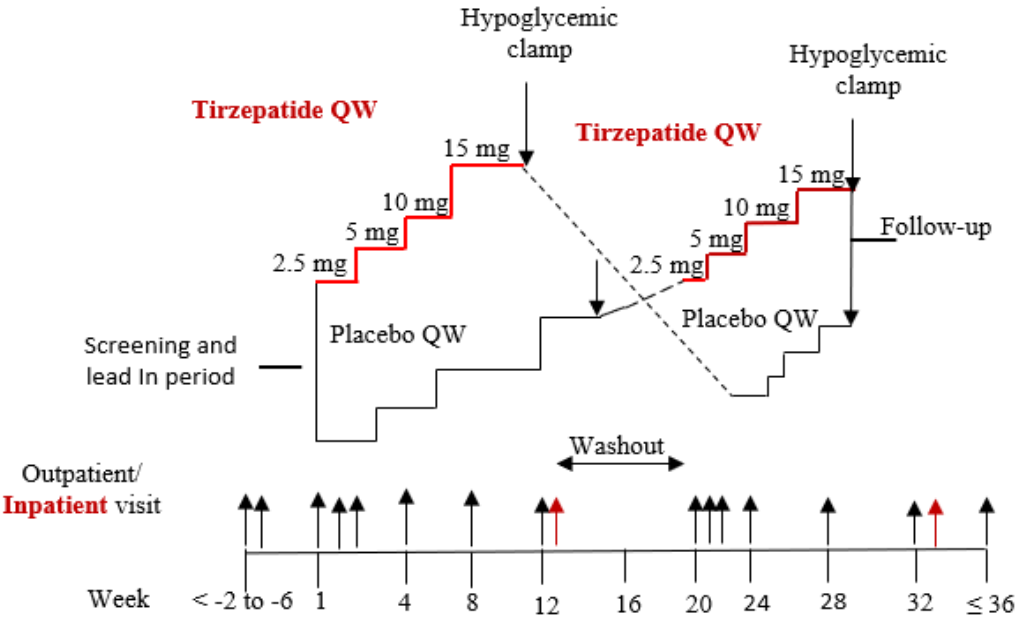


Figure GPHG.1 Illustration of study design for Protocol I8F-MC-GPHG.

5.1.1. Screening, Lead-in, and Randomization

Eligibility for this study will be assessed during the screening period (Visit 1). The patient will sign the informed consent form (ICF) before any study procedures are performed. Screening procedures will be performed according to Section 2 (Schedule of Activities). Final determination of eligibility will occur at the beginning of the lead-in period at Visit 2, after all screening results are available. Eligible patients are those with T2DM treated with diet, exercise, and metformin with or without one other allowed oral antidiabetic medication (OAM) as specified in Inclusion Criterion [2].

Eligibility for this study for patients on metformin only will be assessed at the screening (Visit 1) up to 17 days prior to enrollment (Day -14 ±3) and confirmed at the beginning of the lead-in period (Visit 2). Eligible patients treated with metformin only will proceed to Visit 3 after approximately 1-week lead-in.

Eligible patients who are, in addition to metformin, on 1 more OAM, will discontinue this OAM immediately after Visit 2 and will undergo a 4-week washout between Visit 2 and Visit 3. During this washout period, the investigator will perform appropriate surveillance of the patients (by telephone interview and additional CRU visits, if necessary, at the investigators discretion) to monitor the safety and glycemic control of the patients. Once the 4-week washout period is completed, patients will proceed to Visit 3. Upon entering the study, patients should remain on the same metformin dose throughout the course of the study. Between screening and randomization (Day 1) eligible patients should continue their prestudy therapy with metformin. Patients who do not comply with requirements regarding metformin dosing will be discontinued

from the study prior to randomization. After randomization, the metformin dose can only be reduced in accordance with country-specific label to protect patient safety (see Section 7.7 [Concomitant Therapy] for further details).

Eligible patients will be trained on glucose monitoring and disease management procedures, glucometer use for self-monitoring of plasma glucose (SMPG), study diaries, and study procedures at the lead-in visit (Visit 2). Patients will start performing daily SMPG and record all results, including any hypoglycemia episode, in diaries as soon as their eligibility is confirmed at Visit 2. Patients will also follow the investigator's instructions related to any additional SMPG measurements, when judged to be needed for safety or eligibility assessments. All patients will be encouraged to maintain a stable diet and exercise plan throughout the course of the study

Patients will be randomized on Day 1 of Period 1 after undergoing baseline assessments; eligible patients will be randomized 1:1 to 12 weeks QW tirzepatide followed by 12 weeks QW placebo, or vice versa. Patients will then receive their first dose of study treatment.

5.1.2. Treatment

The tirzepatide treatment period will consist of a step-wise dose escalation. The starting dose will be 2.5 mg QW for 2 weeks, followed by an increase to 5 mg QW for 2 weeks, and 10 mg QW for 4 weeks until the 15-mg dose is reached and maintained for the remainder of the treatment period (4 weeks), see Section 5.5 (Justification for Dose) for further details. Patients will visit the clinical research unit (CRU) as outpatients 1 week after administration of the first dose (Week 2) and for administration of the first of each escalated dose during both the tirzepatide and placebo treatment periods (Weeks 3, 5 and 9 of each treatment period). Study drug will be dispensed to the patient at these visits for self-administration on all other dosing days. Telephone visits will be conducted to ensure that outpatient dosing occurs and to monitor safety.

The schedule of clinic visits and study procedures during the treatment periods, including sampling for immunogenicity and pharmacokinetic (PK) assessments, are provided in Section 2 (Schedule of Activities).

Patients will attend the CRU as outpatients on Week 12 of each treatment period to receive the final dose of study drug. The following day, patients will be admitted to the CRU and will undergo a hypoglycemic clamp procedure as detailed in Appendix 6.

Patients who initiate rescue medication for treatment of severe hyperglycemia (Section 7.4.1.2 Management of Hyperglycemia) during the study may continue in the study but rescue medication will be discontinued 1 week before the clamp procedure to avoid interference with measurements planned during the hypoglycemic clamp.

Patients who permanently discontinue study treatment early, irrespective of the reason, will be discontinued from the study (Section 8.1 Discontinuation from Study Treatment). They will perform an early termination (ET) visit as soon as possible after the decision to discontinue study treatment, followed by a safety follow-up visit up to 4 weeks later.

5.1.3. Washout Between Treatment Periods

There will be a washout period of at least 8 weeks, but not longer than 10 weeks, between the final dose of study drug in the first treatment period (on Week 12) and the first dose of study drug in the second treatment period based on tirzepatide's elimination half-life of approximately 5 days.

5.2. Number of Participants

Approximately 38 patients may be enrolled so that 30 complete the study. For the purposes of this study, a patient completes the study when all scheduled procedures through completion of the second hypoglycemic clamp procedure as per the Schedule of Activities (Section 2) have been finished.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

Study GPHG will employ a crossover design which allows each patient to serve as his or her own control, thereby reducing variability. The study is patient- and investigator-blind to minimize potential bias.

The use of a clamp procedure with regular glucose monitoring will permit the effects of tirzepatide and placebo to be compared in patients with T2DM with standardized, stable measurement conditions, with the highest safety standards with regards to hypoglycemia detection and treatment.

Patients with T2DM are a target population of tirzepatide and therefore the appropriate population for conducting the study.

The dose justification for tirzepatide is provided in Section 5.5 (Justification for Dose).

The rationale for the sample size is provided in Section 10.1 (Sample Size Determination).

5.5. Justification for Dose

The tirzepatide dose of 15 mg administered SC QW is selected based on current preclinical pharmacology, toxicology, and clinical data, and is the highest maintenance dose planned for evaluation in the Phase 3 program.

Tirzepatide dosing will start at a low dose of 2.5 mg QW and will be escalated to 15 mg QW as described in Section 5.1.2 (Treatment). The step-wise increments are based on cumulative understanding of safety and GI tolerability from Phase 1 and 2 studies and are expected to minimize GI tolerability concerns by permitting adequate time for development of tolerance to GI events.

While a steeper dose escalation scheme with a higher starting dose of 5 mg, escalating to 15 mg within 7 weeks was previously implemented in Phase 2 and was found to be safe; this scheme was associated with some GI tolerability concerns.

To minimize the incidence of GI tolerability events, this study will employ a lower starting dose of 2.5 mg to initiate the dose escalation, permitting 8 weeks of step-wise escalation prior to attaining a maintenance dose of 15 mg at Week 9. Treatment will be continued for 4 weeks after reaching the 15-mg maintenance dose, to allow steady-state exposures to be attained.

6. Study Population

Eligibility of patients for the study will be based on the results of screening medical history, physical examination, vital signs, safety laboratory tests, and ECGs.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 45 days prior to start of randomization for patients treated with metformin and one other OAM, who are required to perform a washout during lead-in. For all other patients, screening may occur up to 17 days prior to randomization and perform a minimum 3-day lead-in. Patients who are not enrolled within these time periods may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility. Patients will be dosed only if safety laboratory results not older than 45 days are available.

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 for inclusion in the study only if they meet all of the following criteria at screening and/or at other visits prior to randomization, when indicated:

Disease Characteristics

[1] Have had T2DM for at least 1 year;

[2] Treated with diet and exercise and a stable dose of metformin (3 months prior to study entry) with or without 1 additional OAM other than metformin; doses of metformin will be considered stable if all prescribed doses for the previous 3 months were ±850 mg from the most commonly prescribed dose; allowed OAMs, in combination with metformin are DPP-IV inhibitors, SGLT-2 inhibitors, acarbose, glinides and sulfonylureas; in patients with established cardiovascular disease who are treated with SGLT-2 inhibitors, this therapy should not be discontinued and therefore, these patients will NOT be eligible for participation in the trial.

[3a] Have a hemoglobin A1c value at screening of ≥6.5% and ≤9.0% (48 to 75 mmol/mol), if on metformin only;

[3b] Have a hemoglobin A1c value at screening of ≥6.0% and ≤8.5% (42 to 69 mmol/mol), if on metformin and 1 more allowed OAM;

Patient Characteristics

[4] Male or female patients aged 18 to 70 years, inclusive

[4a] Male patients:

- Men, regardless of their fertility status, with nonpregnant women of childbearing potential (WOCBP) partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days.
    - Men and their partners may choose to use a double–barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined).
    - Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of the study, and withdrawal are not acceptable methods of contraception.
- Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in WOCBP (90 days).
- Men must agree to refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days following last dose of study drug.
- Men who are in exclusively same-sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

[4b] Female patients:

- Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a study, and withdrawal are not acceptable methods of contraception.
- Otherwise, WOCBP participating must agree to use effective contraception, (see contraception guidance below), for the entirety of the study. Contraception must continue following completion of study drug administration for 30 days.

- Women of childbearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 48 hours prior to exposure and at other times as specified in Section 2 (Schedule of Activities).
- Two forms of effective contraception, where at least 1 form is highly effective (less than 1% failure rate, such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) will be used. Effective contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide). It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

- Women who are not of childbearing potential may participate and include those who are:
  - Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis, or
  - Postmenopausal – defined as either
    i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either
       a) cessation of menses for at least 1 year, or
       b) at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or
    ii. A woman at least 55 years of age not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
    iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[5] Have a body mass index between 23.0 kg/m^2 and 45.0 kg/m^2, inclusive, at screening; are of stable weight (±5%) >3 months prior to screening; and agree not to initiate an intensive diet and/or exercise program during the study with the intent of reducing body weight other than lifestyle and dietary measures for diabetes treatment;

[6] Have venous access sufficient to allow for blood sampling as per the protocol.

Informed Consent

[7] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures;

[8] Have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening and/or at other visits prior to randomization, when indicated:

Primary Study Condition - Diabetes Related

[9] Have type 1 diabetes mellitus;

[10] Have had more than 1 episode of severe hypoglycemia, as defined by the American Diabetes Association criteria, within 6 months before screening or has a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms; any patient that cannot communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia prior to the first dose of study drug should also be excluded;

[11] Have had 1 or more episodes of ketoacidosis or hyperosmolar state/coma requiring hospitalization within the 6 months prior to screening;

[12] Have a history of proliferative retinopathy or maculopathy as determined by the investigator based on a recent (<6 months) ophthalmologic examination;

[13] Impaired renal estimated glomerular filtration rate <60 mL/min/1.73 m^2 calculated by Chronic Kidney Disease-Epidemiology. One retest may be performed in case of an initial result <60 mL/min/1.73 m^2. The highest value from the 2 tests will be accepted.

Prior/Concomitant Therapy - Glucose-Lowering Medications

[14] Have taken any glucose-lowering medications other than those indicated in Inclusion Criterion [2] during the last 3 months before screening or during the screening/lead-in period; short-term use of insulin (<14 days) for treatment of acute conditions is allowed in the 3-month period prior to entry and after randomization (see Section 7.7 Concomitant Therapy)

Medical Conditions - General

[15] Have a history or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data

[16] Have acute or chronic pancreatitis or a history of acute idiopathic pancreatitis; patients who had cholecystolithiasis and/or cholecystectomy in the past, with no long-term complications, are eligible for participation;

[17] Have a known clinically significant gastric emptying abnormality (e.g., severe diabetic gastroparesis or gastric outlet obstruction) or have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (e.g., Lap-Band®);

[18] Have a personal or family history of medullary thyroid carcinoma (MTC), multiple endocrine neoplasia syndrome type 2 (MEN 2), or calcitonin ≥20 pg/mL (≥ 5,85 pmol/L) at screening;

[19] Have had acute myocardial infarction, congestive heart failure New York Heart Association Class III or IV, history of or suspected ischemic heart disease, and/or cerebrovascular accident (stroke [including transient ischemic attack]);

[20] Have findings in the 12-lead ECG at screening that, in the opinion of the investigator, may increase the risks of potentially clinically relevant worsening associated with participation in the study;

[21] Have an active or untreated malignancy or have been 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 <5 years prior to screening;

[22] Have evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies;

[23] Have evidence of hepatitis B or positive hepatitis B surface antigen and/or evidence of hepatitis C virus (HCV) or hepatitis C antibody at screening. Patients with a previous diagnosis of HCV who have been treated with antiviral therapy and achieved a sustained virological response may be eligible for inclusion in the study, provided they have no detectable HCV RNA on the screening HCV polymerase chain reaction test. A sustained virological response is defined as an undetectable HCV RNA level 24 weeks after completion of a full, documented course of an approved antiviral therapy for HCV.

