Clinical Study Protocol Version (d) I8F-MC-GPGT

The Effect of Tirzepatide on α and β Cell Function and Insulin Sensitivity in Patients with Type 2 Diabetes Mellitus

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Protocol I8F-MC-GPGT(d)
The Effect of Tirzepatide on α and β Cell Function and Insulin Sensitivity in Patients with Type 2 Diabetes Mellitus

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Confidential Information

Tirzepatide (LY3298176)

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1. Protocol Synopsis

Title of Study:
The Effect of Tirzepatide on α and β Cell Function and Insulin Sensitivity in Patients with Type 2 Diabetes Mellitus

Rationale:
Study I8F-MC-GPGT is a 28-week Phase 1 study designed to examine α and β cell function, insulin sensitivity, glucose and lipid metabolism, food intake, and energy expenditure in patients with type 2 diabetes mellitus (T2DM) treated with tirzepatide. Tirzepatide is a long-acting, dual incretin mimetic (dual agonist) that binds to the glucose-dependent insulinotropic peptide (GIP) receptor (GIPR) and the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R). The available preclinical and clinical data indicate that co-stimulation of these receptors may enhance insulin secretion, improve insulin sensitivity, and reduce body weight beyond the effect of selective GLP-1R stimulation. These actions of dual GIPR and GLP-1R agonism (GIPRA/GLP-1RA) may provide improved glycemic control and reduced risk of chronic macro- and microvascular complications in patients with T2DM.

Objectives/Endpoints:

Objectives	Endpoints
Primary To compare the effect of tirzepatide 15 mg dose and placebo on total cDI after 28 weeks of treatment, including the dose escalation phase, in T2DM patients on metformin.	• The change from baseline in total cDI
Secondary To compare the effects of tirzepatide 15 mg relative to placebo (except for the primary efficacy measure) and semaglutide 1 mg after 28 weeks of treatment on:	
• Insulin secretion and insulin sensitivity combined outcome	• The change in total cDI (for tirzepatide versus semaglutide comparison only)
• Glucose control	• The change from baseline in fasting and postmeal glucose (total and incremental $AUC_{0\text{-}240min}$) during sMMTT • The change from baseline in hemoglobin A1c

Objectives/Endpoints:

Objectives	Endpoints
Secondary (continued) • Insulin secretion	• The change in the first phase incremental $ISR_{0\text{-}8min}$ from hyperglycemic clamp • The change in second phase total $ISR_{20\text{-}120min}$ from hyperglycemic clamp • The change in total $ISR_{0\text{-}120min}$ from hyperglycemic clamp • The change from baseline in insulin response to arginine (incremental $AUC_{arginine0\text{-}10min}$ and incremental $AUC_{arginine0\text{-}30min}$) from hyperglycemic clamp • The change from baseline in β cell GS from hyperglycemic clamp • The change in β cell GS from sMMTT • The change from baseline in ISRg from sMMTT
• Insulin sensitivity	• The change from baseline in hyperinsulinemic euglycemic clamp M-value
• Glucagon secretion	• The change from baseline in glucagon concentration at fasting and postmeal during sMMTT (total and incremental $AUC_{0\text{-}240min}$)
• Appetite and food intake	• The change from baseline in food intake during ad libitum meal served buffet style

Abbreviations: AUC = area under the concentration versus time curve; $AUC_{0\text{-}240min}$ = AUC from time zero to 240 minutes after start of the meal; $AUC_{arginine0\text{-}10min}$ = AUC in response to arginine from time zero to 10 minutes; $AUC_{arginine0\text{-}30min}$ = AUC in response to arginine from time zero to 30 minutes; cDI = clamp disposition index; GS = glucose sensitivity; ISR = insulin secretion rate; $ISR_{0\text{-}8min}$ = first phase insulin secretion rate; $ISR_{0\text{-}120min}$ = total insulin secretion rate from hyperglycemic clamp; $ISR_{20\text{-}120min}$ = second phase insulin secretion rate; ISRg = insulin secretion rate at fixed glucose concentration; sMMTT = standardized mixed-meal tolerance test; T2DM = type 2 diabetes mellitus.

Summary of Study Design:

This is a Phase 1, multicenter, randomized, sponsor, investigator- and patient-blind, parallel arm study in patients with T2DM to compare the effect of tirzepatide 15 mg dose and placebo on total clamp disposition index (cDI) after 28 weeks of treatment, including the dose escalation phase. The study will also compare the effects of tirzepatide 15 mg relative to placebo and semaglutide (positive control) on additional parameters of pancreatic α and β cell function, insulin sensitivity, glucose and lipid metabolism, and energy balance (food intake and energy expenditure).

Treatment Arms and Planned Duration for an Individual Patient:

Patients will be screened up to 56 days prior to start of lead-in on Day -3. The study will consist of 3 periods: approximately 5- to 8-week screening/lead-in period, 28-week treatment period, and a 4-week safety follow-up period. Patients will be randomized in a 3:3:2 ratio to once weekly (QW) tirzepatide 15 mg, semaglutide 1 mg, or placebo.

Number of Patients:

Approximately 117 patients may be enrolled. Approximately 99 patients are expected to complete the study.

Statistical Analysis:
Pharmacodynamic analyses will be conducted on data from all patients who receive at least 1 dose of the investigational product and have evaluable data. Data will be censored once patients discontinue their randomized treatment or initiated additional rescue treatment.

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.

2. Schedule of Activities

Study Schedule Protocol I8F-MC-GPGT: Screening and Lead-In

Procedure	Screening	Lead-In			Comments
Visit	**1**	**2**			
Week of Treatment	**-8 to -1**	**-1**			
Study Day	**-59 to -4**	**-3**	**-2**	**-1**	Screening for patients on metformin: Days -35 to -4. Screening for patients on metformin+other OAMs: Days -59 to -4. This period includes the required 4-week washout.
Screening Procedures					
Informed consent	X				Informed consent will be performed at least 1 day before other screening procedures.
Medical history	X				
Drug and alcohol screen	X				Procedures may be repeated throughout the study as deemed necessary by the investigator.
Physical examination	X	X			
Height	X				
Weight and waist circumference	X	X			
Vital signs (BP/PR/body temperature)	X	X			Vital sign measurements whose nominal times are not listed in the schedule should be taken before PK samples scheduled on the same day. Blood pressure and PR measurements will be taken after at least 5 minutes in the supine position.
ECGs	X	X			Single 12-lead ECGs will be collected. Electrocardiograms must be recorded before collecting any blood samples using equipment available at the study site. Patients must be supine for at least 5 minutes before ECG collection, and remain supine but awake during ECG collection.
Concomitant medications	X	X			
Inclusion/exclusion criteria	X				
Clinical Procedures					
CRU admission		X			
Dispense glucose meters, test strips, diaries, SMPG and disease management training	X				These SMPG-related procedures will be performed after eligibility is confirmed and may commence between screening and start of lead-in.
AEs	X	X	X	X	
Glucose Management					
SMPG	X	X			SMPG will start latest at the beginning of the lead-in period and will be conducted daily throughout the study except while resident at the CRU. Patients subject to OAMs washout should start SMPG during the screening period.

Procedure	Screening	Lead-In			Comments
Visit	**1**	**2**			
Week of Treatment	**-8 to -1**	**-1**			
Study Day	**-59 to -4**	**-3**	**-2**	**-1**	Screening for patients on metformin: Days -35 to -4. Screening for patients on metformin+other OAMs: Days -59 to -4. This period includes the required 4-week washout.
Review of study diary for SMPG		X			Applies to eligible patients after the completion of screening.
Laboratory Tests					
Safety laboratory tests (including fasting glucose)	X	X			See Appendix 2 for details. Patients will fast for at least 8 hours before each blood sample is collected.
Pregnancy test	X			X	Serum pregnancy test at screening and urine pregnancy test on Day -1.
Calcitonin	X				
Hemoglobin A1c	X	X			
Fasting insulin, C-peptide, glucagon			X	X	Full sampling schedule is provided in Appendix 6 for sMMTT on Day -2 and hyperinsulinemic euglycemic and hyperglycemic clamps on Day -1.
Proinsulin			X		Full sampling schedule is provided in Appendix 6 for sMMTT on Day -2.
PP			X		Full sampling schedule is provided in Appendix 6 for sMMTT on Day -2.
Leptin, adiponectin, IGFBP 1 and 2			X		Sampling schedule is provided in Appendix 6 for sMMTT on Day -2.
Lipid panel: • triglycerides • total cholesterol • LDL-C • VLDL-C • HDL-C • ApoB-48 • ApoB-100 • ApoC-III • LPL			X	X	On Day -1, only triglycerides will be collected during the hyperglycemic clamp. On Day -2, full lipid panel will be collected during sMMTT. See Appendix 6 for sampling schedule.
β-hydroxybutyrate, pyruvate, lactate, FFA, glycerol			X	X	Peripheral plasma samples will be taken during microdialysis at fasting, sMMTT, and hyperglycemic clamp. See Appendix 6 for details on sampling schedule.
Glucose, pyruvate, lactate, glycerol, ethanol in dialysate during microdialysis			X	X	Adipose tissue samples during microdialysis at fasting, sMMTT, and hyperglycemic clamp. See Appendix 6 for details on sampling schedule.

Procedure	Screening	Lead-In			Comments
Visit	**1**	**2**			
Week of Treatment	**-8 to -1**	**-1**			
Study Day	**-59 to -4**	**-3**	**-2**	**-1**	Screening for patients on metformin: Days -35 to -4. Screening for patients on metformin+other OAMs: Days -59 to -4. This period includes the required 4-week washout.
Investigative Tests					
Body composition plethysmography		X			See Appendix 6 for details.
Hyperinsulinemic euglycemic clamp				X	Patients will fast for approximately 12 hours before the hyperinsulinemic euglycemic clamp. See Appendix 6 for details of the procedure and sampling plan.
Hyperglycemic clamp				X	Hyperglycemic clamp will follow hyperinsulinemic euglycemic clamp. Hyperglycemic clamp will end with the arginine test. See Appendix 6 for details of the procedure and sampling plan.
sMMTT			X		See Appendix 6 for details of the procedure and sampling plan.
Appetite (VAS) with sMMTT			X		See Appendix 6 for details.
Appetite (VAS) at fasting		X			
Ad libitum food intake		X			Ad libitum meal will be provided at noon. See Appendix 6 for details.
Indirect calorimetry			X		See Appendix 6 for details.
Microdialysis			X	X	See Appendix 6 for details.
Diagnostics					
Nonpharmacogenetic stored samples		X			

Study Schedule Protocol I8F-MC-GPGT: Treatment Period

Procedure	Treatment																					Comments
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	
Week of Treatment	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Study Day	**1**	**3 +1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±1**	**36 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**64 ±1**	**71 ±1**	**78 ±1**	**85 ±1**	**92 ±1**	**99 ±1**	**106 ±1**	**113 ±1**	**120 ±1**	**127 ±1**	**134 ±1**	
Clinical Procedures																						
CRU discharge	X																					
Telephone visit		X																				
Randomization	P																					Performed after baseline procedures.
Weight and waist circumference						P				P				P				P				
Vital signs (BP/PR/body temperature)						P				P				P				P				Refer also to screening and lead-in table.
ECGs						X												X				Refer also to screening and lead-in table.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Investigational Product																						
Dose administration	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Treatment																					Comments
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	
Week of Treatment	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Study Day	**1**	**3 +1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±1**	**36 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**64 ±1**	**71 ±1**	**78 ±1**	**85 ±1**	**92 ±1**	**99 ±1**	**106 ±1**	**113 ±1**	**120 ±1**	**127 ±1**	**134 ±1**	
Glucose Management																						
SMPG	X																					Refer also to screening and lead-in table.
Review of study diary for SMPG	P					X				X				X				X				
Laboratory Tests																						
Safety laboratory tests (including fasting glucose)														P								Refer also to screening and lead-in table.
Pregnancy test (urine)										X								X				
Hemoglobin A1c														X								
Fasting insulin, proinsulin, C-peptide, glucagon, PP														X								
Leptin, adiponectin, IGFBP 1 and 2														X								

Procedure	Treatment																					Comments
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	
Week of Treatment	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Study Day	**1**	**3 +1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±1**	**36 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**64 ±1**	**71 ±1**	**78 ±1**	**85 ±1**	**92 ±1**	**99 ±1**	**106 ±1**	**113 ±1**	**120 ±1**	**127 ±1**	**134 ±1**	
Lipid panel: • triglycerides • total cholesterol • LDL-C • VLDL-C • HDL-C • ApoB-48 • ApoB-100 • ApoC-III • LPL														X								Refer also to screening and lead-in table.
Investigative Tests																						
Appetite (VAS) at fasting						X				X				X				X				
Ad libitum food intake									X								X					Ad libitum meal will be provided at noon. See Appendix 6 for details.
Diagnostics																						
PGx sample	P																					Single sample for PGx analysis taken predose on Day 1.

Procedure	Treatment																					Comments
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	
Week of Treatment	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Study Day	**1**	**3 +1**	**8 ±1**	**15 ±1**	**22 ±1**	**29 ±1**	**36 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**64 ±1**	**71 ±1**	**78 ±1**	**85 ±1**	**92 ±1**	**99 ±1**	**106 ±1**	**113 ±1**	**120 ±1**	**127 ±1**	**134 ±1**	
PK sample	P				P								P									All samples for immunogenicity should be taken predose and time matched with predose PK sample, whenever possible.
Immunogenicity	P				P								P									

Study Schedule Protocol I8F-MC-GPGT: Treatment Period Continued and Follow-Up/Early Termination

Procedure	Treatment											Follow-Up/ET	Comments
Visit	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**			**32**	
Week of Treatment	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**28**	**28**	**28**	**32**	
Study Day	**141 ±1**	**148 ±1**	**155 ±1**	**162 ±1**	**169 ±1**	**176 ±1**	**183 ±1**	**190 ±1**	**191**	**192**	**193**	**Within 4 weeks after last dose**	
Clinical Procedures													
CRU admission									X				
CRU discharge											X		
Physical examination									X				
Weight and waist circumference	P				P				X			X	
Vital signs (BP/PR/body temperature)	P				P				X			X	Refer also to screening and lead-in table.
ECGs	X				X				X				Refer also to screening and lead-in table.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	
Investigational Product													
Dose administration	X	X	X	X	X	X	X	X					
Glucose Management													
SMPG	X											X	Refer also to screening and lead-in table.
Review of study diary for SMPG	X				X			X	X			X	
Laboratory Tests													
Safety laboratory tests (including fasting glucose)	P								X				Refer also to screening and lead-in table.
Pregnancy test	X								X			X	Urine pregnancy test on Days 141 and 191 and serum pregnancy test at follow-up.
Calcitonin											X	X	
Hemoglobin A1c	X								X				

Procedure	Treatment											Follow-Up/ET	Comments
Visit	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**			**32**	
Week of Treatment	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**28**	**28**	**28**	**32**	
Study Day	**141 ±1**	**148 ±1**	**155 ±1**	**162 ±1**	**169 ±1**	**176 ±1**	**183 ±1**	**190 ±1**	**191**	**192**	**193**	**Within 4 weeks after last dose**	
Fasting insulin, C-peptide, glucagon	X									X	X		See sampling schedule for sMMTT on Day 192 and hyperinsulinemic euglycemic and hyperglycemic clamps on Day 193 in Appendix 6.
Proinsulin	X									X			See sampling schedule for sMMTT on Day 192 in Appendix 6.
PP	X									X			See sampling schedule for sMMTT on Day 192 in Appendix 6.
Leptin, adiponectin, IGFBP 1 and 2	X									X			See sampling schedule for sMMTT on Day 192 in Appendix 6.
Lipid panel: • triglycerides • total cholesterol • LDL-C • VLDL-C • HDL-C • ApoB-48 • ApoB-100 • ApoC-III • LPL	X									X	X		On Day 141, fasting samples will be collected. On Day 192, full lipid panel will be collected during sMMTT. On Day 193, only triglycerides will be collected. See Appendix 6 for sampling schedule.
β-hydroxybutyrate, pyruvate, lactate, FFA, glycerol										X	X		Peripheral plasma samples will be taken during microdialysis at fasting, sMMTT, and hyperglycemic clamp. See Appendix 6 for details.

Procedure	Treatment											Follow-Up/ET	Comments
Visit	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**			**32**	
Week of Treatment	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**28**	**28**	**28**	**32**	
Study Day	**141 ±1**	**148 ±1**	**155 ±1**	**162 ±1**	**169 ±1**	**176 ±1**	**183 ±1**	**190 ±1**	**191**	**192**	**193**	**Within 4 weeks after last dose**	
Glucose, pyruvate, lactate, glycerol, and ethanol in dialysate during microdialysis										X	X		Adipose tissue samples during microdialysis at fasting, sMMTT, and hyperglycemic clamp. See Appendix 6 for details.
Investigative Tests													
Body composition plethysmography									X				See Appendix 6 for details.
Hyperinsulinemic euglycemic clamp											X		See Appendix 6 for details.
Hyperglycemic clamp											X		See Appendix 6 for details.
sMMTT										X			See Appendix 6 for details.
Appetite (VAS) with sMMTT										X			See Appendix 6 for details.
Appetite (VAS) at fasting	X				X				X			X	
Ad libitum food intake									X				Ad libitum meal will be provided at noon. See Appendix 6 for details.
Indirect calorimetry										X			See Appendix 6 for details.
Microdialysis										X	X		See Appendix 6 for details.
Diagnostics													
PK samples								P			X	X	Sampling times are relative to the time of dose administration (0 minutes). On Day 193, PK sample will be collected prior to hyperinsulinemic euglycemic and hyperglycemic clamps.

Procedure	Treatment											Follow-Up/ET	Comments
Visit	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**			**32**	
Week of Treatment	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**28**	**28**	**28**	**32**	
Study Day	**141 ±1**	**148 ±1**	**155 ±1**	**162 ±1**	**169 ±1**	**176 ±1**	**183 ±1**	**190 ±1**	**191**	**192**	**193**	**Within 4 weeks after last dose**	
Immunogenicity								P				X	All samples for immunogenicity should be taken predose and time matched with predose PK sample, whenever possible.
Nonpharmacogenetic stored samples	X								X				

Abbreviations: AEs = adverse events; ApoB-48 = apolipoprotein B-48; ApoB-100 = apolipoprotein B-100; ApoC-III = apolipoprotein C-III; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; FFA = free fatty acid; HDL-C = high-density lipoprotein cholesterol; IGFBP = insulin-like growth factor-binding protein; LDL-C = low-density lipoprotein cholesterol; LPL = lipoprotein lipase; OAM = oral antihyperglycemia medication; P = predose; PGx = pharmacogenetic; PK = pharmacokinetics; PR = pulse rate; PP = pancreatic polypeptide; sMMTT = standardized mixed-meal tolerance test; SMPG = self-monitoring of plasma glucose; VAS = visual analog scale; VLDL-C = very low-density lipoprotein cholesterol.

Note: If multiple procedures take place at the same time point, the following order should be used: ECG, vital signs, and venipuncture. Screening for patients who need to undergo washout of OAM treatment may occur from Day -59 to Day -4.

3. Introduction

3.1. Study Rationale

Study I8F-MC-GPGT is a 28-week Phase 1 study designed to examine α and β cell function, insulin sensitivity, glucose and lipid metabolism, food intake, and energy expenditure in patients with type 2 diabetes mellitus (T2DM) treated with tirzepatide. 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). The available preclinical and clinical data indicate that co-stimulation of these receptors may enhance insulin secretion, improve insulin sensitivity, and reduce body weight beyond the effect of selective GLP-1R stimulation (Frias et al. 2018; Coskun et al. 2018). These actions of dual GIPR and GLP-1R agonism (GIPRA/GLP-1RA) may provide improved glycemic control and reduced risk of chronic macro-and microvascular complications in patients with T2DM.

3.2. Background

The incretins GIP and GLP-1 are secreted from enteroendocrine cells in the gut following a meal. Their role is to enhance the physiologic response to food ingestion, including sensation of satiety and insulin secretion (Baggio and Drucker 2007). In addition, GIPRs are present on adipose cells and their stimulation may have an important role in regulation of glucose and triglycerides turnover in this tissue and postprandial nutrient disposal. It has been reported that patients with T2DM have impaired incretin responses (Baggio and Drucker 2007). Several selective GLP-1RAs have been developed for treatment of T2DM. These agents have a beneficial effect on glucose metabolism through the enhancement of glucose-dependent insulin secretion, reduction of inappropriately elevated glucagon levels, delay in gastric emptying, and body weight reduction. The dosing of GLP-1RAs is limited by gastrointestinal (GI) adverse effect. The frequency of these adverse events (AEs) can be reduced by step-wise dose escalation at initiation. Despite the physiological role of GIP in glucose and lipid metabolism regulation, there are no GIPRAs approved for treatment of this disease as of yet.

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors. The structure of tirzepatide is based on the GIP sequence and includes a C20 fatty di-acid moiety CCI [redacted]. Because both GIPR-mediated, as well as GLP-1R-mediated actions are involved in regulation of insulin and glucagon secretion and body energy turnover, tirzepatide may have the potential of reaching greater glucose-lowering effects in comparison to selective GLP-1RAs. Tirzepatide may furthermore attain additional efficacy by recruiting and regulating metabolically active tissues not controlled by GLP-1, for example, adipose tissue. Tirzepatide is currently being investigated in clinical trials to assess its effect on hyperglycemia and other comorbidities associated with T2DM. It is administered once weekly (QW) by subcutaneous (SC) administration.

Results from 4 tirzepatide clinical trials that have completed dosing are available, including 2 Phase 1 studies, Study I8F-MC-GPGA (Study GPGA) and Study I8F-JE-GPGC (Study GPGC), and 2 Phase 2 studies, Study I8F-MC-GPGB (Study GPGB) and Study I8F-MC-GPGF (Study GPGF).

Study GPGA was a combination single-ascending dose (SAD) and a multiple-ascending dose study (MAD) study in healthy subjects and a multidose study in patients with T2DM. The study investigated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of tirzepatide administered as SC injections. Weekly doses of tirzepatide ranged from 0.25 mg to 8 mg in the SAD. Maximum tolerated dose in healthy subjects following single-dose administration was 5 mg. In the 4-week MAD part of the study, doses up to 10 mg in healthy subjects or 15 mg in patients with T2DM were attained via a dose escalation approach. A dose of 15 mg tirzepatide attained by fast dose escalation over 4 weeks (5/5/10/15 mg), while considered to be safe, was associated with high incidence of GI events. Terminal half-life was estimated to be approximately 5 days, thus supporting a QW dosing regimen; with steady-state tirzepatide exposures expected to be attained following at least 4 weeks of QW dosing. Study GPGC was a MAD study to investigate the safety, tolerability, PK, and PD in Japanese patients with T2DM. Patients were randomized to 1 of 4 treatment groups: 2.5/5/10 mg QW titrated, 5/10/15 mg QW titrated, 5 mg QW as a fixed dose, or placebo for 8 weeks. Overall, tirzepatide PK parameters in Japanese patients with T2DM appeared comparable to corresponding parameters from non-Japanese patients with T2DM observed in Study GPGA.

Gastrointestinal 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 in the 2 Phase 1 studies. 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-1RAs. A few subjects experienced transient elevations in lipase and/or amylase levels, but these episodes were not associated with any relevant clinical outcomes. There were no other clinically relevant safety observations in the Phase 1 studies.

Phase 2 studies evaluated the efficacy, tolerability, and safety of QW tirzepatide (including 1 mg, 2.5 mg, 4 mg, 5 mg, 7.5 mg, 10 mg, 12 mg, and 15 mg) in patients with T2DM with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy up to 26 weeks. Results demonstrated that tirzepatide in doses between 5 mg and 15 mg provides a clinically meaningful glucose-lowering and body weight-lowering efficacy. Similar to data from Study GPGA, most of the AEs associated with tirzepatide were GI-related, consisting mainly of nausea, vomiting, and diarrhea and were dose-dependent. In addition, patients treated with tirzepatide reported AEs of decreased appetite more frequently than patients who received 1.5 mg dose of dulaglutide, a selective GLP-1RA.

An integrated clinical and PK/PD assessment of the GI tolerability AEs, and the effect of dose escalation regimens in the Phase 2 trials, suggested that dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5 mg increments every 4 weeks would permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns.

Overall, the safety tolerability, and PK/PD profiles of tirzepatide support further development of tirzepatide in patients with T2DM.

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. No other clinically relevant safety concerns were identified in the dose range up to 15 mg, the highest dose investigated in Phase 1 and Phase 2 trials, 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 are similar to the risks associated with currently available long-acting GLP-1RAs, including semaglutide, the active comparator in this trial. These risks are clinically detectable and manageable, and will be monitored during the trial. Section 7.7.1 (Management of Patients with Gastrointestinal Symptoms) provides detailed information concerning the management of GI AEs.

The patients in the active treatment groups are expected to experience benefits of the study treatments, including improved glycemic control and reduced body weight. The patients in the placebo group may benefit from improved adherence to the non-pharmacological measures of treatment, but will be at higher risk of poor glycemic control. To avoid unacceptably high, prolonged hyperglycemia, the protocol includes several protective measures. In addition to the comprehensive safety monitoring plan for all patients included in this study, blood glucose (BG) levels will be regularly monitored to reduce risks related to acute diabetic complications. Section 9.2.2.2 (Severe, Persistent Hyperglycemia) describes definitions and criteria when diagnosing and categorizing an episode considered to be related to hyperglycemia. If a patient fulfils 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 7.4.1.3 (Treatment of Hypoglycemia and Hypokalemia during Hyperinsulinemic Euglycemic Clamp) describes how episodes of hypoglycemia or hypokalemia will be treated during the hyperinsulinemic euglycemic clamp, if necessary. Section 9.2.2.1 (Hypoglycemia) provides criteria for diagnosis and categorization of episodes of hypoglycemia.

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 GPGT.1 shows the objectives and endpoints of the study.

Table GPGT.1. Objectives and Endpoints

Objectives	Endpoints
Primary To compare the effect of tirzepatide 15 mg dose and placebo on the total cDI after 28 weeks of treatment, including the dose escalation phase, in T2DM patients on metformin.	• The change from baseline in total cDI
Secondary To compare the effects of tirzepatide 15 mg relative to placebo (except for the primary efficacy measure) and semaglutide 1 mg after 28 weeks of treatment on:	
• Insulin secretion and insulin sensitivity combined outcome	• The change in total cDI (for tirzepatide versus semaglutide comparison only)
• Glucose control	• The change from baseline in fasting and postmeal glucose (total and incremental $AUC_{0-240min}$) during sMMTT • The change from baseline in hemoglobin A1c
• Insulin secretion	• The change in the first phase incremental ISR_{0-8min} from hyperglycemic clamp • The change in second phase total $ISR_{20-120min}$ from hyperglycemic clamp • The change in total $ISR_{0-120min}$ from hyperglycemic clamp • The change from baseline in insulin response to arginine (incremental $AUC_{arginine0-10min}$ and incremental $AUC_{arginine0-30min}$) from hyperglycemic clamp • The change from baseline in β cell GS from hyperglycemic clamp • The change in β cell GS from sMMTT • The change from baseline in ISRg from sMMTT
• Insulin sensitivity	• The change from baseline in hyperinsulinemic euglycemic clamp M-value
• Glucagon secretion	• The change from baseline in glucagon concentration at fasting and postmeal during sMMTT (total and incremental $AUC_{0-240min}$)
• Appetite and food intake	• The change from baseline in food intake during ad libitum meal served buffet style

Objectives and Endpoints

Objectives	Endpoints
Exploratory To compare the effects of tirzepatide 15 mg relative to placebo and semaglutide 1 mg after 28 weeks of treatment on:	
• Glucose metabolism and turnover in adipose tissue	• The change from baseline in glucose concentration and blood flow in adipose tissue during hyperglycemic clamp (microdialysis$_{0\text{-}120min}$) • The change from baseline in glucose concentration and blood flow in adipose tissue during sMMTT (microdialysis$_{0\text{-}240min}$)
• Insulin secretion	• The change in basal ISR (ISR$_{[-10\text{-}0min]}$) from hyperglycemic clamp • The change in basal insulin concentration (basal insulin$_{[-10\text{-}0min]}$) from hyperglycemic clamp • The change in the first phase insulin response (incremental AUC$_{0\text{-}10min}$) from hyperglycemic clamp • The change in the second phase insulin response (total AUC$_{20\text{-}120min}$) from hyperglycemic clamp • The change in steady-state ISR (total ISR$_{80\text{-}120min}$) from hyperglycemic clamp • The change in total insulin response (total AUC$_{0\text{-}120min}$) from hyperglycemic clamp • The change in basal ISR (total ISR$_{-10\text{-}0min}$) prior to sMMTT • The change in total ISR (total ISR$_{0\text{-}240min}$) from sMMTT • The change in ISRg adjusted for ISRgb from sMMTT • The change in RS from sMMTT • The change in PFR from sMMTT • The change in ICLb prior to sMMTT • The change in ICLm • The change in ratio of GS from sMMTT and from hyperglycemic clamp • The change in fasting proinsulin to insulin ratio • The change in II$_{30min}$ during the sMMTT • The change in fasting and postmeal insulin (total and incremental AUC$_{0\text{-}240min}$) during the sMMTT • The change in fasting and postmeal C-peptide (total and incremental AUC$_{0\text{-}240min}$) during the sMMTT

Objectives and Endpoints

Objectives	Endpoints
Exploratory (continued) • Insulin sensitivity	• The change from baseline in hyperinsulinemic euglycemic M/I value (M-value divided by total insulin concentration) • The change from baseline in HOMA2-IR • The change from baseline in postprandial insulin sensitivity indices (Matsuda, OGIS, Stumvoll indices) from sMMTT
• Glucagon secretion and PP secretion	• The change from baseline in total glucagon $AUC_{0\text{-}120min}$ during hyperglycemic clamp • The change from baseline in incremental glucagon concentration after arginine stimulation (incremental $AUC_{arginine0\text{-}30min}$) from hyperglycemic clamp • The change in glucagon/insulin ratio at fasting and during sMMTT (ratio of total glucagon $AUC_{0\text{-}240min}$ and total insulin $AUC_{0\text{-}240min}$) • The change in PP concentration at fasting and postmeal (total and incremental $AUC_{0\text{-}240min}$) during sMMTT
• Appetite (VAS) and food intake	• The change in fasting appetite (VAS) • The change in appetite (VAS) score during sMMTT
• Lipid metabolism and turnover in adipose tissue	• The change from baseline in plasma (triglycerides, β-hydroxybutyrate, pyruvate, lactate, FFA, and glycerol) and adipose tissue (glucose, pyruvate, lactate, and glycerol [$microdialysis_{0\text{-}120min}$]) lipid parameters and blood flow during hyperglycemic clamp • The change from baseline in plasma (triglycerides, β-hydroxybutyrate, pyruvate, lactate, FFA, glycerol, ApoB-48, ApoB-100, ApoC-III, LPL) and adipose tissue (glucose, pyruvate, lactate, and glycerol [$microdialysis_{0\text{-}240min}$]) lipid parameters and blood flow at fasting and during sMMTT • The change from baseline in fasting concentration of leptin, adiponectin, IGFBP 1 and 2