Patients who have spontaneously cleared HCV infection, defined as (1): a positive HCV antibody test and (2): a negative HCV RNA test, with no history of anti-HCV treatment, may be eligible for inclusion in the study, provided they have no detectable HCV RNA on screening for this study.

[24] Have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5× the upper limit of normal (ULN) or total bilirubin level (TBL) >1.5× ULN;

[25] Have had a blood donation of 500 mL or more in the last 3 months or any blood donation within the last month prior to screening;

[26] Have had a blood transfusion or severe blood loss within the last 3 months or have known hemoglobinopathy, hemolytic anemia, sickle cell anemia, or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with hemoglobin A1c measurement;

[27] Have a history of drug or alcohol abuse; and/or smoke >10 cigarettes per day or the equivalent; or are unable or unwilling to refrain from nicotine 4 hours before each CRU admission and outpatient visit, and throughout the duration of each CRU visit;

[28] Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits), or are unwilling to stop alcohol consumption 24 hours before each CRU admission and outpatient visit, and throughout the duration of each CRU visit;

[29] Have evidence of significant active neuropsychiatric disease as determined by the investigator;

Prior/Concomitant Therapy - General

[30] Have been treated with prescription drugs that promote weight loss (e.g., sibutramine, mazindol, phentermine, lorcaserin, naltrexone/bupropion, liraglutide) or similar other body weight loss medications, including over-the-counter medications (e.g., alli®) within 3 months prior to screening or between screening and randomization;

[31] Have received chronic (lasting >14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-articular, and inhaled preparations) within 1 month before screening, or between screening and randomization;

[32] Have received treatment with a drug that has not received regulatory approval for any indication within 1 month prior to screening; if the previous study drug has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

Prior/Concurrent Clinical Trial Experience

[33] Are persons who have previously completed or withdrawn from this study;

[34] Have previous exposure or known allergies to tirzepatide or related compounds, or have an intolerance to GLP-1RAs;

[35] Are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.

Other Exclusions

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

[37] Are Eli Lilly and Company, University of Graz, or Covance employees.;

[38] Are deemed unsuitable by the investigator for any other reason.

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, patients may undergo medical assessments and review of compliance with requirements described in this section before continuing in the study.

6.3.1. Meals and Dietary Restrictions

During the study, patients should follow their usual dietary regimen that is a part of their diabetes management, as agreed with the investigator or his/her designee. For certain assessments, the patients will be required to attend the CRU in a fasting state, after an overnight fast lasting at least 8 hours, for safety laboratory tests and hormone assessments, or for longer during the hypoglycemic clamp.

6.3.2. Caffeine, Alcohol, and Tobacco

No alcohol will be allowed at least 24 hours before each CRU admission and outpatient visit and throughout the duration of each CRU visit. Caffeine consumption will not be permitted during the hypoglycemic clamp visits. Between CRU visits, weekly alcohol should not exceed 21 units per week for males and 14 units per week for females (a unit is defined in Section 6.2 Exclusion Criteria). No nicotine use will be allowed at least 4 hours before each CRU admission and outpatient visit and throughout the duration of each CRU visit. While not resident in the CRU, nicotine use must be no more than 10 cigarettes or equivalent per day.

6.3.3. Activity

Patients will be advised to maintain their regular levels of physical activity/exercise during the study. No intense physical activity will be allowed for at least 48 hours before each CRU admission. When certain study procedures are in progress at the CRU, patients may be required to remain recumbent or sitting.

6.4. Screen Failures

Screening may include re-assessment of some parameters (for example, vital signs and ECGs) and laboratory tests at the discretion of the investigator. Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened up to 1 additional time. Additionally, individuals who had been rescreened once and marked as screen failures during the halt in enrolment due to the COVID-19 pandemic may be allowed to be rescreened up to 1 more time. The interval between re-screenings should be at least 2 weeks. When re-screening is performed, the individual must sign a new ICF and will be assigned a new site screening number. If patients are rescreened, they will be assigned a new screening number. Patient numbers/enrollment numbers are assigned at Visit 2 to ensure only eligible patients enter the study.

7. Treatment

7.1. Treatment Administered

This study involves a crossover comparison of tirzepatide 15 mg and placebo administered SC QW for 12 weeks per treatment period with a washout of at least 8 weeks between treatment periods.

Table GPHG.2 shows the treatment regimens and dose escalation plan.

Table GPHG.2. Dose Titration

	Dose Titration Schemes			
Treatment	Week 1-2	Week 3-4	Week 5-8	Week 9-12
Tirzepatide	1 × 2.5-mg PFS	1 × 5-mg PFS	1 × 10-mg PFS	1 × 15-mg PFS
Placebo	1 × PFS	1 × PFS	1 × PFS	1 × PFS

Abbreviations: PFS = prefilled syringe.

All treatments will be administered QW, either at the CRU or self-administered by the patient. All injections will be administered into the SC tissue of the abdominal wall. Injection sites will be alternated weekly between 4 sites (right and left upper quadrants and right and left lower quadrants) of the abdominal wall.

The investigator or designee is responsible for:

- explaining the correct use of the IP to the patient and site personnel
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection
- and returning all unused medication to Lilly or its designee at the end of the study

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

The site will be instructed to discard used medications according to local regulations.

7.1.1. Packaging and Labeling

All strengths of tirzepatide will be provided as prefilled syringes (PFS) containing 0.5-mL solution and provided in individual cartons to be dispensed. Placebo will also be provided as matching 0.5-mL PFS.

The IP will be labeled according to the country's regulatory requirements.

7.1.2. Medical Devices

The medical devices provided for patient use in the study (SMPG) are commercially available glucose meters and lancets.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to receive either tirzepatide 15 mg followed by placebo or vice versa. Assignment to treatment sequence will be determined by a randomization table with treatment codes.

7.2.1. Selection and Timing of Doses

The doses will be administered QW according to the randomization schedule, on the same day of the week and at approximately the same time of the day. Visit windows should be used for dosing only when the patient is unable to attend the CRU on the scheduled day. The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF). If a patient does not receive her/his planned treatment dose on the scheduled day, the dose should be administered as soon as possible and at least 72 hours prior to the next scheduled dose. If the remaining time to the next scheduled dose is less than 72 hours, the dose will not be administered and will be considered a missed dose.

7.3. Blinding

This study is a patient- and investigator-blind study. Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan.

If a patient's study treatment assignment is unblinded, the patient must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist (CP) or clinical research physician (CRP) for the patient to continue in the study. During the study, emergency unblinding should occur only by accessing the patient's emergency code.

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

Upon completion of the study, all codes must be returned to Lilly or its designee.

7.4. Dose Modification

The patient should follow the planned dosing regimen. In the case of poor tolerability during the dose escalation phase of the study, dosing can be interrupted temporarily (Section 8.1.2 Temporary Interruption of Study Drug).

7.4.1. Special Treatment Considerations

Plasma glucose values will be measured daily at fasting by the patient using the BG meter provided during the lead-in period, after the eligibility is confirmed. Additional SMPG

measurements may be required, if needed, and will be agreed between the patient and the investigator or her/his designee.

7.4.1.1. Management of Hypoglycemia

To reduce the risk of hypoglycemia during the study, patients who have experienced more than 1 episode of severe hypoglycemia, as defined by the American Diabetes Association criteria in the 6 months prior to screening, who have a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms, or who cannot communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia prior to the first dose of study drug, will not be enrolled in the study.

If spontaneous hypoglycemia occurs, each episode will be treated according to the standards of care by the investigator and additional monitoring of glucose levels may be requested at the investigator's discretion (American Diabetes Association 2018). If an adjustment in treatment regimen would be needed to address increased frequency of hypoglycemia after randomization, the dose of metformin must be first reduced or, if clinically appropriate, metformin can be discontinued.

Should severe hypoglycemic episodes with coma, seizure, or neurologic impairment occur at any time, the patient may be treated with intramuscular/SC glucagon and/or concentrated intravenous (IV) glucose and will be discontinued from the study. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

For management of hypoglycemia during the clamp procedures, see Section 7.4.1.3 (Treatment of Hypoglycemia during Hypoglycemic Clamp).

For hypoglycemia reporting, see Section 9.2.2.2 (Hypoglycemia).

7.4.1.2. Management of Hyperglycemia

If SMPG records indicate that PG values are exceeding the limits for severe, persistent hyperglycemia described in Section 9.2.2.3 (Severe, Persistent Hyperglycemia), and no intercurrent cause of the hyperglycemia is evident, rescue medications should be considered at the next scheduled clinic visit. The patient will be prescribed a rescue medication that does not interfere with study measurements. Acceptable rescue medications are listed in Section 7.7 (Concomitant Therapy). Patients who initiate rescue medications will be advised to follow appropriate national and international standards of care for management of diabetes, including applicable glycemic targets and SMPG schedule.

7.4.1.3. Treatment of Hypoglycemia during Hypoglycemic Clamp

The aim of the hypoglycemic clamp is to induce hypoglycemia in a controlled manner, with PG closely monitored and variable glucose infusion preventing PG falling below the target concentration. Should the symptoms of hypoglycemia become unacceptable, glucose will be infused to increase PG and this may result in PG concentrations above the target 45 mg/dL (2.5 mmol/L) being considered as the nadir.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all IP received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive IP or study materials, and only authorized site staff may supply IP to patients for self-administration, or administer IP when patients are at the CRU. At the CRU, IP should be stored in an 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. Patients should store supplies for self-administration in accordance with the carton label.

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).

7.6. Treatment Compliance

When the IP is administered at the study site, documentation of treatment administration will occur at the site. When IP is self-administered by the patient, they will document administration in their diary. Patients will be considered compliant if they received at least 75% of their scheduled doses for each 4-week interval during the treatment period. When assessing treatment compliance, the missed doses (Section 7.2.1 Selection and Timing of Doses) and interrupted doses (Section 8.1.2 Temporary Interruption of Study Drug) will be taken into consideration. Patients who are repeatedly (2 or more episodes) noncompliant with the dosing regimen will be reviewed by the investigator and sponsor to determine if the patient should continue treatment or be discontinued from the study.

7.7. Concomitant Therapy

Glucose-Lowering Medications

Section 6.1 (Inclusion Criteria) and Section 6.2 (Exclusion Criteria) provide requirements regarding the use of glucose-lowering medications prior to entry and during the screening period. All patients in the study are required to be treated with stable doses of metformin for at least 3 months prior to study entry. In addition, one additional OAM is allowed prior to randomization (Refer to Inclusion Criterion [2]), but must be discontinued after eligibility is confirmed at Visit 2, in which case a 4-week minimum washout is required.

Refer to Section 5.1.1 and 5.1.3 for additional information on washout period prior to starting study treatment.

Patients are required to continue metformin as their only concomitant antihyperglycemic medication during the entire study. The dose of metformin should remain unchanged during the screening/lead-in and the treatment periods. If the dose of metformin would need to be decreased or discontinued before randomization per country-specific label (for example, because of reduced renal function), the patient will be considered ineligible and will be discontinued from

the study immediately. Dose adjustment or discontinuation after randomization is allowed only if required per country-specific label to protect patient safety, in which case the patient will be allowed to continue her/his participation in the study. If a patient changes the formulation from the immediate-release formulation of metformin to the sustained-release formulation, or vice versa, the change will be on a milligram-per-milligram basis.

Glucose-lowering medications, other than rescue medications after randomization, are not allowed at any time during the 3-month period prior to study entry and any time after study entry until the end of the treatment period. In the case of acute conditions, a short-term (<14 days) use of insulin is allowed any time prior to entry and after randomization, but not during the screening/lead-in period.

The allowed rescue medications in the case of severe, persistent hyperglycemia after randomization are insulin and sulphonylureas. The preference should be given to the use of insulin, with sulphonylurea to be considered only if the patient is not willing to initiate insulin therapy. The sodium-dependent glucose co-transporter-2 (SGLT2) inhibitors should not be used because of possible interference with regulation of glucagon secretion. The GLP-1 RAs and dipeptidyl peptidase IV inhibitors should not be used because these classes of agents share the same mode of action pathways with dual GIP/GLP-1 RAs. Patients will be required to discontinue rescue medications 1 week prior to the clamp procedures.

After the completion of the treatment periods, patients can receive other glucose-lowering agents, except GLP-1 RAs.

Weight-Lowering Medications

Section 6.2 (Exclusion Criteria) provides requirements regarding prescription drugs that promote weight loss prior to entry and during the screening/lead-in period. Prescription or over-the-counter medications to promote weight loss are not allowed after randomization. If used ≤14 days, the patient will be required to discontinue this treatment and continue in the study. If used >14 days after randomization, the patient will be immediately discontinued from the study drug and will perform end-of-study procedures (ET visit and safety follow-up within 4 weeks). If prescription or over-the-counter medications to promote weight loss are used, this will be considered a protocol deviation.

Corticosteroids

Section 6.2 (Exclusion Criteria) provides requirements regarding the use of chronic systemic glucocorticoids prior to entry and during the screening/lead-in period. Patients treated with systemic glucocorticoid therapy after randomization for >14 consecutive days (with the exception of topical, intra-articular, and inhaled preparations) will be discontinued from the study. If used ≤14 days, the patient will be required to discontinue this treatment and continue in the study.

Other Medications

All other concomitant medications that the patient is already taking are allowed. If the need for dose adjustment for the currently used concomitant medications or addition of a new concomitant medication arises, the patient may be continued in the study on study medication if, in the investigator's opinion, the addition of the new medication does not pose a safety risk. Nausea and/or vomiting during this study may be treated with anti-emetics but they should not be used prophylactically. Similarly, antidiarrheal agents are allowed to be prescribed if the patient reports AEs of diarrhea. For details on the use of symptomatic agents for treatment of GI AEs, see Section 7.7.1 (Management of Patients with Gastrointestinal Symptoms).