Objectives and Endpoints

Objectives	Endpoints
Exploratory (continued) • Body composition	• The change from baseline in lean body mass (actual value and %) • The change from baseline in body fat mass (actual value and %) • The change from baseline in body weight • The change from baseline in waist circumference
• Energy expenditure and substrate utilization	• The change in resting metabolic rate (indirect calorimetry) • The change in respiratory quotient, diet-induced thermogenesis, carbohydrate and fat oxidation rates before (-120 and -30 minutes) and 60, 120, 180, and 240 minutes after the start of sMMTT (indirect calorimetry)
• Safety and tolerability	• Adverse events • Safety laboratory parameters • Incidence and rate of hypoglycemia

Abbreviations: ApoB-48 = apolipoprotein B-48; ApoB-100 = apolipoprotein B-100; ApoC-III = apolipoprotein C-III; AUC = area under the concentration versus time curve; $AUC_{0\text{-}10min}$ = first phase insulin response; $AUC_{0\text{-}120min}$ = AUC from time zero to 120 minutes after start of the meal; $AUC_{0\text{-}240min}$ = AUC from time zero to 240 minutes after start of the meal; $AUC_{20\text{-}120min}$ = second phase insulin response; $AUC_{arginine0\text{-}10min}$ = AUC in response to arginine from time zero to 10 minutes; $AUC_{arginine0\text{-}30min}$ = AUC in response to arginine from time zero to 30 minutes; basal $insulin_{\text{-}10\text{-}0min}$ = average insulin concentration between -10 minutes and 0 minutes; cDI = clamp disposition index; FFA = free fatty acid; GS = glucose sensitivity; HOMA2 = Homeostatic Model Assessment of Insulin Resistance; HOMA2-IR = insulin resistance as measured by the HOMA2 method; ICLb = basal insulin clearance; ICLm = insulin clearance during sMMTT; IGFBP = insulin-like growth factor binding protein; II_{30min}= insulinogenic index at 30 minutes; ISR = insulin secretion rate; $ISR_{\text{-}10\text{-}0min}$ = basal insulin secretion rate; $ISR_{0\text{-}8min}$ = first phase insulin secretion rate; $ISR_{0\text{-}120min}$ = total insulin secretion rate from hyperglycemic clamp; $ISR_{20\text{-}120min}$ = second phase insulin secretion rate; $ISR_{0\text{-}240min}$ = total insulin secretion rate during sMMTT; $ISR_{80\text{-}120min}$ = steady-state insulin secretion rate; ISRg = ISR at fixed glucose concentration; ISRgb = ISR at fixed glucose concentration adjusted for basal potentiation; LPL = lipoprotein lipase; $microdialysis_{0\text{-}120min}$ = microdialysis from zero to 120 minutes; $microdialysis_{0\text{-}240min}$ = microdialysis from zero to 240 minutes; OGIS = Oral Glucose Insulin Sensitivity Index; PFR = potentiation ratio; PP = pancreatic polypeptide; RS = rate sensitivity; sMMTT = standardized mixed-meal tolerance test; T2DM = type 2 diabetes mellitus; VAS = visual analog scale.

5. Study Design

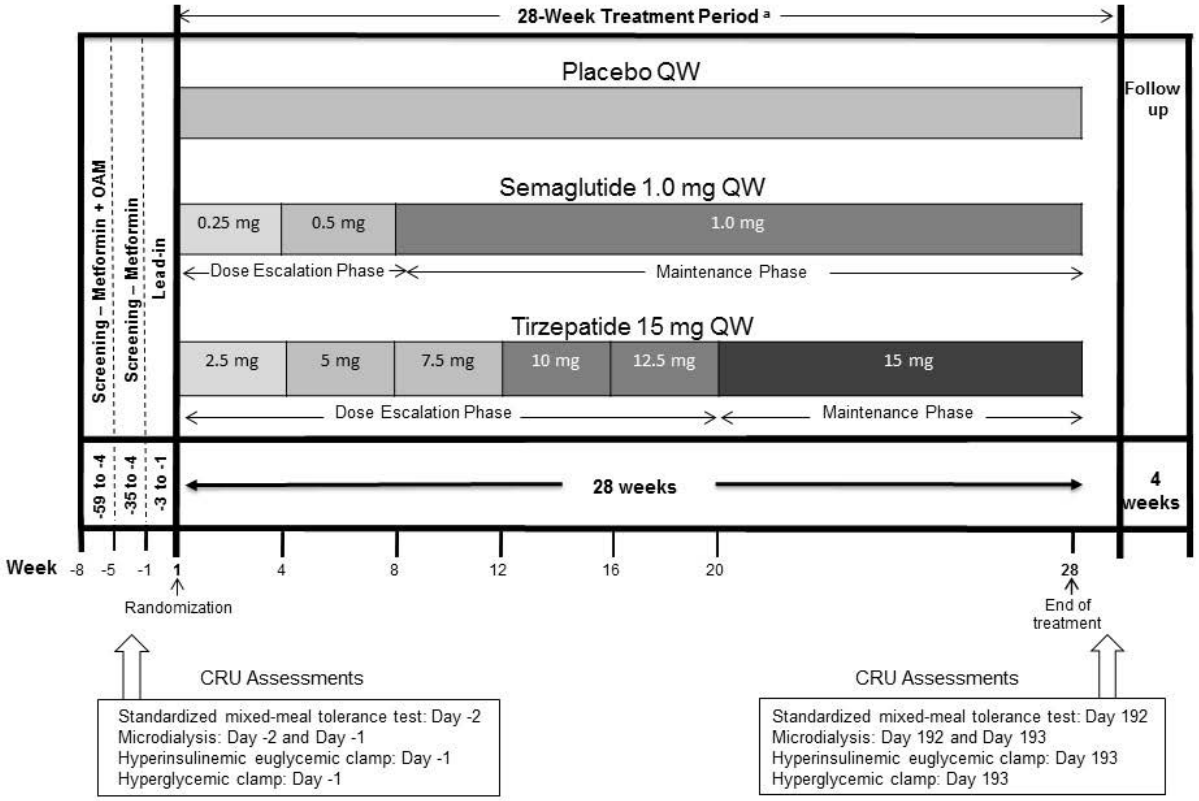
5.1. Overall Design

This is a Phase 1, multicenter, randomized, sponsor, investigator- and patient-blind, parallel arm study in patients with T2DM to compare the effect of tirzepatide 15 mg dose and placebo on total clamp disposition index (cDI) after 28 weeks of treatment, including the dose escalation phase. The study will also compare the effects of tirzepatide 15 mg relative to placebo and a selective GLP-1 RA semaglutide (positive control) on additional parameters of pancreatic α and β cell function, insulin sensitivity, glucose and lipid metabolism, and energy balance (food intake and energy expenditure). Ozempic® (semaglutide) will be used as a positive control for PD of GLP-1 pharmacology to investigate potential differences in the mechanisms of action between a dual GIPRA/GLP-1RA and a selective GLP-1RA.

The study will consist of 3 periods: an approximately 5- to 8-week screening/lead-in period, a 28-week treatment period, and a 4-week safety follow-up period. Patients will be randomized in a 3:3:2 ratio to QW tirzepatide 15 mg, semaglutide 1 mg, or placebo. Active treatments will be initially escalated with lower doses to reduce the risk of GI AEs. Immediately prior to randomization and approximately 1 to 3 days after the last dose of study drug, the patients will be admitted to the clinical research unit (CRU) to perform planned baseline and end-of-treatment inpatient study procedures, respectively. Section 2 (Schedule of Activities) presents all planned study visits and study procedures for this study. After the completion of the treatment period, a follow-up visit will be performed 4 weeks later to assess patient safety.

Study governance considerations are described in detail in Appendix 3.

Figure GPGT.1 illustrates the study design.



Abbreviations: CRU = clinical research unit; OAM = oral antihyperglycemia medication; QW = once weekly.

[a] Patients who are being treated with other OAMs, in addition to metformin, should discontinue these other OAMs after their eligibility is established, and should complete a 4-week washout period. Once the 4-week washout period is completed, patients can be enrolled in the study. Screening for patients who need to undergo washout of an additional OAM may last from Day -59 to Day -4, inclusive. This period includes the required 4-week washout. Screening procedures may be performed before washout from Day -59 to Day -31.

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

5.1.1. Screening and Lead-In

5.1.1.1. Screening

Eligibility for this study will be determined during the screening period. 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).

Eligible patients are those with T2DM treated with metformin, with or without oral antihyperglycemia medications (OAMs) other than metformin. Upon entering the study, patients should remain on the same metformin dose throughout the course of the study. After randomization, the metformin dose can be reduced in accordance with country-specific label to protect patient safety (see Section 7.7 [Concomitant Therapy] for further details). Those patients who are being treated with metformin in combination with other OAMs should discontinue all OAMs other than metformin after their eligibility is established, and should complete a 4-week washout prior to Visit 2 and CRU admission. During the washout period, the investigator will perform appropriate surveillance of the patients (by telephone interview or CRU visits, at the investigator's discretion) to monitor the safety and glycemic control of the patients. Once the 4-week washout period is completed, patients can be enrolled in the study. Screening for patients who need to undergo washout of OAMs other than metformin may last from Day -59 to Day -4, inclusive. Screening procedures may be performed before washout from Day -59 to Day -31. For all other eligible patients, screening may occur between Day -35 to Day -4, inclusive.

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. Patients will start performing daily SMPG and record all results, including any hypoglycemia episode, in diaries as soon as their eligibility is confirmed; these results will be used for glycemia management only. 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 their diet and exercise plan throughout the course of the study.

5.1.1.2. Lead-in

During the lead-in period (Day -3 to Day -1), eligible patients should continue their prestudy therapy with metformin. Patients who do not comply with requirements regarding metformin dosing and discontinuation of OAMs other than metformin (if used at study entry) will be discontinued from the study prior to randomization. In order to perform baseline procedures, including standardized mixed-meal tolerance tests (sMMTTs) and hyperinsulinemic euglycemic and hyperglycemic clamps, the patients will be admitted to the CRU at the beginning of the lead-in period, approximately 3 days prior to randomization. The list and timing of all baseline procedures are provided in Section 2 (Schedule of Activities).

5.1.2. Treatment

After completion of all baseline procedures, and while still in the CRU, eligible patients will be randomized in a 3:3:2 ratio to QW tirzepatide 15 mg, semaglutide 1 mg, or placebo. Following randomization, patients will participate in a 28-week treatment period that consists of a step-wise dose escalation to reach and maintain the highest scheduled dose level of tirzepatide and semaglutide that can be safely administered. The first dose of study drug will be administered shortly after randomization while the patients are still in the CRU. The investigator or qualified designee will review all available inpatient safety data before discharging patients from the CRU on Day 1. Patients may be required to remain at the CRU longer at the investigator's discretion.

A telephone visit will be conducted 2 to 3 days (Days 3 or 4) after the first dose of study drug and as needed, thereafter. At the telephone visits, study sites should check for any AEs, new concomitant medications, and glycemic control status. The patient should enter clinically relevant data in the diary. All data collected in the diaries will be reviewed by the investigator or her/his designee according to Section 2 (Schedule of Activities), and entered into the electronic case report form (eCRF), when applicable.

During the treatment period, the dose of tirzepatide and semaglutide will be escalated within each group according to schedules outlined in Figure GPGT.1. Briefly, the maintenance dose of semaglutide 1.0 mg will be reached after 4 QW doses of 0.25 mg, followed by 4 QW doses of 0.5 mg, as required per label. The starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW for 4 weeks, followed by an increase to 7.5 mg QW for 4 weeks, followed by an increase to 10 mg QW for 4 weeks, followed by an increase to 12.5 mg QW for 4 weeks until the 15 mg dose is reached and maintained for the duration of the study (see Figure GPGT.1). In order to maintain the blinding, all patients (including those on placebo and semaglutide) will undergo assessment by the investigator at 4 weekly intervals (4, 8, 12, 16, and 20) prior to the timed up dose escalation as described in Figure GPGT.1.

The schedule of clinic visits and study procedures during the treatment period, including sampling for immunogenicity and PK assessments, are provided in Section 2 (Schedule of Activities). Patients will return to the CRU every week for QW dose administration for 28 weeks. They will then be readmitted to the CRU within the last week of study (Week 28) to perform end-of-treatment sMMTT, hyperinsulinemic euglycemic, and hyperglycemic clamps. These procedures will be performed approximately 1 to 3 days after the last dose of study drug and according to the same schedule as during the lead-in period. Appendix 6 describes the key procedural features and the blood sampling plan during hyperglycemic clamp, hyperinsulinemic euglycemic clamp, microdialysis, sMMTT, appetite visual analog scale (VAS), ad libitum food intake, plethysmography for body composition, and ventilated hood for respiratory quotient procedures. These procedures will be performed in accordance to site practices and processes.

Patients who initiate rescue medication for treatment of severe hyperglycemia (Section 7.4.1.2 Management of Hyperglycemia) during the study or patients who discontinue study treatment, 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 initiation of rescue medications or discontinuation of study treatment, followed by a safety follow-up visit approximately 4 weeks later.

For the reinstitution of washed out OAMs, the timing of the medication restart will be discussed between the patient and the investigator. The timing of the medication restart (approximately Day 193) is at the discretion of the investigator dependent upon blood glucose control as documented in the SMPG, which will continue in the 4 weeks between Day 193 and follow-up. Additional telephone visits or outpatient visits may be scheduled to monitor the restart of the patient's baseline medication.

5.1.3. Safety Follow-Up

All randomized patients who complete the treatment period or patients who perform ET will complete the safety follow-up within 4 weeks after the last dose according to Section 2 (Schedule of Activities).

5.2. Number of Participants

Approximately 117 patients may be enrolled. Approximately 99 patients are expected to complete the study. Section 10.1 (Sample Size Determination) provides details on sample size calculation.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

The 28-week duration of the treatment period includes a 20-week dose escalation phase and an 8-week maintenance phase on the final 15 mg dose for patients randomized to tirzepatide, and includes an 8-week dose escalation phase and a 20-week maintenance phase on the final 1 mg dose for patients randomized to semaglutide. The semaglutide dosing regimen is based on the regulatory approved label (Ozempic Patient Leaflet, 2018). The tirzepatide dosing regimen reflects the escalation scheme at initiation that is assessed in the Phase 3 tirzepatide development program. These dosing regimens are expected to enable all on-treatment testing procedures to be performed under the steady-state conditions in both groups. The effect on most variables included in the assessment plan is expected to be at its plateau during this period. Differences in the escalation algorithm between active treatment groups are not considered of relevance for the planned assessments and timing of those assessments. The inclusion of a placebo arm in the study will enable characterization of the effects on study measures attributable exclusively to tirzepatide. Semaglutide is a selective GLP-1 RA that is considered the most effective agent in the GLP-1 RA class. The inclusion of semaglutide as a positive control will provide comparative data for a dual GIPR/GLP-1R agonist versus a selective GLP-1 RA.

The T2DM patient population selected to participate in this study, patients treated with up to 2 OAMs (metformin with or without another OAM), are considered to be in an earlier stage in the natural course of disease that is characterized by partial preservation of the β cell function. A preserved β cell function is a prerequisite for glucose-lowering efficacy of incretins and for the investigations of the mechanism of action (Bunck et al. 2009). Patients taking sodium-glucose transport protein 2 (SGLT-2) inhibitors can only be entered and washed out if there is no prior history of cardiovascular disease.