7.7.1. Management of Patients with Gastrointestinal Symptoms

The tirzepatide dose escalation scheme has been designed to reduce the development of intolerable GI symptoms. The escalation period for tirzepatide is considered to be 8 weeks to reach the 15-mg maintenance dose and additional 4 weeks to reach steady-state. During the dose escalation period, every effort should be made by the investigator to be able to escalate and maintain patients on the corresponding study drug dosage.

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

- Advise patients to eat smaller meals, for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full.
- Prescribe symptomatic medication (for example, anti-emetic or anti-diarrheal medication) per local country availability and individual patient needs.
- Temporarily interrupt study drug per guidance provided in Section 8.1.2 (Temporary Interruption of Study Drug).

7.8. Treatment after the End of the Study

Not applicable. Tirzepatide will not be made available to patients after completion of the study.

8. Discontinuation Criteria

Patients discontinuing from the study prematurely for any reason should complete ET visit and safety follow-up visit procedures according to Section 2 (Schedule of Activities).

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of IP:

- The patient requests to discontinue IP
- If a patient is inadvertently enrolled and it is determined that continued treatment with study drug would not be medically appropriate (Section 8.1.3 Discontinuation of Inadvertently Enrolled Patients)
- If a patient is diagnosed with acute or chronic pancreatitis after randomization
- If a patient is diagnosed with 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
- If a patient is diagnosed with a significant study drug-related hypersensitivity reaction
- If a patient is diagnosed at any time, including during the hypoglycemic clamp procedure, with any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
- If a female patient becomes pregnant
- If a patient is diagnosed with type 1 diabetes mellitus
- Drug-related vomiting requiring IV hydration treatment or causing severe distress (prevents daily activities and results in no appetite, or requires an emergency department visit or hospitalization), that cannot be resolved by temporary interruption of study drug (Section 8.1.2 Temporary Interruption of Study Drug)

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

- ALT or AST >8X ULN
- ALT or AST >5X ULN sustained for more than 2 weeks or
- ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio >1.5 or

- 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%)

Patients who discontinue study drug early will also be discontinued from the study after performing ET visit and safety follow-up visit procedures, as specified in Section 2 (Schedule of Activities).

8.1.2. Temporary Interruption of Study Drug

In certain situations, after randomization, for example, if GI tolerability AEs occur, the investigator may need to temporarily interrupt study drug. Temporary interruptions are allowed during the dose escalation phase (i.e., while the dose is lower than 15 mg) and not during the 4-week maintenance phase of dosing with 15 mg. Investigators should immediately inform the sponsor that study drug has been temporarily interrupted. During an event that requires temporary interruption of study treatment, only 1 dose may be skipped. Every effort should be made by the investigator to maintain patients on study drug and to restart study drug after temporary interruption, as soon as it is assessed as safe to do so. The patient should resume study treatment administration at the scheduled dose level, per protocol. If 2 or more episodes of study interruptions occur in the same patient, these cases will be reviewed by the investigator (or his/her designee) and Lilly to assess the feasibility of the patient's further participation in the study. If study drug interruption is due to an AE, the event will be documented and followed according to the procedures specified in Section 9.2 (Adverse Events). The data related to temporary interruption of study treatment will be documented in source documents and entered into the eCRF.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, the patient must be discontinued from the study unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor CRP agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with study drug.

8.2. Discontinuation from the Study

In addition to the situations that result in study drug discontinuation described in Section 8.1.1 (Permanent Discontinuation from Study Treatment), patients will be discontinued from the study in the following circumstances:

- Enrollment in any other clinical study involving an IP 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
- Investigator Decision
    - the investigator decides that the patient should be discontinued from the study for any reason
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, in which case discontinuation from the study occurs prior to introduction of the new agent
- Patient Decision
    - the patient, or legal representative, requests to be withdrawn from the study.

8.3. Patients 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. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the study site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing.

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the approximate number and volume of invasive samples, for all sampling, during the study.

The specifications in this protocol for the timings of safety and sample collections are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be recorded correctly in the eCRF. Failure or delays (i.e., outside stipulated time allowances) in performing procedures or obtaining samples due to legitimate clinical issues (e.g., equipment technical problems, venous access difficulty, or patient defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations but the CRU will still be required to notify the sponsor in writing via a file note.

Unless otherwise stated in 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

Not applicable.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IP or the study, or that caused the patient to discontinue the IP 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.

The investigator will record all relevant AE and SAE information in the eCRF. After the ICF is signed, study site personnel will record, via eCRF, the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under

treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

A "reasonable possibility" means that there is a potential cause and effect relationship between the IP study device and/or study procedure and the AE.

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

If a patient's IP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF.

9.2.1. Serious Adverse Events

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

- 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.

Study site personnel must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, 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.

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the patient has signed informed consent and has received IP. However, if an SAE occurs after signing informed consent, but prior to receiving IP, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued from and/or completed the study (the patient summary 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.

Pregnancy (maternal or paternal exposure to IP) 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.

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 reports as related to IP or procedure. Lilly has procedures that will be followed for the 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. Severe Gastrointestinal Adverse Events

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

9.2.2.2. Hypoglycemia

Patients will collect information on episodes of hypoglycemia starting immediately after their eligibility is confirmed until the last study visit (follow-up visit). For that purpose, patients will be trained during Visit 2 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 Section 2 (Schedule of Activities). Site personnel will enter this information into the eCRF at each visit.

Outside of the hypoglycemic clamp procedure, investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the PG values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips) (American Diabetes Association 2017):

Glucose Alert Value (Level 1):

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia, and has a PG level of ≤70 mg/dL (≤3.9 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).

Clinically Significant Hypoglycemia (Level 2):

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

Severe Hypoglycemia (Level 3):

- **Severe hypoglycemia** is defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. 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.

Other Hypoglycemia Categories:

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

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

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

In each case of suspected or confirmed hypoglycemia, it is important that the event be properly categorized, the effect of the intervention be assessed, and the frequency of hypoglycemia be evaluated. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established. The patient should receive additional education, if deemed appropriate. The concomitant medications may need to be adjusted as outlined in in Section 7.4.1.1 (Management of Hypoglycemia) and Section 7.7 (Concomitant Therapy).

Additional assessments related to hypoglycemia will be performed during the hypoglycemic clamp procedures, including responses of counter-regulatory hormones (glucagon, growth hormone, adrenaline and noradrenaline, and cortisol), symptoms of hypoglycemia, and parameters related to recovery from hypoglycemia. The measures to evaluate these aspects of hypoglycemia are included in the primary, secondary, and exploratory objectives of the study and are described in further details in Section 9.6 (Pharmacodynamics).

9.2.2.3. Severe, Persistent Hyperglycemia

Data on episodes of severe, persistent hyperglycemia will be reported by the investigator during the study. Events of interest related to hyperglycemia are those that require rescue therapy, per the following criteria:

- The average fasting PG is greater than 270 mg/dL (15 mmol/L) over any 2-week period between Day 1 and end of Week 6.
- The average fasting PG is greater than 240 mg/dL (13.3 mmol/L) over any 2-week period between Week 7 and end of Week 12.

Section 7.4.1.2 (Management of Hyperglycemia) and Section 7.7 (Concomitant Therapy) provide treatment guidance for patients with severe, persistent hyperglycemia.

9.2.2.4. Pancreatitis

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

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

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the local laboratory. 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 study drug, and will be discontinued from the study after completing all ET and follow-up procedures. 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 medical data, including concomitant medications, should be conducted to assess potential causes of 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 study drug.

Each patient will have measurements of amylase and lipase, part of safety laboratory tests as shown in Section 2 (Schedule of Activities) to assess the effects of study drug on pancreatic enzyme levels. Serial measures of pancreatic enzymes have limited clinical value for predicting

episodes of acute pancreatitis in asymptomatic patients (Nauck et al. 2017; Steinberg et al. 2017a; Steinberg et al. 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic amylase ≥3X ULN) is not mandated but may be performed based on the investigator's clinical judgement and assessment of the patient's overall clinical condition. If further diagnostic assessment due to asymptomatic hyperenzymemia is warranted, it should follow Lilly standard algorithm for the monitoring of pancreatic enzymes (refer to Appendix 7).

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent clinical endpoint committee. In addition, all cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up, as well as the 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 possible, probable, or definite acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed eCRF page by study site or Lilly staff. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

9.2.2.5. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or MEN 2 will be excluded from the study, as well as those with calcitonin values ≥20 pg/mL (≥5.89 pmol/L) at screening. The assessment of thyroid safety during the study will include reporting of any case of thyroid malignancy including MTC and papillary carcinoma and measurements of calcitonin. This data will be captured in the specific section of the eCRFs. The purpose of calcitonin measurements is to assess the potential of study treatment to affect thyroid C-cell function, which includes development of C-cell hyperplasia and neoplasms.

Patients who develop calcitonin increases ≥50% of the mean of the screening value AND an absolute value ≥20 pg/mL and <35 pg/mL after randomization, will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the patient will be encouraged to undergo additional endocrine assessment and longer term follow-up by an endocrinologist to exclude a serious adverse effect on the gland. Patients who develop calcitonin increases ≥50% of the mean of the screening value AND an absolute value ≥35 pg/mL after randomization will immediately undergo additional endocrine assessment and longer term follow-up by an endocrinologist. Study drug should be discontinued in situations when postrandomization calcitonin value is ≥35 pg/mL. If the calcitonin value decreases below 35 pg/mL on repeat tests, study drug should be restarted if, in the opinion of the investigator, it is safe to do so. If the increased calcitonin value 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.

For patients who require additional endocrine assessment because of increased calcitonin concentration per criteria provided in this section, data from the additional assessment will be collected in the specific section of the eCRF.

9.2.2.6. Major Adverse Cardiovascular Events

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

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

9.2.2.7. Supraventricular Arrhythmias and Cardiac Conduction Disorders

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

9.2.2.8. 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 for any AEs or SAEs that the investigator deems related to study drug via an eCRF created for this purpose. Additional serum samples should also be collected as outlined in Appendix 8. Study drug should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug. Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator. If study drug is permanently discontinued, the patient will receive another glucose-lowering treatment, judged by the investigator to be appropriate based on the patient's clinical status, and will be discontinued from the study (Section 8.1.1 Permanent Discontinuation from Study Treatment).

9.2.2.9. Injection-site Reactions

Injection-site reactions will be collected on the eCRF created for these events (see Section 9.4.6). At the time of AE occurrence, samples will be collected for measurement of tirzepatide anti-drug antibody (ADA) and tirzepatide concentration.

9.2.2.10. Diabetic Retinopathy Complications

Treatment-emergent AEs related to diabetic retinal complications will be assessed by an ophthalmologist and should include dilated fundoscopic examination.

9.2.2.11. Hepatobiliary Disorders

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

cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 9.4.5.1 (Hepatic Safety) and Appendix 4.

9.2.2.12. Acute Renal Events

Renal safety will be assessed based on laboratory renal functional assessment as well as assessment of AEs suggestive of acute renal failure or worsening of chronic renal failure. Patients with GI AEs, including nausea, diarrhea, and vomiting are at increased risk of developing dehydration. Dehydration may 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.

9.2.2.13. Metabolic Acidosis, Including Diabetic Ketoacidosis

Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been reported rarely in patients with T2DM. Patients who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting BG levels, as ketoacidosis may be present even if BG levels are less than 250 mg/dL (13.9 mmol/L). If ketoacidosis is suspected, 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. If lactic acidosis is suspected, metformin should be temporarily discontinued until the resolution of the event.

9.2.2.14. Amputation/Peripheral Revascularization

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

9.2.2.15. Major Depressive Disorder/Suicidal Ideation

The prevalence of depressive symptoms and disorders is increased in patients with T2DM (Anderson et al. 2001). Any AE of major depressive disorder or suicidal ideation should be reported.

9.2.3. Complaint Handling

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

Patients should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP or drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of tirzepatide is considered any dose higher than the dose assigned through randomization or as defined by the protocol. There is no specific antidote. The patient should be watched for GI symptoms and hypoglycemia. Treatment is supportive, depending on the patient's symptoms. For detailed information, refer to the IB for tirzepatide

9.4. Safety

Safety measures to address the primary and secondary objectives of the study include glucagon and other counter-regulatory hormone concentrations, assessment of symptoms of hypoglycemia and AEs, time to reach recovery PG concentrations (72 mg/dL [4.0 mmol/L]), and vital signs measurements taken during the hypoglycemic clamp procedures. See Section 9.6 (Pharmacodynamics) for further details.

9.4.1. Laboratory tests

For each patient, laboratory tests to assess PD and safety of study drug will be performed throughout the study according to the schedule provided in Section 2 (Schedule of Activities). A detailed list of laboratory analytes is provided in Appendix 2.

9.4.2. Vital Signs

For each patient, vital signs should be assessed according to Section 2 (Schedule of Activities). Blood pressure and pulse rate should be measured after at least 5 minutes in the supine position. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period, if warranted.

Systolic and diastolic blood pressure, pulse rates, and body temperature will also be measured throughout the hypoglycemic clamp procedures (see Section 9.6.2).

9.4.3. Electrocardiograms

For each patient, a single 12-lead digital ECG for safety will be collected according to Section 2 (Schedule of Activities).

Electrocardiograms must be recorded before collecting any blood samples. Patients must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will 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, to determine whether the patient meets study entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/QT corrected for heart rate [QTc] interval from baseline) after enrollment, the investigator will determine if the patient can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in patient management is needed, and must document his/her review of the ECG printed at the time of collection. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of study drug, should be reported to Lilly, or its designee, as an AE via eCRF.

Electrocardiogram will be measured throughout the hypoglycemic clamp procedures (see Appendix 6).

9.4.4. Physical Examinations

Physical examinations and routine medical assessments will be conducted as specified in Section 2 (Schedule of Activities) and as clinically indicated.

9.4.5. Safety Monitoring

The Lilly CP or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review the following data:

- regular trial-level safety reviews to assess the overall trends in safety data;
- safety laboratory analytes;
- serious and nonserious AEs, including AEs of special interest, including GI events, pancreatitis, and serious hypoglycemic events.

When appropriate, the Lilly CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

9.4.5.1. Hepatic Safety

If a patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated total bilirubin ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase 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 based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Additional safety data should be collected if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥ 5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥ 2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥ 2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE.

9.4.6. Injection-site Reactions

Injection-site assessments for local tolerability will be conducted, when reported as:

- an AE from a patient, or

- a clinical observation from an investigator.

Reported injection-site reactions will be characterized within the following categories:

- edema
- erythema
- induration
- itching
- pain

All injection-site reactions reported as AEs will be closely monitored until resolution. The report of a clinically significant AE of injection-site reaction may prompt notification of the sponsor, clinical photography, and referral for dermatologic evaluation and consideration of a skin biopsy and laboratory evaluations (ALT, AST, complete blood count with percent eosinophils, and additional immunogenicity testing).

Site staff will be provided with separate instructions/training on how to evaluate injection-site reactions and their severity in a consistent manner. Photographs of injection-site reactions may be taken in a standardized manner for record-keeping purposes; however, the photographs will not be used to evaluate the severity of injection-site reaction.

9.5. Pharmacokinetics

At the visits and times specified in Section 2 (Schedule of Activities), venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of tirzepatide. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded.

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry method. Analyses of samples collected during placebo treatment are not planned.

Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 2 years following last patient visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, or bioanalytical method cross-validation.

9.6. Pharmacodynamics

The samples will be stored for up to a maximum of 1 year after last patient visit for the study at a facility selected by the sponsor.

A description of procedures for obtaining the samples for pharmacodynamic (PD) parameters is detailed in Appendix 6. Briefly, PD assessments will include measurement of glucagon, insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline before and/or during the hypoglycemic clamp, as well as clinical symptoms of hypoglycemia, hypoglycemia awareness, and time to recovery from hypoglycemia following the clamp procedure. Vital signs will also be measured during the procedure and data will be collected in the clinical trial database for analyses.

9.6.1. Primary Pharmacodynamic Assessments and Procedures

The primary PD measure in this study is the mean glucagon concentration change from target PG of 100 mg/dL (5.5 mmol/L) to a target nadir PG of 45 mg/dL (2.5 mmol/L) during induced hypoglycemia for comparison of tirzepatide with placebo.

Glucagon concentration at the PG target concentration of 100mg/dL (5.5 mmol/L) will be calculated as the mean of measurements taken 20, 10, and 0 minutes prior to induction of hypoglycemia. Glucagon concentration at the PG target concentration of 45 mg/dL (2.5 mmol/L) will be calculated as the mean of measurements taken 10, 20, and 30 minutes after reaching a nadir PG of 45 mg/dL (2.5 mmol/L), or a higher nadir PG if 45 mg/dL (2.5 mmol/L) cannot be achieved for practical or safety reasons.

9.6.2. Secondary Pharmacodynamic Assessments and Procedures

The following will be secondary PD measures in the study.

Secondary PD measures to assess the effect of tirzepatide compared to placebo on counter-regulatory hormone, insulin, and C-peptide concentrations.

- Change in mean glucagon concentration (calculated as the mean of 3 measurements during the clamp, measured singly at recovery) from target PG concentration of 100 mg/dL (5.5 mmol/L) to 63 mg/dL (3.5 mmol/L) and after recovery from induced hypoglycemia (PG 72 mg/dL [4.0 mmol/L]).
- Change in mean glucagon concentration (calculated as the mean of 3 measurements during the clamp, measured singly at recovery) from ambient PG to target concentrations of 100, 63, and 45 mg/dL, and after recovery from induced hypoglycemia (PG 72 mg/dL) (5.5, 3.5, 2.5, and 4.0 mmol/L, respectively).
- Change in mean insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations (calculated as the mean of 3 measurements during the clamp, measured singly at recovery) from target PG concentration of 100 mg/dL (5.5 mmol/L) to 63 and 45 mg/dL and after recovery from induced hypoglycemia (72 mg/dL) (3.5, 2.5, and 4.0 mmol/L, respectively).

Secondary PD measures to assess the effect of tirzepatide compared to placebo on time to recovery from hypoglycemia.

- Time from termination of insulin infusion at PG concentration of 45 mg/dL (2.5 mmol/L) to reach recovery PG concentration (72 mg/dL [4.0 mmol/L]) ($t_{PG\_nadir\text{-}72\ mg/dL}$).

Secondary PD measures to assess the effect of tirzepatide compared to placebo on vital signs during hypoglycemia.

- Change in mean systolic and diastolic blood pressure and pulse rates (calculated as the mean of 2 measurements during the clamp, measured singly at recovery) from target PG concentration of 100 mg/dL (5.5 mmol/L) to 63, 45, and 72 mg/dL (3.5, 2.5, and 4.0 mmol/L, respectively).

Secondary PD measures to assess the effect of tirzepatide compared to placebo on clinical hypoglycemia.

- Hypoglycemic symptoms score (calculated as the mean of 2 measurements during the clamp, measured singly at recovery) at target PG concentrations of 100, 63, and 45 mg/dL, and after recovery from induced hypoglycemia (72 mg/dL) (5.5, 3.5, 2.5, and 4.0 mmol/L, respectively).
- Hypoglycemic awareness at PG concentrations of 100, 63, and 45 mg/dL, and after recovery from induced hypoglycemia (72 mg/dL) (5.5, 3.5, 2.5, and 4.0 mmol/L, respectively).

Symptoms of hypoglycemia will be measured using the Edinburgh Hypoglycemia Scale and hypoglycemic awareness will be evaluated based on the patients' response (yes/no) to the question "Do you feel hypoglycemic?".

9.6.3. Exploratory Pharmacodynamic Assessments and Procedures

Exploratory PD measures to assess the effect of tirzepatide compared to placebo on other hypoglycemic clamp parameters and recovery from hypoglycemia including:

- Amount of insulin required to reach PG concentrations of 63 and 45 mg/dL (3.5 and 2.5 mg/dL) from 100 mmol/L (5.5 mmol/L)
- Area under the glucose infusion rate curve from time of termination of insulin infusion until recovery (PG concentration of 72 mg/dL [4.0 mmol/L]) ($AUC_{GIR,PG\_nadir\text{-}72\ mg/dL}$)
- Proportions of patients who require glucose infusion to attain recovery (PG concentration 72 mg/dL [4.0 mmol/L]) and associated total amount of glucose infused (Gtot)
- Plasma glucose achieved at the end of the spontaneous recovery period

9.6.4. Immunogenicity Assessments

For immunogenicity testing, venous blood samples of approximately 10 mL will be collected from each patient according to the Schedule of Activities (Section 2 to determine antibody production against tirzepatide. Additional samples may be collected if there is a possibility that an AE is immunologically mediated (see Section 9.4.6). All samples for immunogenicity testing

should have a time-matched sample for PK analysis. Detailed instructions on the sample collections and handling will be provided by Lilly or its designee. The actual date and 24-hour clock time of each sampling will be recorded.

Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of tirzepatide at a laboratory approved by the sponsor. Antibodies may be further evaluated for their ability to neutralize the activity of tirzepatide on GIP and GLP-1 receptors. Positive tirzepatide ADA samples may be tested for cross-reactivity against native GIP and GLP-1, and, if positive, may then be tested for neutralizing antibodies against native GIP and/or GLP-1.

All patients will have an ADA sample measured at ET and at the safety follow-up visit. A risk-based approach will be used to monitor patients who develop treatment-emergent anti-drug antibodies (TE-ADA), defined in Section 10.3.4 (Evaluation of Immunogenicity).

Clinically significant TE-ADA will be defined as any TE-ADA at the last visit with:

- a high titer (≥1280) or an increasing titer from last measured value
- an association with a moderate-to-severe injection-site reaction or infusion-related reaction

Patients who have clinically significant TE-ADA at early discontinuation or at the safety follow-up visit, should have additional follow-up ADA testing every 3 months until the ADA titers have return to the baseline ADA titer (defined as ADA titer within 2-fold of baseline) or for up to 1 year, whichever is less. A PK sample may be collected at the additional follow-up immunogenicity assessment(s), if warranted and agreed upon by the investigator and sponsor.

Every attempt should be made to contact patients for the additional follow-up immunogenicity assessment; however, if patients are unwilling or unable to return for the visit, this is not considered a protocol deviation.

Patients followed for at least 1 year since last dose who have not returned to baseline as defined above, will be assessed for safety concerns, and if no clinical sequelae are recognized by the clinical team, no further follow-up will be required. Patients who have clinical sequelae that are considered potentially related to the presence of TE-ADA may also be asked to return for additional follow-up testing.

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.

9.6.5. Body Weight

Weight will be measured according to Section 2 (Schedule of Activities). Patients will be weighed at approximately the same time in the morning, before dosing, where applicable, and after an overnight fast and evacuation of the bowel and bladder, if possible. Wherever possible, the same scale will be used for all weight measurements throughout the study and the scale will

not be moved or recalibrated. Weight measurements will be recorded in the source document and the eCRF.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, 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 exposure or response to tirzepatide and to investigate genetic variants thought to play a role in T2DM, obesity, or diabetic complications. 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 investigative site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, for the study at a facility selected by Lilly. 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 is 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, multiplex assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

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

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

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

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 investigative site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by Lilly. 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 is commercially available.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 38 patients are planned to be enrolled so that 30 patients complete the study assuming a 20% discontinuation rate. The calculation is based on the criterion that the width of the 95% confidence interval (CI) for the treatment comparison of the primary endpoint is within ±23.65 pg/mL with approximately 80% probability, provided that the within-subject variability is 40 pg/mL (Korsatko et al. 2018).

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

Demographic and baseline characteristics will be summarized.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

Pharmacodynamic analyses will be conducted on data from all patients who complete both hypoglycemic clamp procedures.

Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted, as deemed appropriate.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

The incidence of AEs for each treatment will be presented by severity and by association with IP, as perceived by the investigator. Adverse events reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

All AEs and SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs (throughout the treatment periods and during the hypoglycemic clamp procedures), TEAEs (including TEAEs of special interest), and SAEs. The parameters will be listed, and summarized using standard descriptive statistics. Additionally, analyses may be performed if warranted upon review of the data. All AEs related to study or protocol procedure will be listed, and if the frequency of events allows, will be also summarized using descriptive methodology.

Hypoglycemia rate outside of the hypoglycemic clamp will be summarized for each treatment group and visit as well as overall by mean, standard deviation, median, minimum, and maximum. Hypoglycemia incidence outside of the hypoglycemic clamp will be summarized for each treatment group and visit as well as overall by percent (%) and n.

Vital signs will be summarized with respect to observed values and change from baseline (Day 1, predose) by treatment at each time point using descriptive statistics.

See Section 10.3.3.1 (Pharmacodynamic Parameter Estimations) for details of analysis of vital signs assessed during the clamp procedures.

10.3.1.3. Injection-site Reactions

Incidence of erythema, induration, pain, itching, and edema will be listed and summarized by treatment.

Additional analyses may be performed, if appropriate.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic samples will be collected according to Section 2 (Schedule of Activities). Tirzepatide concentrations will be determined to support an understanding of tirzepatide exposure over the treatment duration to compare with expected tirzepatide PK.

10.3.2.2. Pharmacokinetic Statistical Inference

No PK parameters will be derived; thus no analyses of PK parameters are planned.

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimations

During the hypoglycemic clamp, for safety considerations, if the target PG concentrations are not achieved within 30 minutes of completion of the previous step, a higher PG concentration will be accepted as the PG concentration at which assessments are conducted. In case 45 mg/dL (2.5 mmol/L) cannot be reached or symptoms of hypoglycemia are unacceptable, nadir at a higher PG concentration will be accepted and data will be included in the analysis.

Mean glucagon, insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations at target PG concentration clamp steps of 100, 63, and 45 mg/dL (5.5, 3.5, and 2.5 mmol/L) will be calculated from the 3 measurements taken during each clamp step. The concentrations are measured singly at ambient PG (glucagon only) and upon recovery to 72 mg/dL (4.0 mmol/L).

Mean systolic and diastolic blood pressure and pulse rate at target PG of 100, 63, and 45 mg/dL (5.5, 3.5, and 2.5 mmol/L) will be calculated using the average of the 2 measurements taken at each corresponding PG level. Blood pressure and pulse rate will be measured singly when recovery PG of 72 mg/dL (4.0 mmol/L) is reached.

10.3.3.2. Pharmacodynamic Statistical Inference

The primary PD parameter for analysis will be the change in mean glucagon concentration between the 100 mg/dL (5.5 mmol/L) clamp step and the nadir target 45 mg/dL (2.5 mmol/L) step. This will be evaluated using a linear mixed-effects model, with treatment, treatment period, treatment sequence as fixed effects, and patient as a random effect.

From the model, the difference between tirzepatide and placebo in least squares means estimates and the corresponding 95% CIs for the difference will be calculated.

The secondary PD measures for statistical analysis are:

- Change in mean glucagon concentration from target PG concentration of 100 mg/dL (5.5 mmol/L) to 63 mg/dL (3.5 mmol/L) and to recovery (PG concentration 72 mg/dL [4.0 mmol/L]) from induced hypoglycemia
- Change in mean glucagon concentration from ambient PG to target PG concentrations of 100, 63, and 45 mg/dL (5.5, 3.5, and 2.5 mmol/L), and recovery (PG concentration 72 mg/dL [4.0 mmol/L]) from induced hypoglycemia
- Change in mean insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations from target PG concentration of 100 mg/dL (5.5 mmol/L), to 63 and 45 mg/dL (3.5 and 2.5 mmol/L), and recovery (PG concentration of 72 mg/dL [4.0 mmol/L]) from induced hypoglycemia
- $t_{PG\_nadir\text{-}72\ mg/dL}$

These parameters will be analyzed using a similar model to that described for the primary endpoint. If the $t_{PG\_nadir\text{-}72\ mg/dL}$ is highly skewed, a log-transformation may be considered. If the assumptions of the model appear to be violated, a non-parametric analysis may be performed.

In addition, the following parameters will be listed and summarized using standard descriptive statistics:

- Change in mean systolic and diastolic blood pressure and pulse rate from target PG concentration 100 mg/dL (5.5 mmol/L) to PG 63, 45, and 72 mg/dL, (3.5, 2.5, and 4.0 mmol/L).
- Hypoglycemic symptom scores at PG concentrations of 100, 63, and 45 mg/dL (5.5, 3.5, 2.5 mmol/L) and after recovery (PG concentration 72 mg/dL [4.0 mmol/L]) from induced hypoglycemia.
- Hypoglycemic awareness scores at PG concentrations of 100, 63, and 45 mg/dL (5.5, 3.5, 2.5 mmol/L) and after recovery (PG concentration 72 mg/dL [4.0 mmol/L]) from induced hypoglycemia.