The cDI is chosen as the primary objective measure for this study because it integrates the effects of randomized treatments on the islet β cell and on insulin action, the 2 key pathophysiologic problems in T2DM. It is a generally accepted measure of the body's capacity to respond to glycemic challenge or the challenge associated with the sMMTT (Ferrannini et al. 2014;

Utzschneider et al. 2009). Other secondary objectives are chosen based on the current understanding of the physiologic and pharmacologic effects of dual GIPRA/GLP-1RA and selective GLP-1RAs (parameters of pancreatic α and β cell function, insulin tissue sensitivity, glucose and lipid metabolism, body weight regulation, and energy balance).

The dose justification for tirzepatide and semaglutide is provided in Section 5.5 (Justification for Dose). It is expected that the 2 treatments have differential effect on the key mechanistic pathways of interest (Pratley et al. 2018). Therefore, the planned assessments of the mechanism of action of these agents may provide an understanding of the key actions responsible for potential difference in glucose- and weight-lowering effects between the dual GIPR/GLP-1R agonist versus the selective GLP-1RA, including the contribution of GIP-specific actions.

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 accompanied by dose escalation in 2.5-mg increments every 4 weeks to attain a final dose of 15 mg. The step-wise increments are expected to permit adequate time for development of tolerance to GI events and are expected to minimize GI tolerability concerns. The proposed escalation scheme matches the escalation steps employed to attain a 15 mg tirzepatide dose in the Phase 3 program.

Tirzepatide 15 mg is predicted to maintain an exposure multiple of 1.6 to 2.4 to the no-observed-adverse-effect level doses in 6-month monkey and rat toxicology studies, respectively.

Table GPGT.2 shows the exposure multiples for SC administration of tirzepatide based on systemic exposure.

The semaglutide 1 mg dose is selected because it is the highest approved dose of this agent that has been shown to provide greater efficacy compared to other GLP-1RA approved for treatment of T2DM (Pratley et al. 2018; Ahmann et al. 2018).

Table GPGT.2. Exposure Multiples for Subcutaneous Administration of Tirzepatide Based on Systemic Exposure

	Dose (mg/kg)	AUC0-τ, Steady-State (µg*hr/mL)	Exposure Multiple
Human (15 mg)	–	205[a]	–
Monkey NOAEL[b]	0.5	337	1.6
Rat NOAEL[c]	3.0	280	2.4
Developmental Rat NOAEL[d]	0.1	4.01	0.082
Developmental Rabbit NOAEL[e]	0.03	14.7	0.072

Abbreviations: AUC = area under the plasma concentration-time curve; AUC0-τ = area under the plasma concentration-time curve from time zero to tau (dosing interval); NOAEL = no-observed-adverse-effect level; PK = pharmacokinetics.

a Plasma PK parameters shown were computed based on the PK model-predicted tirzepatide concentration-time profile (based on baseline body weight of approximately 90 kg).

b NOAEL (0.5 mg/kg) determined in a 6-month repeat-dose toxicity study (8336517). Exposure multiple (EM) is calculated as (AUC0-τ/τ in animals)/(AUC0-τ/τ in humans). τ is 168 hours in monkeys and humans. Therefore, EM in monkey = (337/168)/(human AUC/168).

c NOAEL (3 mg/kg) determined in a 6-month repeat-dose toxicity study (8337876). Exposure multiple is calculated as (AUC0-τ/τ in animals)/(AUC0-τ/τ in humans). τ is 96 hours in rats and 168 hours in humans. Therefore, EM in rat = (280/96)/(human AUC/168).

d NOAEL (0.1 mg/kg) for developmental toxicity in an embryo-fetal development study in rats (WIL-353354). τ is 40 hours in maternal rats. Exposure multiple is calculated as (AUC0-τ/τ in animals)/(AUC0-τ/τ in humans). τ is 40 hours in maternal rats and 168 hours in monkeys and humans. Therefore, EM in maternal rat = (4.01/40)/(human AUC/168).

e NOAEL (0.03 mg/kg) for developmental toxicity in an embryo-fetal development study in rabbits (WIL-353355). Exposure multiple is calculated as (AUC0-τ/τ in animals)/(AUC0-τ/τ in humans). τ is 168 hours in rabbits and humans. Therefore, EM in rabbits = (14.7/168)/(human AUC/168).

6. Study Population

Eligibility of patients for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiograms (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 56 days prior to start of lead-in on Day -3 for patients treated with OAMs other than metformin, who are required to perform a washout for at least 4 weeks prior to lead-in. For all other patients, screening may occur up to 32 days prior to lead-in. All patients will then perform a 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 1 week 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 (Visit 1):

Disease Characteristics

[1] Have T2DM for at least 6 months;

[2] Treated with diet and exercise and stable dose(s) of metformin, with or without 1 additional stable dose of OAM other than metformin, 3 months prior to study entry; doses of metformin will be considered stable if all prescribed doses for this period were ±850 mg from the most commonly prescribed dose; allowed OAMs, in combination with metformin, are dipeptidyl peptidase-4 (DPP-IV) inhibitors, SGLT-2 inhibitors, acarbose, and sulfonylureas; the second OAM dose will be considered stable if the prescribed dose is unchanged for at least 3 months prior to study entry.

[3] Have a hemoglobin A1c value at screening (Visit 1) of ≥7.0% and ≤9.5% if on metformin only; or ≥6.5% and ≤9.0% if on metformin in combination with OAMs other than metformin;

Patient Characteristics

[4] Male or female patients between the ages of 20 and 74 years, inclusive

[4a] Male patients:

- Men, regardless of their fertility status, with nonpregnant woman 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 methods 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 (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a 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 (eg, 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).

- The inclusion of WOCBP requires use of a highly effective contraceptive measure (Appendix 8). Contraception should be maintained during treatment and until the end of estimated relevant potential exposure (90 days).

- Must not be breastfeeding
- 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 no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

[5] Have a body mass index between 25 kg/m^2 and 45 kg/m^2, inclusive, at screening (Visit 1); are of stable weight (±5%) >3 months prior to screening (Visit 1); and agree to not initiate an intensive diet and/or exercise program during the study with the intent of reducing body weight other than 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 (Visit 1) 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 (Visit 1) 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 (Visit 1);

[12] Have a history of proliferative retinopathy or maculopathy as determined by the investigator based on a recent (<1.5 years) ophthalmologic examination;

[13] Impaired renal estimated glomerular filtration rate <45 mL/min/1.73 m^2 calculated by Chronic Kidney Disease-Epidemiology.

Prior/Concomitant Therapy - Glucose-Lowering Medications

[14] Have taken any glucose-lowering medications other than allowed OAMs any time during the last 3 months before screening (Visit 1) or during the screening 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; after their eligibility is confirmed, patients will be required to discontinue all OAMs other than metformin and will then perform a required 4-week washout prior to lead-in (Visit 2); in patients with established cardiovascular disease who are treated with SGLT-2 inhibitors, this therapy should not be discontinued; therefore, these patients will NOT be eligible for participation in the trial;

Medical Conditions - General

[15] Have a history or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, haematological 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 (eg, severe diabetic gastroparesis or gastric outlet obstruction) or have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (eg, Lap-Band®);

[18] Have a personal or family history of medullary thyroid carcinoma (MTC), multiple endocrine neoplasia syndrome type 2 (MEN 2), or a screening calcitonin ≥20 pg/mL at screening (Visit 1);

[19] Have had acute myocardial infarction, congestive heart failure NYHA class III or IV, and/or cerebrovascular accident (stroke]) within 3 months prior to screening (Visit 1); for patients taking SGLT-2 inhibitors: any history of congestive heart failure, myocardial infarction, unstable angina, or stroke;

[20] Have findings in the 12-lead ECG at screening (Visit 1) 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 (Visit 1);

[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 [Visit 1]). 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) >2.5X the upper limit of normal (ULN) or total bilirubin level (TBL) >1.5X ULN;

[25] Have had a blood donation of 450 mL or more in the last 3 months or any blood donation within the last month prior to screening (Visit 1);

[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 during CRU admission;

[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 dosing and until discharge from the CRU;

[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 (eg, Meridia® [sibutramine], Sanorex® [mazindol], Adipex® [phentermine], BELVIQ® [lorcaserin], Mysimba [naltrexone/bupropion], Saxenda® [liraglutide]) or similar other body weight loss medications, including over-the-counter medications (eg, alli®) within 3 months prior to screening (Visit 1) or between Visit 1 and randomization (Visit 2);

[31] Have received chronic (lasting >14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-articular, and inhaled preparations) within 1 month before screening (Visit 1), or between Visit 1 and randomization (Visit 2);

[32] Have received treatment with a drug that has not received regulatory approval for any indication within 1 month prior to screening (Visit 1); 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 after randomization 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, Profil, and 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 come to the CRU in a fasting state, after an overnight fast lasting at least 8 hours for safety laboratory tests, 10 hours indirect calorimetry, or 12 hours for hyperinsulinemic euglycemic clamp as specified in Section 2 (Schedule of Activities). Additional dietary requirements for the planned assessments in the CRU at baseline and Week 28 (for example, hyperinsulinemic euglycemic and hyperglycemic clamp procedures, sMMTT) are described in detail in Appendix 6.

6.3.2. Caffeine, Alcohol, and Tobacco

No alcohol, caffeine, and/or methylxanthine-containing products will be allowed at least 24 hours before each CRU admission, and each outpatient visit and throughout the duration of each CRU visit. 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 each outpatient visit and throughout the duration of each CRU visit. While not resident in the CRU, patients must consume 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 study site, 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) or were unable to complete OAM washout may be re-screened up to 1 time. Individuals who had been rescreened once and marked as screen failures during the halt in enrollment due to the Coronavirus Disease 2019 (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 screening number. Screening number, starting with 501 or 301 based on study site, will be assigned at the screening visit. If patients are re-screened, they will be assigned a new screening number. Patient numbers/enrollment numbers are assigned in the morning of Day 1 to ensure only eligible patients enter the study.

7. Treatment

7.1. Treatment Administered

Patients will receive up to 15 mg of tirzepatide, up to 1.0 mg of semaglutide, or placebo, all administered SC QW for 28 weeks.

Table GPGT.3 shows the study treatments and dose escalation for tirzepatide and semaglutide.

Table GPGT.3. Study Treatments and Dose Escalation

Dose Escalation Schemes (dose in mg)							
Treatment	**Week 1-4**	**Week 5-8**	**Week 9-12**	**Week 13-16**	**Week 17-20**	**Week 21-24**	**Week 25-28**
Tirzepatide	2.5	5	7.5	10	12.5	15	15
Semaglutide	0.25	0.5	1.0	1.0	1.0	1.0	1.0
Placebo	X	X	X	X	X	X	X

All treatments will be administered QW at the CRU. 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. Patients will be blinded to study drug administration by means of a blindfold.

Whenever possible, study drug administration should be carried out by the same personnel. The personnel who administer study drug will not be performing any study assessments with patients.

The investigator or designee is responsible for:

- explaining the correct use of the IP to the 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 sites will be instructed to discard used medications according to local regulations.

7.1.1. Packaging and Labeling

Tirzepatide for SC administration after reconstitution will be provided as a lyophilized study drug in clear glass vials. Each vial of tirzepatide will contain 5 mg. Matching placebo vials will be provided as lyophilized excipient. Tirzepatide and matching placebo will be supplied by Lilly. The diluent will be sterile water for injection (1.1 mL to give 5 mg/mL) and will be site sourced.

Semaglutide will be the positive control and the commercially available formulation (Ozempic pen) will be supplied by Lilly.

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

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to one of the study treatment arms on Day 1 after completion of all baseline procedures and prior to dosing (Visit 2). Assignment to treatment arms will be determined by a randomization table with treatment codes. Patients will be randomized in a 3:3:2 ratio to receive QW tirzepatide 15 mg, semaglutide 1 mg, or placebo.

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 (±1 day) and at approximately the same time of the day. The actual time of all dose administrations will be recorded in the patient's 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 48 hours prior to the next scheduled dose. If the remaining time to the next scheduled dose is less than 48 hours, the dose will not be administered and will be considered a missed dose.

7.3. Blinding

For tirzepatide, semaglutide, and placebo, the dosing will be sponsor, investigator, and patient blinded. To preserve the blinding of the study for treatment allocation, all study site personnel, except staff who prepare, dispense, and administer study medication, will be blinded to treatment allocation. Tirzepatide and placebo will be prepared by the site pharmacy in accordance to the pharmacy preparation instructions. Semaglutide will be administered in accordance to its package insert instructions. The site staff will take the necessary steps to ensure that patients will remain blinded to the treatment administration.

Blinding of tirzepatide, semaglutide, and placebo will be maintained throughout the conduct of the study until all data are cleaned to an acceptable level of quality and locked. The details are included in the separate Blinding/Unblinding Plan.

The staff who prepare and dispense study medication will receive a randomization table with treatment codes to enable preparation of blinded doses.

Emergency codes will be available to the investigator. A code, which reveals the treatment for a specific study patient, may be opened during the study only if the patient's well-being requires knowledge of the patient's treatment assignment.

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 study participant to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient'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. The investigator should make every effort to contact the Lilly CP or CRP before unblinding a study patient's treatment assignment unless this could delay emergency treatment of the patient. If a study patient's treatment assignment is unblinded, Lilly must be notified immediately.

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 at any time during the study, dosing can be interrupted temporarily (Section 8.1.2 Temporary Interruption of Study Drug).

7.4.1. Special Treatment Considerations

Fasting plasma glucose (FPG) values will be measured daily by the patient using the BG meter provided during the screening period, after the eligibility is confirmed (between Visits 1 and 2). 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

If 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.

For management of hypoglycemia during the clamp procedures see Section 7.4.1.3 (Treatment of Hypoglycemia and Hypokalemia during Hyperinsulinemic Euglycemic Clamp).

For hypoglycemia reporting see Section 9.2.2.1 (Hypoglycemia).

7.4.1.2. Management of Hyperglycemia

If SMPG records indicate that plasma glucose (PG) values are exceeding the limits for severe, persistent hyperglycemia described in Section 9.2.2.2 (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 at the discretion of the investigator. Rescue medications will be prescribed by the health care professional responsible for the patient's usual medical care. Only the GLP-RAs are not allowed as rescue medications to avoid interference with safety assessments during the safety follow-up. Patients who receive rescue therapy will be discontinued from the study after performing ET visit and safety follow-up visit 4 weeks later. If hyperglycemia occurs during the follow-up period, the patient will remain in the study until completion of the planned follow-up.

For criteria for hyperglycemia reporting see Section 9.2.2.2 (Severe, Persistent Hyperglycemia).

7.4.1.3. Treatment of Hypoglycemia and Hypokalemia during Hyperinsulinemic Euglycemic Clamp

During hyperinsulinemic euglycemic clamp, excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia can be treated with glucose. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/SC glucagon or concentrated intravenous (IV) glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

7.5. Preparation/Handling/Storage/Accountability

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

Only patients enrolled in the study may receive IP or study materials, and only authorized site staff may supply or administer IP. All 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.

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

The IP will be administered at the study site and documentation of treatment administration will occur at the site. 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 maintenance doses 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/lead-in 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. Patients are required to continue metformin as their only concomitant antihyperglycemic medication during the entire trial. 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 as 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 trial. 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.