Analysis of exploratory objectives will be detailed in the statistical analysis plan.

10.3.4. Evaluation of Immunogenicity

The frequency and percentage of patients with preexisting ADA and with TE-ADA+ to tirzepatide will be tabulated. Treatment-emergent ADA are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). The minimum required dilution of the ADA assay is 1:10. For the TE-ADA+ patients, the distribution of maximum titers will be described. The frequency of neutralizing antibodies if performed, will be tabulated in TE-ADA+ patients. If cross-reactivity to native GLP-1 and GIP or neutralizing antibodies against native GLP-1 and GIP assays are performed, the frequency of each will be reported.

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

10.3.5. Interim Analyses

No interim analyses are planned for this study, although data may be reviewed periodically on an ongoing basis. If an unplanned interim analysis is deemed necessary, the Lilly CP, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

11. References

[ADA] American Diabetes Association. Glycemic targets. Sec. 6. In Standards of Medical Care in Diabetes—2017. *Diabetes Care*. 2017;40(suppl 1):S48-S56.

[ADA] American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes—2018. *Diabetes Care*. 2018;41(suppl 1):S55–S64.

Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of co-morbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001;24(6):1069–1078.

Balijepalli C, Druyts E, Siliman G, Joffres M, Thorlund K, Mills EJ. Hypoglycemia: a review of definitions used in clinical trials evaluating hyperglycemic drugs for diabetes. Clin Epidemiol. 2017;23(9):291-296.

Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379-2400.

Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab*. 2013;17(6):818-837.

Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, Cui X, Briere DA, Cabrera O, Roell WC, Kuchibhotla U, Moyers JS, Benson CT, Gimeno RE, D'Alessio DA, Haupt A. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. *Mol Metab*. 2018;18:3-14.

Danne T, Philotheou A, Goldman D, Guo X, Ping L, Cali A, Johnston P. A randomized trial comparing the rate of hypoglycemia – assessed using continuous glucose monitoring – in 125 preschool children with type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study). *Pediatr Diabetes*. 2013;14(8):593-601.

EMA 2012. European Medicines Agency Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes Mellitus. 2012. [Accessed December 5, 2016]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf

Finan B, Müller TD, Clemmensen C, Perez-Tilve D, DiMarchi RD, Tschöp MH. Reappraisal of GIP pharmacology for metabolic disease. Trends Mol Med. 2016;22(5):359-376.

Frias JP, Nauck MA, Van J, Kutner ME, Cui X, Benson C, Urva S, Gimeno RE, Milicevic Z, Robins D, Haupt A. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet*. 2018;392(10160): 2180-2193.

Koizumi M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, Sekimoto M, Hirota M, Kimura Y, Takeda K, Isaji S, Otsuki M, Matsuno S; JPN. JPN Guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2006;13(1):25-32.

Morales J, Schneider D. Hypoglycemia. *Am J Med*. 2014. 127(10 suppl):S17-24.

Nauck MA, Frossard J-L, Barkin JS, Anglin G, Hensley I, Harper KD, Milicevic Z. Assessment of pancreas safety in the development program of once-weekly GLP-1 receptor agonist dulaglutide. *Diabetes Care*. 2017;40(5):647.

Korsatko S, Jensen L, Brunner M, Sach-Friedl S, Tarp MD, Holst AG, Heller SR, Pieber TR. Effect of once-weekly semaglutide on the counterregulatory response to hypoglycaemia in people with type 2 diabetes: A randomized, placebo-controlled, double-blind, crossover trial. *Diabetes Obes Metab*. 2018;20(11):2565-2573.

Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 2013;36(5):1384–1395.

Steinberg WM, Buse JB, Ghorbani MLM, Ørsted DD, Nauck MA; LEADER Steering Committee; LEADER Trial Investigators. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: results from the LEADER Randomized Trial. *Diabetes Care*. 2017a;40(7):966-972.

Steinberg WM, Rosenstock J, Wadden TA, Donsmark M, Jensen CB, DeVries JH. Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: secondary analyses of pooled data from the SCALE clinical development program. *Diabetes Care*. 2017b;40(7):839-848.

Weinberg ME, Bacchetti P, Rushakoff RJ. Frequently repeated glucose measurements overestimate the incidence of inpatient hypoglycemia and severe hyperglycemia. *J Diabetes Sci Technol*. 2010;4(3):577-582.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{GIR,PG\_nadir\text{-}72\ mg/dL}$	area under the glucose infusion rate curve from time of termination of insulin infusion until recovery (plasma glucose concentration of 72 mg/dL)
BAT	basophil activation test
BG	blood glucose
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
CI	confidence interval
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	Clinical Pharmacologist
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.

CRU	clinical research unit
CT	computed tomography
ECG	Electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ET	early termination
GCP	Good Clinical Practice
GI	Gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIPR	glucose-dependent insulinotropic polypeptide receptor
GIPRA	glucose-dependent insulinotropic polypeptide receptor agonism
GIR	glucose infusion rate
GLP-1	glucagon-like peptide 1
GLP-1R	glucagon-like peptide 1 receptor
GLP-1RA	glucagon-like peptide 1 receptor agonist
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
IgE	Immunoglobulin E
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	Intravenous
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
MAD	multiple ascending dose
MEN 2	multiple endocrine neoplasia syndrome type 2
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NMH	*N*-methylhistamine
Non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical study, but is provided to patients and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
randomize	The process of assigning patients to an experimental group on a random basis.
PG	plasma glucose
PFS	prefilled syringe
PK/PD	pharmacokinetic/pharmacodynamic
QW	once-weekly
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous(ly)
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SMPG	self-monitoring of plasma glucose
SUSARs	suspected unexpected serious adverse reactions

T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TE-ADA	treatment-emergent anti-drug antibody
TEAE	treatment-emergent adverse event: Any 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
$t_{PG\_nadir\text{-}72\ mg/dL}$	time from termination of insulin infusion at plasma glucose concentration of 45 mg/dL to reach recovery plasma glucose concentration 72 mg/dL
ULN	upper limit of normal
WOCBP	women of childbearing potential

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology	**Clinical Chemistry (fasting)**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Glucose
Platelets	Blood urea nitrogen
Absolute counts of:	Uric acid
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Total bilirubin
Eosinophils	Alkaline phosphatase
Basophils	Alanine aminotransferase
	Aspartate aminotransferase
	Creatinine
	Lipase
	Amylase
	Total cholesterol
	Triglyceride
	Hemoglobin A1c
Urinalysis	
Specific gravity	**Endocrine**
pH	Follicle-stimulating hormone[a]
Protein	Calcitonin[b]
Glucose	
Ketones	**Serology[c]**
Bilirubin	Hepatitis B surface antigen
Urobilinogen	Hepatitis C antibody, hepatitis C RNA[d]
Blood	HIV antibody
Leukocytes	
Nitrite	Pregnancy test (urine, serum)[e]
Microscopy[a]	Drug and alcohol screen[f]

Abbreviations: HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered a protocol deviation.

[a] If clinically indicated, per investigator's discretion.

[b] Calcitonin assay performed at central laboratory.

[c] At screening only (unless previously performed within the last 6 months with reports available for review).

[d] See exclusion criteria (Section 6.2) for further details.

[e] Pregnancy tests will be performed for women of childbearing potential. Serum pregnancy test is done at screening and urine pregnancy is performed at all other visits.

[f] Performed at screening. Procedures may be repeated throughout the study as deemed necessary by the investigator.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product (IP).
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients, where applicable. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonization (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 sites. Lilly or its representatives must approve the ICF before it is used at the investigative sites. 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 current IB and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

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

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

Protocol Signatures

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

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

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

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

Data Quality Assurance

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

- provide instructional material to the study site, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the electronic case report forms (eCRFs), 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 eCRF data and/or 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 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 the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of patient personal information collected will be provided in a written document to the patient by the sponsor.

Study and Site Closure

Discontinuation of Study Site

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.

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 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

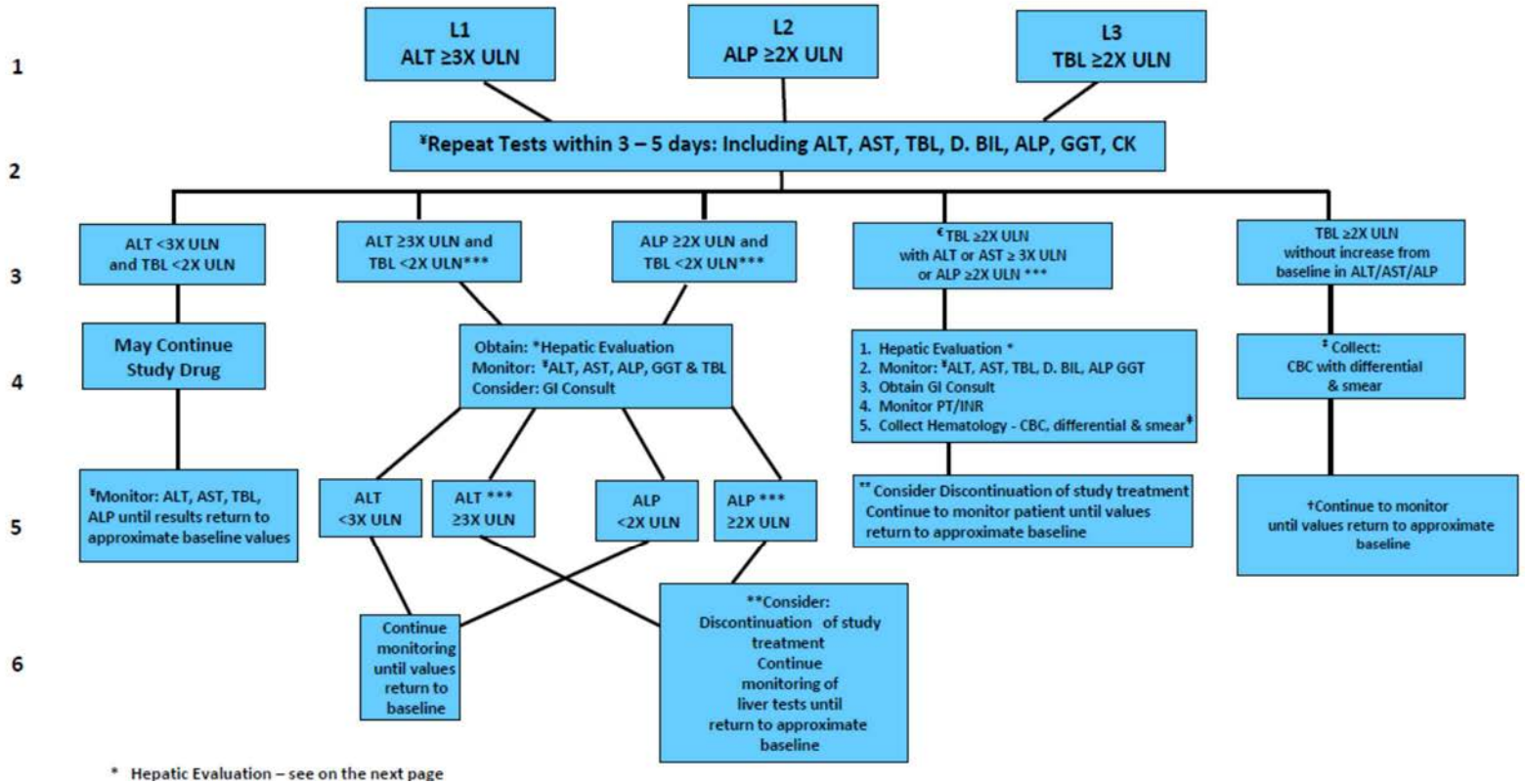
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

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

Hepatic Safety Monitoring Algorithm:**
For subjects with no known liver disease, and normal or near normal baseline liver tests
(ALT <2X ULN, TBL <1.5X ULN, ALP <1.5X ULN)

If at any point during monitoring, a condition at the 3rd row of the algorithm is met, then proceed down that branch of the algorithm



* Hepatic Evaluation – see on the next page

** This flow chart is designed to assist in timely collection of data which will aid in assessment and monitoring of liver injury during a clinical trial. It is not designed to recommend specific discontinuation rules. See next page for background information on hepatic discontinuation.

*** **Refer to the protocol instructions regarding potential eCRF completion**

¥ These tests are all included in the hepatic chemistry panel.

€ The combination of ALT≥3X ULN AND TBL≥ 2X ULN may suggest a Hy's Law case when occurring in the absence of significant cholestasis and no other cause of liver injury

‡ Testing for serum haptoglobin level may be considered when differential and smear are not available

† Isolated elevation of TBL (predominantly indirect) may be due to Gilbert's syndrome. In these cases fluctuation in TBL levels may be a part of the patient's normal pattern

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol I8F-MC-GPHG Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	23	1	23
Safety laboratory tests[a]	15	6	90
Pharmacokinetics	3	8	24
Fasting blood glucose	2	4	8
Plasma glucose sampling (clamp)	20 (per clamp)	2	40
Fasting insulin, C-peptide	2.5	22	55
Glucagon	2	24	48
Growth hormone, cortisol	4	20	80
Adrenaline, noradrenaline	5	20	100
Immunogenicity	10	8	80
Pharmacogenetics	10	1	10
Nonpharmacogenetics	9	4	36
Total			594
Total for clinical purposes			600

[a] Additional samples may be drawn if needed for safety purposes.

Appendix 6. Hypoglycemic Clamp Procedure

The patient will be asked to attend the clinical unit at approximately 18:00 hours in the evening of Day 79 of each treatment period. The patient will be served a standardized dinner at approximately 19:00 hours and thereafter will be fasted until the end of the clamp procedure on Day 80. The clamp procedure will be initiated on Day 79 (clamp run-in period) and the hypoglycemic induction will be performed on Day 80 of each period.

Invasive procedures

For sampling of arterialized venous blood, a hand or antecubital vein of one arm will be cannulated. This hand will remain in a heating environment throughout the procedure. The heating of the hand results in an arterialization of the venous blood due to a reflective opening of arteriovenous shunts. The patency of the cannulation will be maintained with a 154 mmol/L NaCl infusion throughout the procedure.

An antecubital vein in the contralateral arm will be cannulated for the infusion of human soluble insulin and/or glucose 20%.

Clamp Run-in period

At approximately 22:00 hours in the evening of Day 79, a variable intravenous (IV) infusion of human soluble insulin (40 IU insulin lispro [100 IU/mL] in 99.6 mL saline) or a variable IV infusion of glucose will be initiated in order to obtain a plasma glucose (PG) target level of 100 mg/dL (5.5 mmol/L). The insulin infusion should be stopped completely if glucose has to be infused and vice versa. The rates of the variable glucose infusion will be recorded whenever the infusion rate is changed (at least every 30 minutes). The insulin infusion rate needed until initiation of the high constant insulin infusion will also be recorded whenever the infusion rate is changed (at least every 30 minutes).

Between 07:00 hours and 08:00 hours on Day 80, PG should be stable at 100 mg/dL (5.5 mmol/L) ±30% and no glucose should be infused. In case this PG target range of 100 mg/dL (5.5 mmol/L) ±30% cannot be achieved, this period can be extended until 10:00 hours.

At 08:00 hours (10:00 hours latest), the insulin infusion rate will be increased to a constant rate of 2.5 mU/kg/min, based on patient body weight at Day 78 of each period.

Hypoglycemic induction

A PG target level of 100 mg/dL (5.5 mmol/L) ±30% should be kept constant from 60 minutes to 30 minutes prior to hypoglycemia induction by a controlled variable glucose infusion. Moreover, the PG target level of 100 mg/dL (5.5 mmol/L) ±10% should be kept constant for the last 30 minutes prior to hypoglycemia induction while performing all assessments of plateau 100 mg/dL (5.5 mmol/L).

Hypoglycemic induction is defined as stop of glucose infusion after assessment plateau 100 mg/dL (5.5 mmol/L) is completed.

After 30 minutes (09:00 hour) on the 100 mg/dL (5.5 mmol/L) assessment plateau, the glucose infusion will be interrupted, the PG will be allowed to decline to 63 mg/dL (3.5 mmol/L) and by restarting a variable glucose infusion, if needed, kept stable at 63 mg/dL (3.5 mmol/L). Assessments on the assessment plateau 63 mg/dL (3.5 mmol/L) will be performed.

After 30 min on the 63 mg/dL (3.5 mmol/L) assessment plateau, the glucose infusion will be interrupted and the PG will be allowed to decline to 45 mg/dL (2.5 mmol/L) or nadir at a higher PG concentration in case 45 mg/dL (2.5 mmol/L) cannot be reached or symptoms of hypoglycemia are unacceptable. By restarting a variable glucose infusion, if needed, the PG will be kept stable at 45 mg/dL (2.5 mmol/L) or nadir, and assessments on the 45 mg/dL (2.5 mmol/L) or nadir assessment plateau, will be performed.

As soon as the 45 mg/dL (2.5 mmol/L) or nadir assessment plateau has been reached, the constant high insulin infusion will be terminated. The 45 mg/dL (2.5 mmol/L) or nadir plateau will be further kept, if possible, for the total duration of 30 min.

Recovery phase

After, at the latest, 30 minutes' duration of the 45 mg/dL (2.5 mmol/L) or nadir assessment plateau, the glucose infusion will be switched off to allow a spontaneous recovery from hypoglycemia.

The PG will not be allowed to fall below 40 mg/dL (2.2 mmol/L), if so, the variable glucose infusion will be initiated to raise the PG to 45 mg/dL (2.5 mmol/L).

If the PG has not reached ≥72 mg/dL (4.0 mmol/L) 45 minutes after termination of the constant insulin infusion, a constant glucose infusion (5.5 mg/kg/min, based on patient body weight at Day 78 of each period) will be initiated in order to increase the PG to 72 mg/dL (4.0 mmol/L). For medical reasons (e.g., if symptoms of hypoglycemia are unacceptable) the constant glucose infusion can be initiated earlier as judged by investigator.

As soon as PG 72 mg/dL (4.0 mmol/L) is reached, assessments on the recovery time point will be performed. When the assessments are finished, PG will actively be raised to 100 mg/dL (5.5mmol/L) by a variable glucose infusion and the whole clamp procedure terminated when deemed safe by the investigator. Thereafter, patients will receive a meal (containing carbohydrates) and will be discharged after having achieved stable medical conditions, as judged by the investigator.

Safety considerations for assessment plateaus

In case a patient's PG does not decrease from 100 mg/dL (5.5 mmol/L) to 63 mg/dl (3.5 mmol/L) within 30 minutes, the 63 mg/dL (3.5 mmol/L) assessment plateau will be initiated in any case 30 minutes after the end of the assessment plateau at 100 mg/dL (5.5 mmol/L).

In case a patient's PG does not decrease from 63 mg/dL (3.5 mmol/L) to 45 mg/dL (2.5 mmol/L) within 30 minutes, the 45 mg/dL (2.5 mmol/L) assessment plateau will be initiated in any case 30 minutes after the end of the assessment plateau at 63 mg/dL (3.5 mmol/L).

In the above cases, the glucose infusion should not be initiated at the start of the assessment plateaus to allow a further decrease in PG levels to the scheduled target PG levels.

Based on the clinical judgement of the investigator, the PG can be increased to euglycemia by a variable glucose infusion at any time during the whole clamp procedure.

From the start of the constant high insulin infusion rate until end of the recovery phase, PG measurements (using SuperGL device) have to be performed every 5 to 30 minutes or more often as judged by investigator.

After initiation of the constant high insulin infusion rate, potassium concentration will be measured at the discretion of the investigator and potassium substituted if necessary.

Electrocardiogram will be continuously monitored from start of the constant high insulin infusion rate until completion of the recovery phase. Twelve-lead ECG will be recorded within 15 minutes prior to start of the high insulin infusion rate, at timepoint 15 minutes (±5 minutes) of assessment plateau 45 mg/dL (2.5 mmol/L) or nadir assessment plateau and before discharge.

The clamp will be terminated for safety reasons should the patient experience symptoms of cardiovascular stress (tachycardia, bradycardia, or other relevant changes in ECG), or neurological symptoms related to neuroglycopenia, as judged by the investigator.

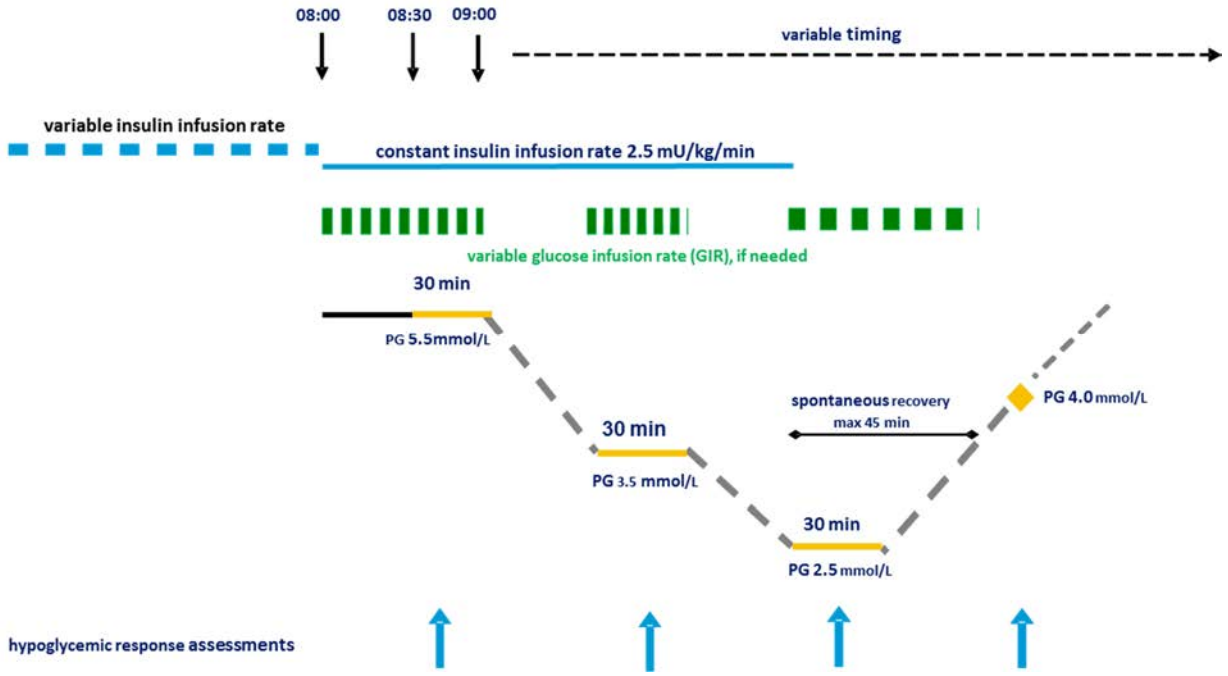


Figure GPHG.2 Hypoglycemic clamp

Abbreviations: PG = plasma glucose.
Glucagon, fasting insulin, C-peptide, cortisol, growth hormone, adrenaline, and noradrenaline measured at 10, 20 and 30 minutes of each clamp plateau and once PG 72 mg/dL (4.0 mmol/L) is reached.
Blood pressure and pulse rate measured at 0 and 30 minutes of each plateau and once PG 72 mg/dL (4.0 mmol/L) is reached.
Hypoglycemic symptom score and hypoglycemic symptom awareness assessed at 0 and 30 minutes of each plateau and once PG 72 mg/dL (4.0 mmol/L) is reached.

Approximate hour	**Nominal timing**	**Procedure**	**Clamp glucose level**	**Blood sampling:** **- Glucagon** **- Fasting insulin** **- C-peptide** **- Growth hormone** **- Cortisol** **- Adrenaline** **- Noradrenaline**	**Hypoglycemia symptoms awareness Hypoglycemic symptoms score**	**Vital signs and ECG**	**Glucose and GIR recorded**
				glucagon at ambient PG sample taken in pre-prandial state prior to clamp initiation			
22:00	-11 hours	Start run-in period: variable infusion of glucose or insulin lispro (40 IU [100 IU/mL] in 99.6 mL saline) targeting PG 100 mg/dL (5.5 mmol/mL) (±30%)	100 mg/dL (5.5 mmol/L)				Glucose every 30 minutes GIR at least every 30 minutes and every time GIR is changed until time *M*
7:00	-2 to -1 hours	Variable insulin infusion, no glucose infusion, targeting PG 100 mg/dL (5.5 mmol/L) (±30%)	100 mg/dL (5.5 mmol/L)				Glucose every 5 to 30 minutes or more often as judged by investigator
8:00	-1 hours to -30 minutes	Increase insulin flow (2.5 mU/kg/min) Variable infusion of glucose targeting PG 100 mg/dL (5.5 mmol/L) (±30%)	100 mg/dL (5.5 mmol/L)			Start of continuous ECG measurement	Glucose every 5 to 30 minutes or more often as judged by investigator

Approximate hour	**Nominal timing**	**Procedure**	**Clamp glucose level**	**Blood sampling:** **- Glucagon** **- Fasting insulin** **- C-peptide** **- Growth hormone** **- Cortisol** **- Adrenaline** **- Noradrenaline**	**Hypoglycemia symptoms awareness Hypoglycemic symptoms score**	**Vital signs and ECG**	**Glucose and GIR recorded**
8:30	-30 minutes	Insulin flow (2.5 mU/kg/min) . Variable infusion of glucose to maintain PG 100 mg/dL (5.5 mmol/L) (±10%)	100 mg/dL (5.5 mmol/L)	-20 minutes, -10 minutes, 0 minutes	-30 minutes 0 minutes	Vital signs -30 minutes 0 minutes 12-lead ECG -15 minutes	Glucose every 5 to 10 minutes or more often as judged by investigator
9:00	0 minutes	Start of hypoglycemic induction. Terminate glucose infusion					Glucose every 5 minutes or more often as judged by investigator until Timepoint *K*
	I minutes	PG 63 mg/dL (3.5 mmol/L) reached Variable glucose infusion if needed to maintain PG 63 mg/dL (3.5 mmol/L)	63 mg/dL (3.5 mmol/L)	*I* + 10 minutes *I* + 20 minutes *I* + 30 minutes	*I* min *I* + 30 minutes	Vital signs *I* min *I* + 30 minutes	
	I + 30 minutes	Terminate glucose infusion					
	J minutes	PG 45 mg/dL (2.5 mmol/L) or nadir reached Variable glucose infusion started, if needed, to maintain PG 45 mg/dL (2.5 mmol/L) or nadir Terminate insulin infusion	45 mg/dL (2.5 mmol/L)	*J*+ 10 minutes *J* + 20 minutes *J* + 30 minutes	*J* minutes *J* + 30 minutes	Vital signs *J* minutes *J* + 30 minutes 12-lead ECG *J* + 15 minutes	
	J + 30 minutes	Switch off glucose infusion (infusion will restart if PG falls below 40 mg/dL until 45 mg/dL is reached)					

Approximate hour	Nominal timing	Procedure	Clamp glucose level	Blood sampling: - Glucagon - Fasting insulin - C-peptide - Growth hormone - Cortisol - Adrenaline - Noradrenaline	Hypoglycemia symptoms awareness Hypoglycemic symptoms score	Vital signs and ECG	Glucose and GIR recorded
	J + 45 minutes	Start of constant glucose infusion (5.5 mg/kg/min) until PG ≥72 mg/dL (4.0 mmol/L) is reached					
	K minutes	Time of recovery: PG reaches 72 mg/dL (4.0 mmol/L) Start variable glucose infusion	≥72 mg/dL (4.0 mmol/L)	*K* minutes	*K* minutes	Vital signs *K* minutes	Glucose every 5 to 30 minutes or more often as judged by investigator
	M minutes	PG reaches 100 mg/dL (5.5 mmol/L). End of clamp. Blood glucose controlled with insulin infusion. Patient served a meal				End of continuous ECG 12-lead ECG prior to discharge	

Abbreviations: ECG = electrocardiogram; GIR = glucose infusion rate; *I* = time at which PG 63 mg/dL (3.5 mmol/L), or 30 minutes after the end of the 100 mg/dL (5.5 mmol/L) assessment plateau, whichever is sooner; *J* = time at which PG 45 mg/dL (2.5 mmol/L), or 30 minutes after the end of the 63 mg/dL (3.5 mmol/L) assessment plateau, whichever is sooner; *K* = time at which PG reaches 72 mg/dL (4.0 mmol/L); *M* = time at which PG reaches 100 mg/dL (5.5 mmol/L) at the end of the clamp; PG = plasma glucose.