Patients treated with other OAMs at study entry, in addition to metformin, are allowed to participate in the study (refer to Inclusion Criteria [2] and [3] for details) but must discontinue OAMs other than metformin as soon as their eligibility is confirmed, and must complete a 4-week washout period prior to the lead-in period and randomization. Once the 4-week washout period is completed, patients can be enrolled in the study. The allowed OAMs, in combination with metformin, are DPP-IV inhibitors, SGLT-2 inhibitors, acarbose, and sulfonylureas.

Short-term (<14 days) use of insulin for treatment of acute conditions is allowed 3 months prior to screening (Visit 1) and after randomization. If used >14 days after randomization, the patient will be discontinued from study treatment and from the study.

Other glucose-lowering medications 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. After the completion of the treatment period, patients can receive other glucose-lowering agents, except GLP-RAs. The patients who receive glucose-lowering agents that are prohibited during the treatment period for >14 days, including patients who initiate rescue interventions for severe hyperglycemia, will be immediately discontinued from the study treatment and from the study after the completion of the end-of-study procedures (ET visit and 4-week safety follow-up). If used ≤14 days for any other reason, the patient will be required to discontinue this treatment and continue in the trial.

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 trial. 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 4-week safety follow-up). 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 should not be used prophylactically. Similarly, anti-diarrheal agents are allowed to be prescribed if the patient reports AE 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).

If an additional concomitant medication that is either prohibited per study protocol or may interfere with efficacy or safety assessment is started, the site monitor and sponsor should be informed as soon as possible. Any new medications used during the course of the study (including those not requiring sponsor notifications) must be documented in the eCRF.

7.7.1. Management of Patients with Gastrointestinal Symptoms

The tirzepatide and semaglutide dose escalation schemes have been designed to minimize the development of intolerable GI symptoms. The escalation period for tirzepatide is considered to be 20 weeks to reach the 15 mg maintenance dose and additional 4 weeks to reach steady-state. The escalation period for semaglutide is considered to be 8 weeks to reach the 1 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 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 and semaglutide 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
- 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 with any other treatment-emergent adverse event (TEAE), SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
- If female patient becomes pregnant
- If a patient is diagnosed with type 1 diabetes mellitus
- If a patient experiences severe, persistent hyperglycemia (Section 7.4.1.2 and Section 9.2.2.2)

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%)
- 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).

Patients who discontinue study drug early will be also 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 and not during the maintenance phase. 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 more than 2 episodes of study interruptions occur in the same patient, these cases will be reviewed by the investigator (or his/her designee) and Lilly sponsor 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 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, 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 (including tolerance limits for timing).

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

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

Appendix 6 describes methods for assessment of glucose and lipid metabolism, and appetite and food intake during the study (hyperglycemic clamp, hyperinsulinemic euglycemic clamp, microdialysis, sMMTT, appetite (VAS), ad libitum food intake, plethysmography for body composition, and ventilated hood for respiratory quotient procedures, including the sampling plan). A complete description of each of these procedures is included in operation manuals available at the study site.

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 (eg, equipment technical problems, venous access difficulty, or patient defaulting or turning up late for 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

In this study, the measures used to assess mechanisms of action of study treatments on glucose and lipid metabolism, appetite and food intake are considered efficacy measures. The planned assessments will be performed at baseline and at the end of the treatment period at 28 weeks.

All parameter calculations, when applicable, and analyses are described in Section 10.3 (Statistical Analyses) and in the statistical analysis plan (SAP).

9.1.1. Primary Efficacy Assessments and Procedures

The primary efficacy measure in the study is the change from baseline to Week 28 in total cDI for comparison of tirzepatide with placebo. Total cDI, which is a product of insulin secretion and insulin sensitivity, will be calculated from total insulin secretion rate during the 120-minute hyperglycemic clamp determined from C-peptide concentrations using the deconvolution technique ($ISR_{0\text{-}120min}$) divided by glucose area under the concentration versus time curve from

0 to +120 minutes (total AUC from time zero to 120 minutes after start of the hyperglycemic clamp [$AUC_{0\text{-}120min}$]) and insulin sensitivity expressed as M-value from hyperinsulinemic euglycemic clamp, respectively (Van Cauter et al. 1992; Sjaarda et al. 2012).

9.1.2. Secondary Efficacy Assessments and Procedures

The change in total cDI measure will also be used for secondary objective to compare tirzepatide with semaglutide.

Secondary efficacy measure to assess the effect of study treatments on glucose control:

- fasting and postmeal glucose (total and incremental AUC from time zero to 240 minutes after start of the meal [$AUC_{0\text{-}240min}$]) during sMMTT;
- hemoglobin A1c

Secondary efficacy measures to assess the effect of study treatments on β cell function:

- $ISR_{0\text{-}8min}$ from hyperglycemic clamp, defined as average incremental insulin secretion (incremental ISR AUC/time interval), during the 0 to +8 minute clamp period (first phase insulin secretion index);
- $ISR_{20\text{-}120min}$ from hyperglycemic clamp, defined as average total insulin secretion (ISR AUC/time interval) during the +20 to +120-minute clamp period (second phase insulin secretion index);
- $ISR_{0\text{-}120min}$ from hyperglycemic clamp, defined as average total insulin secretion (ISR AUC/time interval) during the entire clamp 120-minute period;
- Insulin $AUC_{arginine0\text{-}10min}$ and $AUC_{arginine0\text{-}30min}$ from hyperglycemic clamp, defined as incremental insulin AUC/time interval, between +120 to +130 minute and +120 to +150 minute of clamp period, respectively;
- β cell glucose sensitivity (GS) from hyperglycemic clamp, defined as [$ISR_{80\text{-}120min}$-$ISR_{-10\text{-}0min}$]/[glucose increment from basal to final period]; mean glucose in the basal and final periods are calculated during the same time interval in which $ISR_{-10\text{-}0min}$ and $ISR_{80\text{-}120min}$ are determined;
- β cell GS from sMMTT, defined as the slope of the dose-response for insulin secretion versus glucose during the sMMTT, determined by modeling analysis;
- ISR at fixed glucose concentration (ISRg) from sMMTT, defined as insulin secretion corresponding to a fixed glucose level representative of the basal value in the study population, and calculated from the dose-response;

Secondary efficacy measures to assess the effect of study treatments on insulin sensitivity:

- hyperinsulinemic euglycemic clamp M-value, calculated from glucose infusion rate (GIR) over the last 30 minutes, corresponding to steady-state (+150 to +180 minutes), corrected for space (DeFronzo et al. 1979);

Secondary efficacy measures to assess the effect of study treatments on glucagon secretion:

- glucagon concentration at fasting and postmeal during sMMTT (total and incremental $AUC_{0\text{-}240min}$);

Secondary efficacy measures to assess the effect of study treatments on appetite and food intake:

- ad libitum caloric intake with standardized meal served buffet style;

9.1.3. Exploratory Efficacy Assessments and Procedures

Exploratory efficacy measures to assess the effect of study treatments on glucose metabolism and turnover in adipose tissue:

- glucose concentration in adipose tissue microdialysis from zero to 120 minutes ($microdialysis_{0\text{-}120min}$) during hyperglycemic clamp, estimated from the average of measurements from dialysate performed every 30 minutes starting at time point 0, and from changes in tissue blood flow;
- glucose concentration in adipose tissue microdialysis from zero to 240 minutes ($microdialysis_{0\text{-}240min}$) during sMMTT, estimated from the average of measurements from dialysate performed every 60 minutes starting at time point 0, and from changes in tissue blood flow;

Exploratory efficacy measures to assess the effect of study treatments on β cell function:

- basal insulin secretion rate ($ISR_{-10\text{-}0min}$) from hyperglycemic clamp, defined as average insulin secretion (ISR AUC/time period) between -10 minutes and 0 minutes;
- basal insulin concentration ($basal\ insulin_{-10\text{-}0min}$) from hyperglycemic clamp, defined as average insulin concentration between -10 minutes and 0 minutes;
- first phase insulin response (incremental $AUC_{0\text{-}10min}$) from hyperglycemic clamp, defined as incremental insulin AUC between 0 minutes and +10 minutes;
- second phase insulin response (total $AUC_{20\text{-}120min}$) from hyperglycemic clamp, defined as total insulin AUC between +20 minutes and +120 minutes;
- steady-state insulin secretion rate (total $ISR_{80\text{-}120min}$) from hyperglycemic clamp, defined as average total insulin secretion (ISR AUC/time interval) during the +80 minute to +120 minute clamp period;
- total insulin response (total $AUC_{0\text{-}120min}$) from hyperglycemic clamp, defined as total insulin AUC from time 0 minutes to +120 minutes;
- basal ISR prior to sMMTT; defined as average insulin secretion at time point from -10 to 0 minutes;

- total insulin secretion rate (total $ISR_{0\text{-}240min}$) from sMMTT; defined as average total insulin secretion (ISR $AUC_{0\text{-}240min}$/time interval) during the entire sMMTT 240-minute period;
- ISRg adjusted for basal potentiation (ISRgb) from sMMTT, defined as ISRg multiplied by the basal potentiation factor value;
- rate sensitivity from sMMTT, determined by modeling analysis;
- potentiation ratio (PFR) from sMMTT, defined as relative enhancement of ISR, as predicted by the dose-response from basal to +120 minute (PFR_{120}), +180 minute, (PFR_{180}) and +240 minute (PFR_{240}) time points, determined by modeling analysis;
- basal insulin clearance (ICLb) prior to sMMTT, defined as the ratio of insulin secretion to insulin concentration at fasting prior to sMMTT;
- insulin clearance during sMMTT (ICLm), defined as the ratio of insulin secretion to insulin concentration AUCs during the sMMTT;
- ratio of GS from sMMTT and from hyperglycemic clamp (estimate of the incretin effect);
- fasting proinsulin to insulin ratio;
- insulinogenic index at 30 minutes (II_{30min}), defined as the ratio of increments in insulin and glucose concentrations from time point 0 to +30 minutes during the sMMTT;
- fasting and postmeal insulin (total and incremental $AUC_{0\text{-}240min}$) during the sMMTT;
- fasting and postmeal C-peptide (total and incremental $AUC_{0\text{-}240min}$) during the sMMTT;

Exploratory efficacy measures to assess the effect of study treatments on insulin sensitivity:

- hyperinsulinemic euglycemic M/I value, defined as the M-value divided by total insulin over the same time period (+150 to +180 minutes).
- insulin resistance as measured by the HOMA2 method (HOMA2-IR) (Hill et al. 2013);
- postprandial insulin sensitivity indices from sMMTT, as previously published (Matsuda Index [Schlichtkrull et al. 1965; Matsuda and DeFronzo 1999; Service and O'Brien 2001], Oral Glucose Insulin Sensitivity [OGIS] Index [Mari et al. 2001], and Stumvoll Index [Stumvoll et al. 2000]);

Exploratory efficacy measures to assess the effect of study treatments on glucagon and pancreatic polypeptide (PP) secretion:

- total glucagon $AUC_{0\text{-}120min}$ during hyperglycemic clamp;
- incremental glucagon AUC/time interval after arginine stimulation from hyperglycemic clamp between +120 and +150 min;
- glucagon/insulin ratio at fasting and during sMMTT, defined as ratio of total glucagon $AUC_{0\text{-}240min}$ and total insulin $AUC_{0\text{-}240min}$;

- PP concentration at fasting and postmeal (total and incremental $AUC_{0\text{-}240min}$) during sMMTT;

Exploratory efficacy measures to assess the effect of study treatments on appetite (VAS) and food intake:

- appetite sensations VAS scores for hunger, fullness, satiety, prospective food consumption, desire for specific foods, and the overall appetite score, assessed at fasting and during sMMTT (van Can et al. 2014; Flint et al. 2000; Flint et al. 2013);

Exploratory biomarkers to assess the effect of study treatments of lipid metabolism and turnover in adipose tissue:

- plasma (triglycerides, β-hydroxybutyrate, pyruvate, lactate, free fatty acid (FFA), and glycerol) and adipose tissue (glucose, pyruvate, lactate, and glycerol [$microdialysis_{0\text{-}120min}$]) lipid parameters and blood flow during hyperglycemic clamp;
- plasma (triglycerides, β-hydroxybutyrate, pyruvate, lactate, FFA, glycerol, apolipoprotein B-48 [ApoB-48], apolipoprotein B-100 [ApoB-100], apolipoprotein C-III [ApoC-III], lipoprotein lipase [LPL]) and adipose tissue (glucose, pyruvate, lactate, FFA, and glycerol [$microdialysis_{0\text{-}240min}$]) lipid parameters and blood flow at fasting and during sMMTT;
- fasting concentration of leptin, adiponectin, insulin-like growth factor binding protein (IGFBP) 1 and 2;

Exploratory efficacy measures to assess the effect of study treatments on body composition, assessed with air displacement plethysmography, and body weight and waist circumference:

- lean body mass (actual value and %);
- body fat mass (actual value and %);
- body weight;
- waist circumference;

Exploratory efficacy measures to assess the effect of study treatments on energy expenditure and substrate utilization assessed with indirect calorimetry using ventilated hood system:

- resting metabolic rate obtained by indirect calorimetry;
- respiratory quotient, diet-induced thermogenesis, carbohydrate and fat oxidation rates before (-120 and -30 minutes) and 60, 120, 180, and 240 minutes after the start of sMMTT, obtained by indirect calorimetry;

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. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

The investigator will record all 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. For each AE, the onset and duration, the seriousness and severity, and the actions taken will be recorded.

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 CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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. Hypoglycemia

Patients will collect information on episodes of hypoglycemia starting immediately after their eligibility is confirmed until the last study visit (follow-up visit or ET visit). For that purpose, patients will be trained between Visit 1 and 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.

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. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.

Other Hypoglycemia Categories:

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

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

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

In each case of suspected or confirmed hypoglycemia, it is important that the event be properly categorized, the effect of the intervention be assessed, and the frequency of hypoglycemia be evaluated. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established. The patient should receive additional education, if deemed appropriate. 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).

9.2.2.2. 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 FPG is greater than 240 mg/dL (13.3 mmol/L) over any 2-week period between baseline and end of Week 12, as well as during the 4-week washout period for those discontinuing OAMs other than metformin use before randomization
- The average FPG greater than 200 mg/dL (11.1 mmol/L) over any 2-week period between Week 13 and end of the treatment period

Section 7.4.1.2 (Management of Hyperglycemia) provides treatment guidance for patients with severe, persistent hyperglycemia.

9.2.2.3. Pancreatitis

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

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

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase 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 therapy with IP(s), and will be discontinued from the study after completing all end-of-the trial 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 case of AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug(s).

Each patient will have measurements of amylase and lipase, part of safety laboratory tests as shown in Section 2 (Schedule of Activities) to assess the effects of study treatments on

pancreatic enzyme levels. Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Steinberg et al. 2017a; Steinberg et al. 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic amylase ≥3X ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the patient's overall clinical condition. If further diagnostic assessment due to asymptomatic hyperenzymemia will be 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.

9.2.2.4. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or MEN 2 will be excluded from the study, as well as those with values above 20 pg/mL 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 treatments 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 ng/mL. If the calcitonin value decrease below 35 ng/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 follow-up assessment will be collected in the specific section of the eCRF.

9.2.2.5. 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

9.2.2.6. 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.

9.2.2.7. Hypersensitivity Events

All allergic or hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Additional data, such as type of reaction and treatment received, will be collected for any AEs or SAEs that the investigator deems related to study drug(s) via a CRF created for this purpose. Additional serum samples should also be collected as outlined in Section 9.6.1 (Immunogenicity Assessments). Study drug(s) should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug(s). Study drug(s) may be restarted when/if it is safe to do so, in the opinion of the investigator. If study drug(s) is permanently discontinued, the patient will receive another glucose-lowering treatment, judged by the investigator to be appropriate based on the patient's clinical status, and will be discontinued from the study (Section 8.1.1 Permanent Discontinuation from Study Treatment).