Based on the clinical judgement of the investigator, PG can be increased to euglycemia by a variable glucose infusion at any time during the clamp procedure.

The insulin infusion rate will be recorded whenever the infusion rate is changed (at least every 30 minutes). The end time of each clamp step, time to reach each plateau, and PG achieved at each plateau will be recorded. Glucose infusion rates will also be captured.

Symptoms of hypoglycemia will be measured using the Edinburgh Hypoglycemia Scale and hypoglycemic awareness will be evaluated based on the patients' response (yes/no) to the question "Do you feel hypoglycemic?".

The assessments scheduled for the same time point on each plateau will be performed in following order (priority): blood glucose, vital signs, blood sampling, hypoglycemia symptoms awareness, hypoglycemic symptoms score. The exact timing of each procedure will be recorded.

Appendix 7. Pancreatic Monitoring

Glucagon-like peptide-1 agonists have been associated with a possible risk of acute pancreatitis. In 2006, the United States prescribing information for exenatide was revised to include the event of pancreatitis. In 2007, the United States prescribing information for this medication was amended to include pancreatitis under "Precautions." Epidemiologic studies have indicated that there is an increased incidence and prevalence of pancreatitis in persons with type 2 diabetes mellitus (T2DM).

To enhance understanding of the natural variability of pancreatic enzymes in the T2DM population and, in order to assess for any potential effects of tirzepatide on the exocrine pancreas, amylase and lipase values will be monitored in all current and future clinical trials with tirzepatide.

Additional monitoring will be requested for amylase and/or lipase values ≥3 × the upper limit of normal (ULN) at any visit, even in asymptomatic patients (see figure below). Lipase and amylase values may also be obtained at any time during the clinical trials for any subject suspected of having symptoms suggestive of exenatide pancreatitis (such as severe gastrointestinal (GI) signs and/or symptoms), at the investigator's discretion.

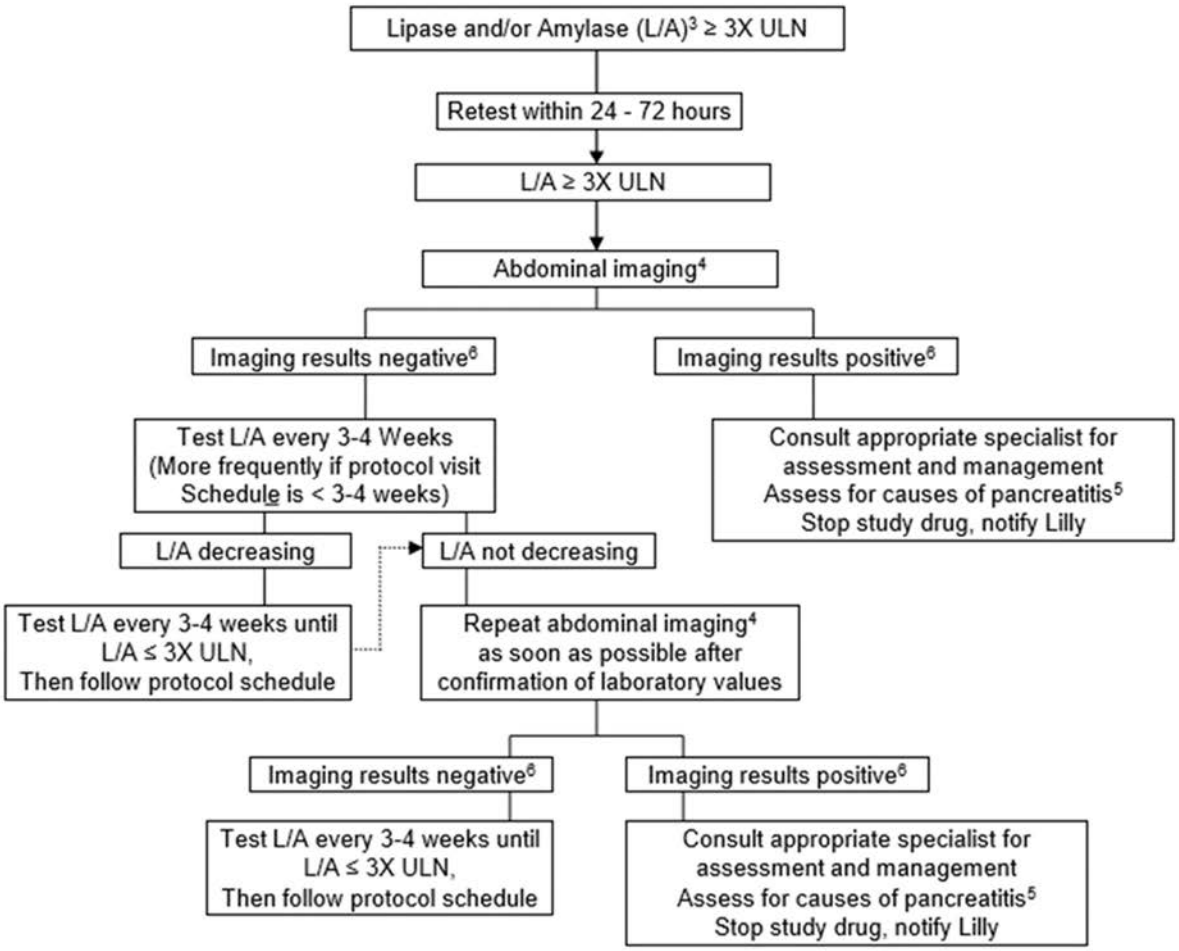
Acute pancreatitis is an adverse event (AE) defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems.
The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase ≥3× ULN
- characteristic findings of acute pancreatitis on computed topography scan or magnetic resonance imaging

Most patients with acute pancreatitis experience abdominal pain that is located generally in the epigastrium, and radiates to the back in approximately one-half of the cases. The pain is often associated with nausea and vomiting. However, experience with GLP-1 agonists has demonstrated that some patients asymptomatic for classic pancreatitis may demonstrate significant elevations of lipase and/or amylase. For patients considered by investigators to be asymptomatic for pancreatitis, but whose value(s) for lipase and/or amylase are ≥3× ULN, an algorithm is in place to follow these patients safely and to quickly reach (or not reach) a diagnosis of pancreatitis.

Pancreatic Enzymes: Safety Monitoring Algorithm for Subjects/Patients without Symptoms of Pancreatitis[1,2]

Follow this algorithm when the value(s) for serum lipase and/or amylase are ≥ 3X ULN.



1. Symptomatic – related primarily to abdominal pain consistent with pancreatitis; however, severe nausea, vomiting and other symptoms may be considered by the investigator as symptomatic as well.

2. If, at any time, in the opinion of the investigator, patient/subject has symptoms of acute pancreatitis irrespective of L/A results:
   (a) Consult appropriate specialist for assessment and management
   (b) Assess for causes of pancreatitis
   (c) Stop study drug
   (d) Notify Lilly

3. L/A = Lipase and/or amylase. Either or both enzymes can be measured and either or both can be used to meet the algorithm criteria.

4. Abdominal imaging is most valuable when performed at the time of elevated enzyme values. If in the opinion of the radiologist or investigator, it is safe for the patient/subject to receive contrast, an enhanced abdominal CT is preferred. MRI is also an acceptable imaging modality.

5. As minimum, test hepatic analytes, triglycerides, and calcium, and record all concomitant medications

6. Imaging results positive or negative for signs of acute pancreatitis

Abbreviations: CT = computed tomography; L/A = lipase and/or amylase; MRI = magnetic resonance imaging; ULN = upper limit of normal.

Patients diagnosed with pancreatitis will be discontinued from the study. Investigators will be responsible for following, through an appropriate healthcare option, these pancreatitis AEs until the events resolve or are explained. Adverse events that meet the diagnostic criteria of acute pancreatitis will be captured as serious adverse events (SAEs). For all other pancreatic AEs (such as idiopathic or asymptomatic pancreatic enzyme abnormalities), the investigator will be responsible for determining the seriousness of the event (AE or SAE) and the relatedness of the event to study drug.

Appendix 8. Hypersensitivity Laboratory Testing

Laboratory testing should be performed at the time of a Systemic Hypersensitivity Event. Important information about why, when, and what to test for are provided below. The management of the adverse event may warrant lab testing beyond that described below and should be performed as clinically indicated.

Laboratory testing during a Systemic Hypersensitivity Event is not performed for diagnostic purposes. The intent is several fold:

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

When should labs be obtained?

- In the presence of generalized urticaria or if anaphylaxis is suspected.
- After the patient has been stabilized, obtain a sample within 1-2 hours of the event, however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

What labs should be obtained?

- Tryptase*
- ADA and tirzepatide concentration (PK)
    - ADA testing should include drug specific immunoglobulin E (IgE)
    - If a drug specific IgE assay isn't available, a commercially available alternative test that can indicate the presence of drug specific IgE in serum is the basophil activation test (BAT)[#]
- Complement
    - C3a and C5a
- Cytokines
    - IL-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines)

*If a tryptase sample is obtained more than 2 hours after the event (i.e., within 2-12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine for N-methylhistamine (NMH) testing. Note that for tryptase serum samples obtained within 2-12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

The BAT is an in vitro cell based assay that only requires a serum sample. It is a surrogate assay for drug specific IgE but is not specific for IgE. If an in vivo assay is called for, the passive cutaneous anaphylaxis assay may be performed in rodents or non-human primates, is commercially available, and also only requires a serum sample. Skin prick testing in humans is a sensitive and specific assay for drug specific IgE but requires qualification of the method in negative controls and patients with documented Type I hypersensitivity to the drug.

Appendix 9. Protocol Amendment I8F-MC-GPHG(d) Summary: A Randomized, Placebo-Controlled, Crossover Study to Investigate the Effect of Once-Weekly Tirzepatide on the Counter-Regulatory Response to Hypoglycemia in Patients with Type 2 Diabetes Mellitus

Overview

Protocol I8F-MC-GPHG, A Randomized, Placebo-Controlled, Crossover Study to Investigate the Effect of Once-Weekly Tirzepatide on the Counter-Regulatory Response to Hypoglycemia in Patients with Type 2 Diabetes Mellitus, has been amended. The new protocol is indicated by Amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

This protocol amendment is considered substantial as the updated criteria expands access to more patients. As the changes were driven specifically by modifications to the Inclusion / Exclusion criteria, a full sponsor scientific peer review was not deemed necessary.

This protocol was amended to update the inclusion / exclusion criteria for consistency within the tirzepatide mechanism of action program. The overall changes made to this protocol are as follows:

- The schedule of activities (Section 2), protocol synopsis were updated to reflect the additional requirements for enrolling patients who require OAM washout
- Study duration was updated to include 4-week washout period
- Modified Inclusion Criteria [2] and [3] to include enrolling subjects on one additional OAM other than metformin, and Criterion [5] BMI cutoffs to align with other protocols within the tirzepatide program
- Exclusion Criterion [14] was edited in response to the changes to Inclusion Criterion [2]
- Sections 5.1, 5.1.1, 5.1.3, 6, 7.7 and Figure GPHG.1. were edited to reflect the operational changes required as a result of the modification to Inclusion Criterion [2]
- Modified Appendix 6 to make changes to the insulin infusion rate at -1 hour to -30 minutes and -30 minutes
- Minor editorial changes and formatting corrections were made but are not necessarily documented in the revision below.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

1. Protocol Synopsis

Rationale:

Study I8F-MC-GPHG (Study GPHG) is an approximately 38 to 42 week Phase 1 study designed to examine the effect of tirzepatide (LY3298176) on hypoglycemic counter-regulation in patients with type 2 diabetes mellitus (T2DM) when compared to placebo treatment. Tirzepatide is a long-acting, dual incretin mimetic (dual agonist) that binds to the glucose-dependent insulinotropic polypeptide receptor (GIPR) and the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R). Dual GIPR and GLP-1R agonism may provide improved glycemic control in patients with T2DM, engaging multiple physiologic pathways, including glucagon secretion by the pancreatic α cell. Since glucagon plays a key role in defense against hypoglycemia, it is important to assess the effects of tirzepatide on the physiologic response to hypoglycemia. Understanding the effect of tirzepatide on the counter-regulatory response to a hypoglycemic stimulus will provide important safety information for potential future clinical use.

Objectives	Endpoints
Secondary To compare the effect of tirzepatide 15 mg QW and placebo in T2DM patients following 12 weeks of treatment on: • Other counter-regulatory hormone responses during hypoglycemia, insulin and C-peptide	• Change in mean glucagon concentration from target PG concentration of 100 mg/dL to 63 mg/dL and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Change in mean glucagon concentration from ambient PG to target PG concentrations of 100, 63, and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Change in mean insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations from target PG concentration of 100 mg/dL to 63 and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia

Summary of Study Design:

Eligibility for this study for patients on metformin only will be assessed at the screening (Visit 1) up to 17 days prior to enrollment (Day -14 ±3) and confirmed at the beginning of the lead-in period (Visit 2), ~~approximately 10 to 4 days prior to randomization (Day -7 ±3).~~

Eligibility for patients on metformin and one other oral antidiabetic medication (OAM) will be assessed at the screening (Visit 1) up to 45 days prior to enrollment and confirmed at the beginning of the lead-in period (Visit 2), followed by discontinuation and a washout period for OAMs, other than metformin. The washout period for these patients will last at least 4 weeks between Visit 2 and Visit 3.

Eligible patients will undergo 2 treatment periods and will be randomized (Visit 3) to receive tirzepatide 15 mg QW in 1 period followed by placebo in the other, or vice versa, in a crossover fashion. Tirzepatide 15 mg will be attained via step-wise dose escalation to reduce the risk of gastrointestinal AEs.