9.2.2.7.1. Injection Site Reactions

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

9.2.2.8. Diabetic Retinopathy Complications

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

9.2.2.9. Hepatobiliary Disorders

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

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

9.2.2.10. Severe Gastrointestinal Adverse Events

Tirzepatide and semaglutide 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).

9.2.2.11. 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.

9.2.2.12. Metabolic Acidosis, Including Diabetic Ketoacidosis

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

9.2.2.13. Amputation/Peripheral Revascularization

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

9.2.2.14. Major Depressive Disorder/Suicidal Ideation

The prevalence of depressive symptoms and disorders is increased in patients with 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 patients with suspected or confirmed overdose with tirzepatide or semaglutide, 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 and package insert for semaglutide.

9.4. Safety

9.4.1. Laboratory Tests

For each patient, laboratory tests to assess efficacy and safety of study treatments will be performed throughout the study and at the end of the safety follow-up period according to the schedule provided in Section 2 (Schedule of Activities). 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.

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 inclusion 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/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.

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, and reported and adjudicated pancreatitis and cardiovascular 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 study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP according to Lilly standard hepatic monitoring algorithm. 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/subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

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 from placebo-treated patients are not planned.

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

9.6. Pharmacodynamics

The sample(s) 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.

The description of the procedures for obtaining the samples for PD parameters is detailed in Appendix 6. Briefly, PD assessments will include hyperinsulinemic euglycemic clamps for measure of insulin sensitivity; hyperglycemic clamp to assess β cell function/insulin secretion and α cell function; arginine stimulation test; microdialysis; a sMMTT to assess α and β cell function, insulin sensitivity, nutrient utilization, and metabolic flexibility under physiological conditions; VAS to determine effects of study treatments on appetite sensations and desire for specific food; ad libitum food intake test to determine effect of study treatments on meal intake; plethysmography for body composition, and indirect calorimetry to determine metabolic rate.

9.6.1. Immunogenicity Assessments

For immunogenicity testing, venous blood samples of approximately 10 mL will be collected from each patient according to Section 2 (Schedule of Activities) to determine antibody production against tirzepatide. Additional samples may be collected if there is a possibility that an AE is immunologically mediated. All samples for immunogenicity testing should have a time-matched sample for PK analysis. Detailed instructions on the sample collections will be provided by Lilly or its designee.

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

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

A 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 are TE-ADA positive at the last scheduled assessment or discontinuation visit will have additional samples taken at 3, 6, 9 (optional), and 12 months after the last assessment until the titer returns to within 2-fold of baseline titer or for up to 1 year, whichever is less. 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. If no clinical sequelae are recognized by the clinical team, then 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. A PK sample may be collected at the 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 follow-up immunogenicity assessment; however, if patients are unwilling or unable to return for the visit, this is not considered a protocol violation.

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.

9.6.2. Body Weight and Waist Circumference

Weight and waist circumference will be measured according to Section 2 (Schedule of Activities). Patients will be weighed at approximately the same time in the morning, before dosing, 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. Waist circumference will also be measured on each scheduled occasion. Both weight and waist circumference 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. 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 nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

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

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the 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 or 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 117 patients are planned to be randomized so that 99 patients complete the clamp procedures assuming 15% discontinuation rate. The 117 patients will be randomized in a 3:3:2 ratio to QW tirzepatide 15 mg, semaglutide 1 mg, or placebo. To power the study, simulated data from PK/PD models were used. The log-scale variability of cDI is estimated to be 0.586 from the model and previous trials and the log-scale treatment difference is estimated to be 0.913 (tirzepatide minus placebo) and 0.417 (tirzepatide minus semaglutide). This provides over 90% power to show greater cDI for tirzepatide relative to placebo and 85% power for the comparison of tirzepatide versus semaglutide.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description 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 by treatment group.

10.2.3. Treatment Compliance

No analyses of treatment compliance are planned.

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 receive at least 1 dose of the IP and have evaluable data. Data will be censored once patients discontinue their randomized treatment or initiate additional rescue treatment.

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 study drug 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, ECGs, TEAEs (including TEAEs of special interest), and SAEs. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will 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 will be summarized for each treatment group and visit as well as overall by mean, SD, median, minimum, and maximum. Hypoglycemia incidence 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. For change from baseline values, a mixed-model repeated-measure (MMRM) method with treatment, visit, and treatment-by-visit interaction as fixed effects, patient as random effect, and baseline as covariate will be used. An unstructured variance-covariance matrix will be used to model within-patient effects.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Sparse PK samples will be collected across the 28-week treatment duration 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 summaries and analyses of PK parameters are planned.

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

All AUC measures will be calculated using the trapezoidal rule.

Incremental AUC measures use the time zero value relative to the AUC measured unless otherwise specified.

The following variables will be calculated using the collected insulin and C-peptide measurements to be then included in the SAP:

Clamp disposition index:

- cDI is defined as the product of the M-value derived from the hyperinsulinemic euglycemic clamp over the last 30 minutes and total insulin secretion ($ISR_{0\text{-}120min}$) derived from the insulin secretion rate based on C-peptide using the using the deconvolution technique divided by the total glucose $AUC_{0\text{-}120min}$ from the hyperglycemic clamp portion of the study

- cDI = $[(ISR_{0\text{-}120min})/(\text{glucose } AUC_{0\text{-}120min})] \times$ M-value

Insulin sensitivity:

- M-value from hyperinsulinemic euglycemic clamp is the measure of insulin sensitivity; M-value is defined as the GIR over the last 30 minutes of the clamp (+150 to +180 minutes) minus a correction factor for non-constant glucose level divided by body weight (DeFronzo et al. 1979).

ISR based on C-peptide using the deconvolution technique (Van Cauter et al. 1992):

- ISR during the first phase calculated by the deconvolution method between time zero and the 8th minute of the hyperglycemic clamp ($ISR_{0\text{-}8min}$)
- ISR during the second phase calculated by the deconvolution method between the 20th and 120th minute of the hyperglycemic clamp ($ISR_{20\text{-}120min}$)
- Insulin secretion rate calculated by the deconvolution method between time zero and the 120th minute of the hyperglycemic clamp, ($ISR_{0\text{-}120min}$)
- β cell GS from hyperglycemic clamp, defined as $[ISR_{80\text{-}120min}\text{-}ISR_{\text{-}10\text{-}0min}]$/[glucose increment from basal to final period]; mean glucose in the basal and final periods are calculated during the same time interval in which $ISR_{\text{-}10\text{-}0min}$ and $ISR_{80\text{-}120min}$ are determined.

Insulin secretion based on insulin AUC:

- Insulin secretion during the first phase defined as the incremental AUC under the insulin concentration curve between time zero and 10th minute of the hyperglycemic clamp ($AUC_{0\text{-}10min}$)
- Insulin secretion during the second phase defined as the AUC under the insulin concentration curve between 20th and 120th minute of the hyperglycemic clamp ($AUC_{20\text{-}120min}$)
- Insulin secretion defined as the AUC under the insulin concentration between time zero and 120th minute of the hyperglycemic clamp ($AUC_{0\text{-}120min}$)

Ad libitum food intake:

- The VAS scales will be analyzed as continuous variables on the 0-100 scale for individual components. Overall appetite score is calculated as the average of the 4 individual scores−satiety + fullness + (100-prospective food consumption) + (100-hunger) / 4 (van Can et al. 2014; Flint et al. 2000; Flint et al. 2013). The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

Other PD measures and exploratory measures will be described in the SAP.

10.3.3.2. Pharmacodynamic Statistical Inference

The primary endpoint (change from baseline in cDI) will be calculated by first log transforming the data then computing the change from baseline. The primary analysis will be analyzed using an analysis of covariance model which has effects for treatment and baseline of the parameter measured to compare tirzepatide versus placebo.

Other PD parameters that are scheduled to be measured only once postbaseline will be analyzed using a similar model with baseline of the covariate measured as the covariate and a fixed effect for treatment. Insulin secretion rate AUC measures, insulin AUC measures, and C-peptide AUC measures will be log-transformed prior to being analyzed. If the incremental insulin AUC and incremental ISR AUC values are positive for all patients and highly skewed, a log-transformation may be considered. Other parameters that are positive and skewed may be log-transformed.

Other PD parameters that are scheduled to be measured at least twice post baseline will be analyzed using an MMRM method, which will have effects for treatment, visit, treatment-by-visit interaction, and baseline of parameter measured. An unstructured variance-covariance matrix will be used to model the within-patient effects.

All analyses will show least squares means of each treatment and the treatment difference transformed back to the original scale as well as standard error and 95% confidence interval (CI). All tests will be done at the 2-sided 0.05 α level unless otherwise specified.

Tirzepatide will be claimed to have a statistically significantly greater change in cDI than placebo if lower limit of the 2-sided CI of tirzepatide – placebo on the log scale is greater than 0, and a significantly greater change in cDI than semaglutide if the lower limit of the 2-sided CI of tirzepatide – semaglutide on the log scale is greater than 0.

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 ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). The minimum required dilution of the ADA assay is 1:10. For the TE-ADA+ patients the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated in TE-ADA+ patients.

The relationship between the presence of antibodies and the PK parameters 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 blinded data may be reviewed periodically on an ongoing basis. If an unplanned interim analysis is deemed necessary, the

appropriate Lilly CP, CRP/investigator, or designee, will consult with the appropriate medical director or designee to determine whether it is necessary to amend the protocol.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation 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
ApoB-48	apolipoprotein B-48
ApoB-100	apolipoprotein B-100
ApoC-III	apolipoprotein C-III
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{0\text{-}10min}$	first phase insulin response
$AUC_{0\text{-}120min}$	AUC from time zero to 120 minutes after start of the meal
$AUC_{0\text{-}240\ min}$	AUC from time zero to 240 minutes after start of the meal
$AUC_{20\text{-}120min}$	second phase insulin response
$AUC_{arginine0\text{-}10min}$	AUC in response to arginine from time zero to 10 minutes
$AUC_{arginine0\text{-}30min}$	AUC in response to arginine from time zero to 30 minutes
$AUC_{glucose0\text{-}120min}$	AUC of glucose from time zero to 120 minutes
basal $insulin_{\text{-}10\text{-}0min}$	average insulin concentration between -10 minutes and 0 minutes
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/or 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 is aware of the treatment received.

cDI	clamp disposition index
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 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.
COVID-19	Coronavirus Disease 2019
CP	Clinical Pharmacologist
CRF/eCRF	case report form/electronic case report form
CRP	Clinical Research Physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CT	computed tomography
DPP-IV	dipeptidyl peptidase-4
ECG	electrocardiogram
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 representative(s).
ERB	ethical review board
ET	early termination
FFA	free fatty acid
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
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 agonism
GS	glucose sensitivity
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HOMA2	Homeostatic Model Assessment of Insulin Resistance
HOMA2-IR	insulin resistance as measured by the HOMA2 method
IB	Investigator's Brochure
ICF	informed consent form
ICLb	basal insulin clearance
ICLm	insulin clearance during sMMTT
IGFBP	insulin-like growth factor binding protein
II_{30min}	insulinogenic index at 30 minutes
I_{mean}	average steady-state plasma insulin response
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.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
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.

ISI	insulin sensitivity index
ISR	insulin secretion rate
$ISR_{-10-0min}$	basal insulin secretion rate
ISR_{0-8min}	first phase insulin secretion rate
$ISR_{0-120min}$	total insulin secretion rate from hyperglycemic clamp
$ISR_{20-120min}$	second phase insulin secretion rate
$ISR_{0-240min}$	total insulin secretion rate during sMMTT
$ISR_{80-120min}$	steady-state insulin secretion rate
ISRg	ISR at fixed glucose concentration
ISRgb	ISR at fixed glucose concentration adjusted for basal potentiation
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.
LPL	lipoprotein lipase
MAD	multiple-ascending dose
MCR	metabolic clearance rate of glucose
MEN 2	multiple endocrine neoplasia syndrome type 2
$microdialysis_{0-120 min}$	microdialysis from zero to 120 minutes
$microdialysis_{0-240 min}$	microdialysis from zero to 240 minutes
MMRM	mixed-model repeated-measure
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
OAM(s)	oral antihyperglycemia medication(s)
OGIS	Oral Glucose Insulin Sensitivity
PFR	potentiation ratio
PFR_{120}	potentiation ratio from sMMTT, defined as relative enhancement of ISR, as predicted by the dose-response from basal to +120 minute

PFR_{180}	potentiation ratio from sMMTT, defined as relative enhancement of ISR, as predicted by the dose-response from basal to +180 minute
PFR_{240}	potentiation ratio from sMMTT, defined as relative enhancement of ISR, as predicted by the dose-response from basal to +240 minute
PG	plasma glucose
PK/PD	pharmacokinetic/pharmacodynamic
PP	pancreatic polypeptide
QT	QT interval
QTc	QT interval corrected for heart rate
QW	once weekly
randomize	the process of assigning patients to an experimental group on a random basis
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SGLT-2	sodium-glucose transport protein 2
sMMTT	standardized mixed-meal tolerance test
SMPG	self-monitoring of plasma glucose
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
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

ULN	upper limit of normal
VAS	visual analog scale
WOCBP	woman 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 (fasting)
Absolute counts of:	Blood urea nitrogen
Neutrophils	Uric acid
Lymphocytes	Total protein
Monocytes	Albumin
Eosinophils	Total bilirubin
Basophils	Alkaline phosphatase
Platelets	Alanine aminotransferase
Hemoglobin A1c	Aspartate aminotransferase
	Lipase (fasting)
	Amylase
Urinalysis	**Endocrine**
Specific gravity	Follicle-stimulating hormone[a]
pH	Calcitonin
Protein	
Glucose	**Serology[b]**
Ketones	Hepatitis B surface antigen
Bilirubin	Hepatitis C antibody, hepatitis C RNA[c]
Urobilinogen	HIV antibody
Blood	
Leukocytes	Pregnancy test (urine, serum)[d]
Microscopy[a]	Drug and alcohol screen[e]

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

Note: Results of these assays will be validated by the central or 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 violation.

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

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

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

[d] Pregnancy tests (females, as appropriate) will be performed for women of childbearing potential. Serum pregnancy test is done at screening and follow-up and urine pregnancy is performed at all other visits.

[e] Performed at screening. Drugs for drug screen include amphetamine, barbiturates, benzodiazepines, cannabis, cocaine, methadone, methamphetamine, opiates, phencyclidine, and tricyclic antidepressants. 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 (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- 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. 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 site(s). Lilly or its representatives must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on good clinical practice (GCP).

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

- the 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:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) 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 final report coordinating investigator or designee will sign the clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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 sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the 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 Sites

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

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 CRP.

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**
CPK	**antibody)[a]**

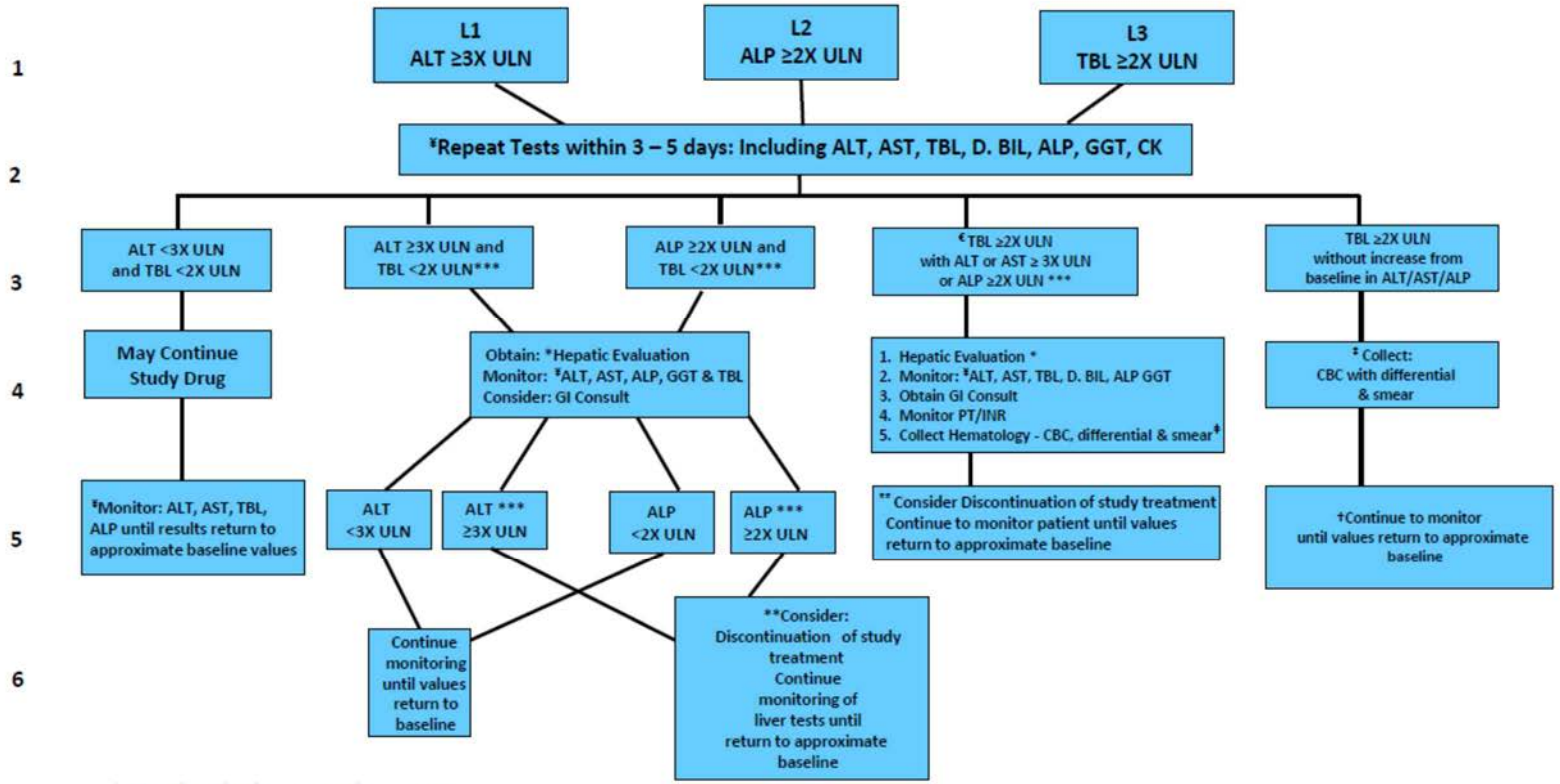
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

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

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

* Hepatic Evaluation:

- Obtain history and conduct a physical examination. Determine if symptoms or signs of liver disease are present (e.g. flu-like symptoms, nausea, vomiting, fever, confusion, right upper quadrant discomfort or tenderness, jaundice, fatigue, poor appetite, increased abdominal girth, itching).
- Obtain blood samples for laboratory analysis of ALT, AST, CK, TBL, D. BIL, ALP, GGT, viral serology for HAV, HBV, HCV, HEV and autoimmune serology (see below). Utilize the hepatic evaluation kit from the central lab, if available. Fractionated bilirubin is determined for the differential diagnosis of non-hepatic etiologies such as hemolysis, and Gilbert's syndrome. An elevated unconjugated (indirect) bilirubin with normal aminotransferases during fasting is likely to be Gilbert's syndrome, when TBL is less than 3 mg/dL. In patients with elevated ALP of unclear origin consider testing for ALP isoenzymes.
- Complete the hepatic safety data collection as described in the protocol.
- Recommend viral serology tests during monitoring of a clinical study includes: HBs Ag, HBs Ab, HBc Ab, HAV Ab (IgG and IgM), HCV Ab, and HEV Ab (IgG and IgM).
- Recommended serology tests for autoimmune hepatitis includes: ANA, ASMA (or anti-actin antibody.)

Clinical Background Regarding Hepatic Discontinuation
for Subjects with no known liver disease, and normal or near normal baseline liver tests
(ALT <2X ULN, TBIL <1.5X ULN, ALP <1.5X ULN) (Based on current FDA's Guidance on Drug Induced Liver Injury)

- Increases in blood levels of aminotransferases (ALT and AST) to more than 3x upper limit of normal (ULN) are commonly observed during clinical trials. Such increases are often self limiting despite continuation of the drug and rarely progress to severe drug induced liver injury (DILI).
- Reversible asymptomatic increase in aminotransferase-levels during drug treatment is a nonspecific phenomenon (often called "adaptation") and is not a reliable predictor of the drug's potential to cause severe DILI.
- Therefore, discontinuation of a study drug upon finding of an elevated ALT or AST of >3x ULN (but <8x ULN) is often unnecessary, and will not permit learning whether adaptation occurs.
- On the other hand, rising bilirubin level (TBL) or prolongation of prothrombin time (PT or INR) may indicate a significant liver injury and, when caused by a drug, are considered to have stronger predictive power of the drug's potential to cause severe DILI.
- Hy's Law: The combination of drug related elevation of ALT ≥3x ULN and TBIL ≥2x ULN, in the absence of significant cholestasis (i.e. ALP <2X ULN), and in the absence of other causes of liver injury, is known collectively as a "Hy's Law," and is considered highly predictive of a drug's ability to cause severe DILI.
- Based on these considerations, the FDA has recommended using the following criteria as hepatic discontinuation rules. These criteria are also recommended by the Lilly Liver and GI Safety Advisory Committee for use in Lilly development programs, in subjects with no known liver disease and normal or near normal baseline liver tests (ALT< 2x ULN, TBIL <1.5x ULN, ALP <1.5x ULN):
  - ALT or AST >8x ULN
  - ALT or AST >5x ULN for more than 2 weeks
  - ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5
  - ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Although there are currently no specific recommendations in the FDA guidance regarding discontinuation in patients with elevated ALP, it is recommended to consider discontinuation in a patient with ALP elevation which meets one of the following criteria and is deemed to be of liver origin and drug related
  - ALP >3x ULN
  - ALP >2.5x ULN and TBL > 2x ULN
  - ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Whenever possible, the decision to discontinue the investigational product for abnormal liver tests should be made by the investigator in consultation with the Lilly designated medical monitor

Glossary

Acronym	Name
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
ASMA	Anti smooth-muscle antiboy
AST	Aspartate aminotransferase
CBC	Complete Blood Count
CK	Creatine kinase
D. BIL	Direct Bilirubin
GGT	Gamma glutamyl transpeptidase (or transferase)
GI	Gastro Intestinal, Gastroenterology
HAV	Hepatitis A virus
HAV Ab	Hepatitis A virus antibody
HBc Ab	Hepatitis B core antibody
HBs Ab	Hepatitis B surface antibody
HBV	Hepatitis B virus
HBs Ag	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HEV	Hepatitis E virus
HEV Ab	Hepatitis E virus antibody
IgG	Immunglobulin G
IgM	Immunglobulin M
PT/INR	Prothrombin time/ International Normalized Ratio
TBL	Total Bilirubin
ULN	Upper Limit of Normal

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-GPGT Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	10	1	10
Safety laboratory tests (including fasting glucose and hemoglobin A1c)[a]	6	4	24
Tirzepatide pharmacokinetics	3	6	18
Immunogenicity	10	5	50
Pharmacodynamics			
β-hydroxybutyrate/FFA during sMMTT	2	6 x 2	24
β-hydroxybutyrate/FFA during hyperglycemic clamp	2	6 x 2	24
Calcitonin	2	3	6
Fasting insulin/C-peptide	2.5	2	5
Insulin/C-peptide during sMMTT	2.5	9 x 2	45
Insulin/C-peptide during clamps	2.5	33 x 2	165
Glucagon	2	2	4
Glucagon during sMMTT	2	6 x 2	24
Glucagon during clamps	2	33 x 2	132
Glucose during sMMTT	0.2	11 x 2	4.4
Glucose during clamps	0.2	34 x 2	13.6
Glucose for clamp calibration	0.2	12 x 2	4.8
Glycerol during sMMTT	2	6 x 2	24
Glycerol during clamp	2	6 x 2	24
IGFBP 1 and 2	5	2	10
IGFBP 1 and 2 during sMMTT	5	1 x 2	10
Lactate during sMMTT	2	6 x 2	24
Lactate during clamp	2	6 x 2	24
Leptin, Adiponectin	4	2	8
Leptin, Adiponectin during sMMTT	4	1 x 2	8
Lipid panel	-	-	-
TG on Days -1 and 193	2.5	6 x 2	30
TG, total cholesterol, LDL-C, VLDL-C, HDL-C	7.5	2	15
TG, total cholesterol, LDL-C, VLDL-C, HDL-C during sMMTT	7.5	6 x 2	90
Apo B-48, Apo B-100, Apo C-III	3.5	2	7
Apo B-48, Apo B-100, Apo C-III during sMMTT	3.5	6 x 2	42
LPL	2.5	2	5

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
LPL during sMMTT	2.5	6 x 2	30
PP	5	2	10
PP during sMMTT	5	6 x 2	60
Proinsulin	2.5	2	5
Proinsulin during sMMTT	2.5	1 x 2	5
Pyruvate during sMMTT	2	6 x 2	24
Pyruvate during clamp	2	6 x 2	24
Pharmacogenetics	10	1	10
Pregnancy test (follow-up/ET)	2	1	2
Nonpharmacogenetic stored sample	10	3	30
Total			1074.8
Total for clinical purposes [rounded up to nearest 10 mL]			1080

Abbreviations: ApoB-48 = apolipoprotein B-48; ApoB-100 = apolipoprotein B-100; ApoC-III = apolipoprotein C-III; EDTA = ethylenediaminetetraacetic acid; ET = early termination; FFA = free fatty acid; HDL-C = high-density lipoprotein cholesterol; IGFBP = insulin-like growth factor-binding protein; LDL-C = low-density lipoprotein cholesterol; LPL = lipoprotein lipase; PP = pancreatic polypeptide; sMMTT = standardized mixed-meal tolerance test; TG = triglycerides; VLDL-C = very low-density lipoprotein cholesterol.

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

Appendix 6. Assessments of Glucose and Lipid Metabolism and Appetite and Food Intake

6.1. Hyperinsulinemic Euglycemic Clamp for Assessment of Insulin Sensitivity

Hyperinsulinemic euglycemic clamp (HEC) technique for assessment of insulin sensitivity has been previously described (De Fronzo et al. 1979). The aim of the HEC is to maintain glucose concentrations close to a predefined target during a constant insulin infusion rate (IIR), by means of variable glucose infusion rate (GIR), to reach the steady-state conditions. The varying GIR reflects the pharmacodynamic (or glucodynamic) effects of the insulin. After the steady-state conditions are achieved, the parameters of interest (insulin, C-peptide, and glucagon) are measured over a period of the next 30 minutes. The steady-state is defined as stable GIR under stable IIR over a period of time. The M-value is calculated from the parameters obtained during the steady-state period of the HEC. The parameters that will be obtained are listed in Section 9.1 (Efficacy Assessments).

Patients will be trained and informed to strictly follow their dietary plan during the last 3 days prior to admission to the CRU. The night before the clamp procedure, the patients will be served a standardized evening meal. Investigator will ensure that the patient is fasting from 23:00 the night before and until the end of the clamp procedure (12 hour fast).

The HEC will be performed by means of an automated clamp system (ClampArt™) that performs continuous blood glucose (BG) measurements, and controls a variable glucose infusion adjusted to keep the BG concentration at a constant level (Benesch et al. 2015; Kuhlenkötter et al. 2017). ClampArt automatically calculates the appropriate adjustments of the GIR using an algorithm based on the actual measured BG concentration and the grade of variability in the preceding 1 minute.

The patients will be connected to ClampArt at approximately 8:00 AM. The patient will remain fasting and will stay in a supine or semi-supine position during HEC and will be allowed to consume water ad libitum during the procedure, but will otherwise have no oral intake.

For sampling of arterialised venous blood for ClampArt BG concentration measurements, a catheter will be inserted into a vein of a hand or forearm. This hand will remain under a heating pad (about 55ºC) throughout the clamp procedure. The heating of the hand results in an arterialisation of the venous blood, that is, increasing oxygen and glucose content to values comparable to arterial blood mediated by the vasodilator effect from heating. A low dose heparin solution (100 U heparin/mL [10,000 U heparin/100 mL saline]) will be used to prevent blood clotting in the ClampArt double lumen catheter. The heparin solution will be taken up with blood used for ClampArt BG measurement in the other lumen of the catheter. A second catheter will be inserted into a vein of the same arm for obtaining blood samples. This cannula will be kept patent by use of a mandrin/stylet. A third catheter will be inserted into a vein of the

contralateral arm for the infusion of insulin (50 IU of regular insulin in 49 mL isotonic saline and 1 mL of the patient's own blood) or 20% glucose solution to maintain the defined HEC BG target level of 5.5 mmol/L (100 mg/dL). The GIR necessary to keep the BG concentration at the clamp target level will be adjusted and recorded every minute. Frequently or at least every 30 minutes throughout the glucose clamp, BG measurements for safety glucose monitoring and for verification of ClampArt measurements will be performed using the Super GL Glucose Analyzer.

At nominal time t = 0 min, immediately after blood sampling, a primed infusion of regular insulin will be established starting with an infusion rate of 255.2 mU/min/m^2 which will be adapted from t = 0 min to t = 10 min (Table GPGT.4). The prime is followed by a constant regular insulin infusion at a rate of 80 mU/min/m^2 lasting until t = 180 min.

Blood samples for analysis of glucose, insulin, C-peptide, and glucagon will be drawn according to sampling scheme in Table GPGT.4.

Table GPGT.4. Time Schedule for Hyperinsulinemic Euglycemic Clamp

Approximate Hour	Nominal Time[a] (Minutes)	Target Clamp Level	Sampling for Analysis			Comment
			Insulin Infusion [mU·min-1·m-2]	Glucose[b]	Insulin, C-Peptide, Glucagon	
07:40	-20	-	-	X	X	
07:50	-10	-	-	X	X	
08:00	0	100 mg/dL	255.2	X	X	Insulin priming period
08:01	1		227.2	Approximately every 30 minutes	-	
08:02	2		202.2		-	
08:03	3		180.4		-	
08:04	4		160.4		-	
08:05	5		142.8		-	
08:06	6		127.2		-	
08:07	7		113.6		-	
08:08	8		100.2		-	
08:09	9		90.0		-	
08:10	10		80.0		-	
09:00	60		80.0		X	
09:30	90		80.0		X	
10:00	120		80.0		X	
10:30	150		80.0	X	X	Steady-state period[c]
10:40	160		80.0	X	X	
10:50	170		80.0	X	X	
11:00	180		80.0	X	X	

Abbreviation: eCRF = electronic case report form.