There will also be a washout period of at least 8 weeks between the last dose of study drug in Period 1 and the first dose in Period 2.

Treatment Arms and Planned Duration for an Individual patient:

The planned study duration for an individual patient from screening through safety follow-up will be approximately 38 to 42 weeks.

2. Schedule of Activities:

Procedure	Screening	Lead-in (with or without washout)	Randomization and Dose 1, Treatment Period 1	Dose 1, Treatment Period 2	Comments
Study Period Week	~~-3~~ -6/-2[a]	~~-2~~ -5/-1[a]	1	1	
Study Period Day	-14 ±3[a] or -42 ±3[a]	-7 ±3[a] or -35 ±3[a] (prior to randomization)	1	1	Patients on metformin only should perform Visits 1 and 2 approximately 2 and 1 week prior to Visit 3. Patients on metformin and one OAM should perform Visit 1 about 6 weeks prior to Visit 3, in order to permit eligibility assessment at Visit 2. OAMs other than metformin will be discontinued immediately after Visit 2 followed by at least 4 weeks washout between Visit 2 and Visit 3
SMPG		X		X	For patients undergoing OAM washout, phone interviews will be conducted during lead-in to assess acceptability of glycemic control. Refer to Section 5.1.1 for further details.

3.1 Study Rationale:

Study I8F-MC-GPHG (Study GPHG) is an approximately 38-42 week Phase 1 study designed to evaluate the effect of tirzepatide (LY3298176) on hypoglycemic counter-regulation in patients with type 2 diabetes mellitus (T2DM) when compared to placebo treatment. Tirzepatide is a long-acting, dual incretin mimetic (dual agonist) that binds to the glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) and the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R). Dual GIPR and GLP-1R agonism (GIPRA/GLP-1RA) may provide improved glycemic control in patients with T2DM, engaging multiple physiologic pathways, including glucagon secretion by the pancreatic α cell. Since glucagon plays a key role in defense against hypoglycemia, it is important to assess the effects of tirzepatide on the physiologic response to hypoglycemia. Understanding the effect of tirzepatide on the counter-regulatory response to a hypoglycemic stimulus will provide important safety information for potential future clinical use.

3.3 Benefit Risk Assessment

During the hypoglycemic clamp procedures, plasma glucose (PG) levels will be closely monitored and glucose infused, if necessary, to prevent PG dropping below the target values. Should the symptoms of hypoglycemia become unacceptable, glucose will be infused to increase PG. Vital signs and continuous electrocardiogram (ECG) will be monitored during the clamp procedures and the clamp will be terminated should the patient experience symptoms of cardiovascular stress (tachycardia, bradycardia, or other relevant changes in ECG), or neurological symptoms related to ~~neuroglucopenia~~ neuroglycopenia.

4. Objectives and Endpoints

Table GPHG. 1. Objectives and Endpoints

Objectives	Endpoints
Secondary To compare the effect of tirzepatide 15 mg QW and placebo in T2DM patients following 12 weeks of treatment on: Other counter-regulatory hormone responses during hypoglycemia, insulin and C-peptide	• Change in mean glucagon concentration from target PG concentration of 100 mg/dL to 63 mg/dL and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Change in mean glucagon concentration from ambient PG to target PG concentrations of 100, 63, and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Change in mean insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations from target PG concentration of 100 mg/dL to 63 and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia

5. Study Design

5.1 Overall Design

Eligibility for this study will be assessed at ~~the~~ screening (Visit 1) ~~up to 17 days (Day -14 ± 3) prior to enrollment~~ and confirmed at the beginning of the lead-in period (Visit 2)~~, 10 to 4 days prior to randomization (Day -7 ± 3) when laboratory test results are available.~~ After eligibility is confirmed at Visit 2, patients will receive training and information on how to subsequently monitor their own diabetes condition. Where applicable, patients will be required to undergo a washout of OAMs other than metformin between Visit 2 and Visit 3 (refer to Section 5.1.1 for details).

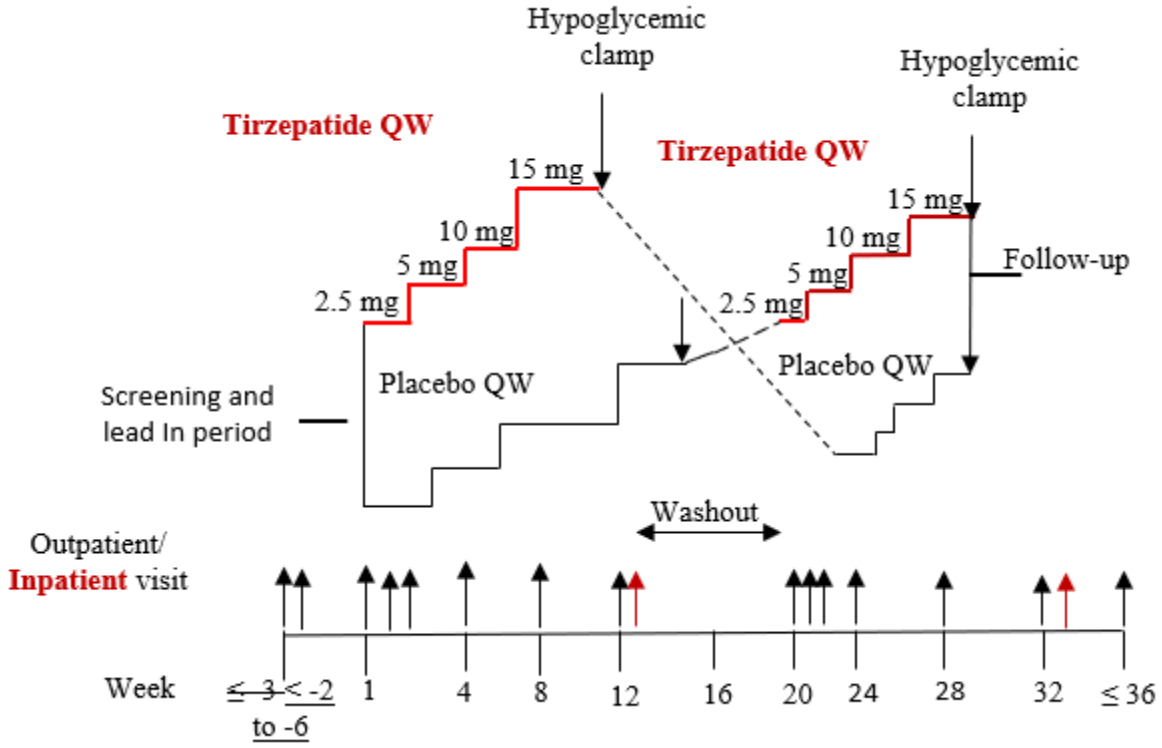


Figure GPHG.1 Illustration of study design for Protocol I8F0MC-GPHG.

5.1.1. Screening, Lead-in and Randomization

Eligibility for this study will be assessed during the screening period (Visit 1). The patient will sign the informed consent form (ICF) before any study procedures are performed. Screening procedures will be performed according to Section 2 (Schedule of Activities). Final determination of eligibility will occur at the beginning of the lead-in period at Visit 2, after all screening results are available. Eligible patients are those with T2DM treated with diet, exercise, and metformin with or without one other allowed oral antidiabetic medication (OAM) as specified in Inclusion Criterion [2].

Eligibility for this study for patients on metformin only will be assessed at the screening (Visit 1) up to 17 days prior to enrollment (Day -14 ±3) and confirmed at the beginning of the lead-in period (Visit 2). Eligible patients treated with metformin only will proceed to Visit 3 after approximately 1-week lead-in.

Eligible patients who are, in addition to metformin, on 1 more OAM, will discontinue this OAM immediately after Visit 2 and will undergo a 4-week washout between Visit 2 and Visit 3. During this washout period, the investigator will perform appropriate surveillance of the patients (by telephone interview and additional CRU visits, if necessary, at the investigators discretion) to monitor the safety and glycemic control of the patients. Once the 4-week washout period is completed, patients will proceed to Visit 3. Upon entering the study, patients should remain on the same metformin dose throughout the course of the study. Between screening and randomization (Day 1) eligible patients should continue their prestudy therapy with metformin. Patients who do not comply with requirements regarding metformin dosing will be discontinued from the study prior to randomization. After randomization, the metformin dose can only be reduced in accordance with country-specific label to protect patient safety (see Section 7.7 [Concomitant Therapy] for further details).

Eligible patients will be trained on glucose monitoring and disease management procedures, glucometer use for self-monitoring of plasma glucose (SMPG), study diaries, and study procedures at the lead-in visit (Visit 2) ~~10 to 4 days prior to randomization (Day -7 ±3).~~ Patients will start performing daily SMPG and record all results, including any hypoglycemia episode, in diaries as soon as their eligibility is confirmed at Visit 2. Patients will also follow the investigator's instructions related to any additional SMPG measurements, when judged to be needed for safety or eligibility assessments. All patients will be encouraged to maintain a stable diet and exercise plan throughout the course of the study.

5.1.3 Washout Between Treatment Periods

6. Study Population

Screening may occur up to ~~17~~ 45 days prior to ~~enrollment (Day -14 ±3). All patients will then perform a lead-in~~ start of randomization for patients treated with metformin and one other OAM, who are required to perform a washout during lead-in. For all other patients, screening may occur up to 17 days prior to randomization and perform a minimum 3-day lead-in. Patients who are not enrolled within these time periods may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility. Patients will be dosed only if safety laboratory results not older than ~~17~~ 45 days are available.

6.1 Inclusion Criteria

[2] Treated with diet and exercise and a stable dose of metformin (3 months prior to study entry) with or without 1 additional OAM other than metformin; doses of metformin will be considered stable if all prescribed doses for the previous 3 months were ±850 mg from the most commonly prescribed dose~~.~~; allowed OAMs, in combination with metformin are DPP-IV inhibitors, SGLT-2 inhibitors, acarbose, glinides and sulfonylureas; in patients with established cardiovascular disease who are treated with SGLT-2 inhibitors, this therapy should not be discontinued and therefore, these patients will NOT be eligible for participation in the trial.

[3a] Have a hemoglobin A1c value at screening of ≥6.5% and ≤9.0% (48 to 75 mmol/mol), if on metformin only;

[3b] Have a hemoglobin A1c value at screening of ≥6.0% and ≤8.5% (42 to 69 mmol/mol), if on metformin and 1 more allowed OAM;

[5] Have a body mass index between ~~25.0~~ 23.0 kg/m^2 and ~~40.0~~ 45.0 kg/m^2, inclusive, at screening; are of stable weight (±5%) >3 months prior to screening; and agree not to initiate an intensive diet and/or exercise program during the study with the intent of reducing body weight other than lifestyle and dietary measures for diabetes treatment;

6.2 Exclusion Criteria

[14] Have taken any glucose-lowering medications other than ~~metformin anytime~~ those indicated in Inclusion Criterion [2] during the last 3 months before screening or during the screening/lead-in period; short-term use of insulin (<14 days) for treatment of acute conditions is allowed in the 3-month period prior to entry and after randomization (see Section 7.7 Concomitant Therapy)

7.7 Concomitant Therapy

Glucose-Lowering Medications

Section 6.1 (Inclusion Criteria) and Section 6.2 (Exclusion Criteria) provide requirements regarding the use of glucose-lowering medications prior to entry and during the screening period. All patients in the study are required to be treated with stable doses of metformin for at least 3 months prior to study entry.

In addition, one additional OAM is allowed prior to randomization (Refer to Inclusion Criterion [2]), but must be discontinued after eligibility is confirmed at Visit 2, in which case a 4-week minimum washout is required.

Refer to Section 5.1.1 and 5.1.3 for additional information on washout period prior to starting study treatment.

Appendix 6 Hypoglycemic Clamp Procedure

Clamp Run-In Period

At 08:00 hours (10:00 hours latest), the insulin infusion rate will be increased to a constant rate of 2.5 mU/kg/min, based on patient body weight at Day 78 of each period.

Recovery Phase

If the PG has not reached ≥72 mg/dL (4.0 mmol/L) 45 minutes after termination of the constant insulin infusion, a constant glucose infusion (5.5 mg/kg/min, based on patient body weight at Day 78 of each period) will be initiated in order to increase the PG to 72 mg/dL (4.0 mmol/L). For medical reasons (e.g., if symptoms of hypoglycemia are unacceptable) the constant glucose infusion can be initiated earlier as judged by investigator.

Safety considerations for assessment plateaus

The clamp will be terminated for safety reasons should the patient experience symptoms of cardiovascular stress (tachycardia, bradycardia, or other relevant changes in ECG), or neurological symptoms related to ~~neuroglucopenia~~ neuroglycopenia, as judged by the investigator.

Approximate hour	Nominal timing	Procedure	Clamp glucose level	Blood sampling: - Glucagon - Fasting insulin - C-peptide - Growth hormone - Cortisol - Adrenaline	Hypoglycemia symptoms awareness Hypoglycemic symptoms score	Vital signs and ECG	Glucose and GIR recorded

				Noradrenaline			
8:00	-1 hours to -30 minutes	Increase insulin flow (2.5 mU/kg/min) ~~(±30%).~~ Variable infusion of glucose targeting PG 100 mg/dL (5.5 mmol/L) (±30%)	100 mg/dL (5.5 mmol/L)			Start of continuous ECG measurement	Glucose every 5 to 30 minutes or more often as judged by investigator
8:30	-30 minutes	Insulin flow (2.5 mU/kg/min) ~~(±30%).~~ Variable infusion of glucose to maintain PG 100 mg/dL (5.5 mmol/L) (±10%)	100 mg/dL (5.5 mmol/L)	-20 minutes, -10 minutes, 0 minutes	-30 minutes 0 minutes	Vital signs -30 minutes 0 minutes 12-lead ECG -15 minutes	Glucose every 5 to 10 minutes or more often as judged by investigator

The assessments scheduled for the same time point on each plateau will be performed in following order (priority): blood glucose, vital signs, blood sampling, hypoglycemia symptoms awareness, hypoglycemic symptoms score. The exact timing of each procedure will be recorded.

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Approver: PPD

Approval Date & Time: 16-Sep-2020 15:04:31 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 17-Sep-2020 01:26:42 GMT

Signature meaning: Approved