[a] Nominal time is approximate. Blood samples should be taken ± 1 minute from nominal time and actual time should be recorded in the eCRF.

[b] Glucose concentrations will be checked with a laboratory glucose analyzer (Super GL).

[c] Steady-state assessments can be delayed, if necessary, until the target glucose clamp level has been reached.

Glucose concentrations ≤70 mg/dL will not routinely be recorded as hypoglycemic events during the HEC procedure. However, at the discretion of the investigator, decrease in glucose

concentrations may be recorded as a hypoglycemic event based on clinical concern or related to technical issues resulting in hypoglycemia.

At the end of the steady-state period, the insulin infusion will be stopped. The ClampArt device will still infuse at a variable rate to keep the patients' BG concentrations close to the target level of 100 mg/dL, if necessary. The infusion will cease once the BG values increase above the target level.

6.2. Hyperglycemic Clamp for Assessment of First and Second Phase Insulin Secretion and Arginine Stimulation Test

The aim of the hyperglycemic clamp is to assess β cell function and insulin secretion, as well as α cell function. Hyperglycemic clamp is a validated method in which the GIR needed to ensure constant BG at a predetermined level is used to determine islet β cell glucose sensitivity and insulin secretion capacity at various stages of the glucose exposure and after arginine stimulation under hyperglycemic conditions (Hannon et al. 2018; Shah et al. 2016). The parameters that will be obtained are listed in Section 9.1 (Efficacy Assessments).

The target glucose concentration will be 16 mmol/L (216 mg/dL). The primed glucose infusion of 200 mg/kg body weight should start at approximately 13:00 (1PM; at least 120 minutes after the completion of the hyperinsulinemic euglycemic clamp and -120 minutes before the intravenous [IV] arginine bolus), followed by variable infusion of 20% glucose to maintain the target glucose level. At approximately 15:00 (3PM), a 5 g arginine bolus will be administered by IV injection over 30 seconds (baseline time point 0). The procedure will be completed at 15:30, or after 150 minutes of duration.

Blood samples for analysis of glucose, insulin, C-peptide, and glucagon will be drawn according to sampling scheme in Table GPGT.5.

Table GPGT.5. Time Schedule for Hyperglycemic Clamp and Arginine Stimulation

Nominal Time (Minutes)	Scheduled Time[a]	Target Clamp Level	Intervention	β-hydroxybutyrate, Pyruvate, Lactate, FFA, Glycerol, Triglycerides	Microdialysis Sampling		Glucose[b]	Glucagon, Insulin, C-peptide[b]
					Glucose, Pyruvate, Lactate, Glycerol	Ethanol		
-20	12:40	216 mg/dL					X	X
-10	12:50						X	X
0	13:00		Start hyperglycemic clamp[c]	X	X	X	X[d]	X[d]
2	13:02						X	X
4	13:04						X	X
6	13:06						X	X
8	13:08						X	X
10	13:10						X	X
20	13:20						X	X
30	13:30			X	X	X	X	X
60	14:00			X	X	X	X	X
90	14:30			X	X	X	X	X
100	14:40						X	X
110	14:50						X	X

Time Schedule for Hyperglycemic Clamp and Arginine Stimulation

Nominal Time (Minutes)	Scheduled Time[a]	Target Clamp Level	Intervention	β-hydroxybutyrate, Pyruvate, Lactate, FFA, Glycerol, Triglycerides	Microdialysis Sampling		Glucose[b]	Glucagon, Insulin, C-peptide[b]
					Glucose, Pyruvate, Lactate, Glycerol	Ethanol		
120	15:00		IV injection 5 g arginine	X	X	X	X[e]	X[e]
122	15:02						X	X
123	15:03						X	X
124	15:04						X	X
125	15:05						X	X
130	15:10						X	X
135	15:15						X	X
140	15:20						X	X
150	15:30		End of hyperglycemic clamp	X	X	X	X	X

Abbreviations: eCRF = electronic case report form; FFA = free fatty acid; IV = intravenous.

[a] Scheduled starting time is approximate. Blood samples should be taken ± 1 minute from nominal time and actual time should be recorded in the eCRF.

[b] Blood sampling for assessment of concentration versus time profiles of glucose (Super GL glucose analyzer), insulin, glucagon, and C-peptide. Basal concentrations of glucose, insulin, or C-peptide = mean concentrations at t = -20, -10, and 0 minutes.

[c] The IV primed (200 mg/kg body weight) variable infusion of 20% glucose for adjustment of clamp level (16 mmol/L/216 mg/dL) starting at time = 0 minutes

[d] The t = 0 samples will be collected prior to the glucose bolus initiation.

[e] Blood samples to be drawn immediately prior to IV injection of arginine

6.3. Microdialysis

Microdialysis is a minimally-invasive procedure to measure concentration of substances in the extracellular fluid of a tissue (Felländer et al. 1996). It is considered the standard technique to investigate adipose tissue physiology and the effects of interventions on subcutaneous abdominal lipolysis (Arner et al. 1988; Coppack et al. 1996). The parameters that will be obtained are listed in Section 9.1 (Efficacy Assessments).

The microdialysis technique includes insertion of a semipermeable probe in the tissue of interest. The inlet of the probe is connected to a microdialysis pump and reservoir containing a physiological solution called the perfusate. The perfusate is pumped at a low flow rate (typically between 0.3 and 2 µL/min) through the probe. Once inserted, small solutes from the tissue fluid cross the membrane of the probe into the perfusate by passive diffusion. The solution leaving the probe (dialysate) is collected in a sample vial for the determination of substance concentrations (Felländer et al. 1996).

On assessments days, a microdialysis probe will be placed in the abdominal subcutaneous adipose tissue at areas different from the areas used for study drug administration. Sterile Ringer solution and ethanol will be used as perfusate and the dialysate will be analyzed for concentrations of glucose, pyruvate, lactate, glycerol, and ethanol. Ringer solution will be perfused at approximately 0.3 µL/minute for 2 hours, before the infusion rate will be increased to 1.0 µL/minute 30 minutes before the start of the sMMTT and with the start of the hyperglycemic clamp procedure. One dialysate sample will be collected per 30 minutes after start of the sMMTT and hyperglycemic clamp. Table GPGT.5 and Table GPGT.7 provide the time points at which dialysate samples will be analysed for pre-specified metabolic parameters.

6.4. Standardized Mixed-Meal Tolerance Test

The key objectives of the sMMTT are to assess α and β cell function, insulin sensitivity, nutrient utilization and metabolic flexibility under physiological conditions. The parameters that will be obtained are listed in Section 9.1 (Efficacy Assessments). The measurements that will be collected during the test and then used for parameter calculations are provided in Table GPGT.7.

During the morning before the start of the sMMTT, 2 IV cannulas (catheters) will be inserted, one cannula for serial measurements of BG, and one more in the contralateral arm for controlled variable infusion of glucose or rapidly-acting insulin glulisine (Apidra®), if needed to prevent hypoglycemia or hyperglycemia, respectively. Blood glucose will be analysed using the Super GL Glucose Analyzer.

The start of the meal will be defined as time point 0 (zero). A fixed nutrient ratio solid mixed meal (example is shown in Table GPGT.6) will be served and consumed by the patient, preferably within 15 minutes. The standardized meal will be individualized for each individual randomized in the study with a fixed nutrients ratio.

The individual patients' characteristics (weight, height, age, and gender) are used for the calculation of the resting metabolic rate (RMR) based on Müller equation (Müller et al. 2004). A standard physical activity level (PAL) of 1.2 (20%) and a diet-induced thermogenesis of 10% are

assumed and added to the RMR to achieve a weight-preserving energy intake per day during the inpatient period (FAO 2001). The sMMTT will account for 35% of the total energy intake at the respective day. Individually tailored menus are created by a Research Dietician or Head Metabolic Ward using a special software (PRODI).

The individual MMTTs will be identical at baseline and end of treatment.

The patient should refrain from eating until 4 hours after the meal (end of meal test). Water consumption will not be allowed during the first 2 hours after the start of the test.

Table GPGT.6. Approximate Composition of an Individualized Standardized Meal with a Fixed Nutrient Ratio (900 kcal Meal Example)

Energy Supply	901	cal		
	3766	kJ		
	Amount			
Protein	33.8	g	15	%
Fat	40.1	g	40	%
Carbohydrates	101.4	g	45	%

During the test meal procedure, patients will be asked to lie in a semi-supine position. Blood samples will be collected immediately before the start of the test meal (time point 0), followed by sampling after the start of the meal for measurement of the parameters of interest per schedule provided in Table GPGT.7. Sampling times may be adjusted as necessary.

In case a patient's BG concentration falls below 2.8 mmol/L (50 mg/dL), the patient must be treated to alleviate the hypoglycemia; the meal test procedure will be terminated and the date and time of termination will be documented in the eCRF. In case a patient's BG concentration rises above 25 mmol/L (450 mg/dL), prandial insulin will be administered IV. Likewise, patients with BG concentrations above 20 mmol/L (360 mg/dL) at the end of the meal test procedure will receive prandial insulin IV to quickly normalise concentrations.

After the end of the meal test procedure, the patient will be served a meal. All calculations and analyses are described in Section 9.1 (Efficacy Assessments) and Section 10.3 (Statistical Analysis) and in the statistical analysis plan.

During sMMTT, blood samples will be drawn according to sampling scheme in Table GPGT.7.

Table GPGT.7. Standardized Mixed-Meal Tolerance Test

Time[a]	Nominal Time (Minutes)	Indirect Calorimetry	Meal	Sampling for Analysis						Microdialysis	Microdialysis Sampling for Analysis		VAS	Comment
				Blood Glucose	Insulin, C-peptide	Glucagon, PP	β-hydroxy-butyrate, Pyruvate, Lactate, FFA, Glycerol	Leptin, Adiponectin, IGFBP 1 and 2, Proinsulin Sample	Lipid Panel[b]	Perfusion Rate (µL/min)	Glucose, Pyruvate, Lactate, Glycerol	Ethanol		
07:00	-180													Place microdialysis catheters
08:00	-120	Start								0.3				
08:20	-100	Stop								0.3				
09:00	-60									0.3	X			
09:30	-30	Start								1.0	X			
09:50	-10	Stop		X	X					1.0				
09:59	-1			X	X	X	X		X	1.0	X		X	
10:00	0		Start					X		1.0				
10:15	15		Stop	X	X					1.0				
10:30	30			X	X					1.0				
11:00	60	Start		X[c]	X[c]	X[c]	X[c]		X[c]	1.0	X[c]	X[c]	X[c]	
11:20	80	Stop								1.0				
11:30	90			X	X	X	X		X	1.0				

Standardized Mixed-Meal Tolerance Test

Time[a]	Nominal Time (Minutes)	Indirect Calorimetry	Meal	Sampling for Analysis						Microdialysis	Microdialysis Sampling for Analysis		VAS	Comment
				Blood Glucose	Insulin, C-peptide	Glucagon, PP	β-hydroxy-butyrate, Pyruvate, Lactate, FFA, Glycerol	Leptin, Adiponectin, IGFBP 1 and 2, Proinsulin Sample	Lipid Panel[b]	Perfusion Rate (µL/min)	Glucose, Pyruvate, Lactate, Glycerol	Ethanol		
12:00	120	Start		X	X	X	X		X	1.0	X	X	X	
12:20	140	Stop								1.0				
12:30	150			X						1.0				
13:00	180	Start		X	X	X	X		X	1.0	X	X	X	
13:20	200	Stop								1.0				
13:30	210			X						1.0				
14:00	240	Start		X	X	X	X		X	1.0	X	X	X	
14:20	260	Stop								1.0				

Abbreviations: FFA = free fatty acid; IGFBP = insulin-like growth factor binding protein; VAS = visual analogue scale.

[a] Approximate times only.

[b] Lipid panel: triglycerides, total cholesterol, low-density lipoprotein, very low-density lipoprotein, high-density lipoprotein, apolipoprotein B-48, apolipoprotein B-100, apolipoprotein C-III, and lipoprotein lipase. On Day -2 and Day 192, a full lipid panel will be collected during sMMTT. On Day -1 and Day 193, only triglycerides will be collected.

[c] Immediately before start of indirect calorimetry.

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6.5. Visual Analog Scales For Assessment of Appetite Sensations

The aim of the appetite visual analogue scale (VAS) is to determine the effects of study treatments on appetite sensations and desire for specific foods. The parameters that will be obtained are listed in Section 9.1 (Efficacy Assessments).

Patients will be asked to rate their feelings on hunger, satiety, fullness, prospective food consumption, and desire for specific foods on a 10-cm (100-mm) line; anchored by verbal descriptors, usually "extremely" and "not at all." The ratings will include the following 8 questions (Flint et al. 2000):

- How hungry do you feel right now?
- How satisfied do you feel right now?
- How full do you feel right now?
- How much food do you think you could eat right now?
- Would you like to eat something sweet?
- Would you like to eat something salty?
- Would you like to eat something savoury?
- Would you like to eat something fatty?

Patients will see the 10-cm line on a validated electronic device that will measure and record the exact position of the patient's rating on the respective lines. For assessment of postprandial appetite sensations and desire for specific foods during sMMTT, the scores will be obtained immediately prior to the start of the meal (time point -1), and 60, 120, 180, and 240 minutes after the start of the meal . Overall appetite score is calculated as described in Section 10.3.3.1 (Pharmacodynamic Parameter Estimation).

6.6. Ad Libitum Food Intake Test

The aim of the ad libitum food intake is to determine the effects of study treatments on meal intake. Brunch items will be served in a buffet-style setting. Ad libitum intake of food during a period of 45 minutes will be recorded by the site staff. Incompletely consumed items will be weighed and the weight will be recorded in the source data. The total amount of calories as well as the amount of calories consumed from carbohydrates, protein, and fats will be calculated from the respective nutritional information of the food items. The parameters that will be obtained are described in Section 9.1 (Efficacy Assessments).

6.7. Plethysmography for Body Composition

The aim of plethysmography is to measure body composition (Fields et al. 2000; Dempster and Aitkens 1995). Patients will undergo body composition assessment by way of noninvasive air displacement plethysmography (BOD POD® measurement system, COSMED, Rome, Italy). The device utilizes whole body densitometry to estimate the amount of fat and lean tissue in the

body. Whole body densitometry is based on the calculation of body density by measuring body mass and volume. Body mass is measured using an electronic scale, and body density is measured in a fiberglass test chamber (Dempster and Aitkens1995). Body composition will be performed according to Section 2 (Schedule of Activities) and more details will be provided in a separate operation manual. The parameters that will be obtained are listed in Section 9.1 (Efficacy Assessments). Note: Due to chamber size, measurements in patients with body weight above 150 kg are cumbersome. It will be decided on an individual basis whether the measurement can be performed. In case patients do not fit inside the chamber, investigations can be skipped.

6.8. Indirect Calorimetry

The aim of indirect calorimetry is to determine metabolic rate (Frayn 1983; Ferrannini 1988). The indirect calorimetry system (Quark RMR, COSMED, Rome, Italy) measures gas exchange by means of a ventilated canopy hood and experiments are performed under resting conditions. The system measures the patient's oxygen consumption (VO_2) and carbon dioxide production (VCO_2) (Frayn 1983; Ferrannini 1988). These measurements are used to calculate energy expenditure and substrate oxidation rates. The ratio of VO_2 and VCO_2 depends on the substrate used as energy source (fat, carbohydrate, or protein) and is the so-called respiratory exchange ratio and provides information on the substrate oxidation preference (Frayn 1983; Ferrannini 1988). The parameters that will be obtained are listed in Section 9.1 (Efficacy Assessments).

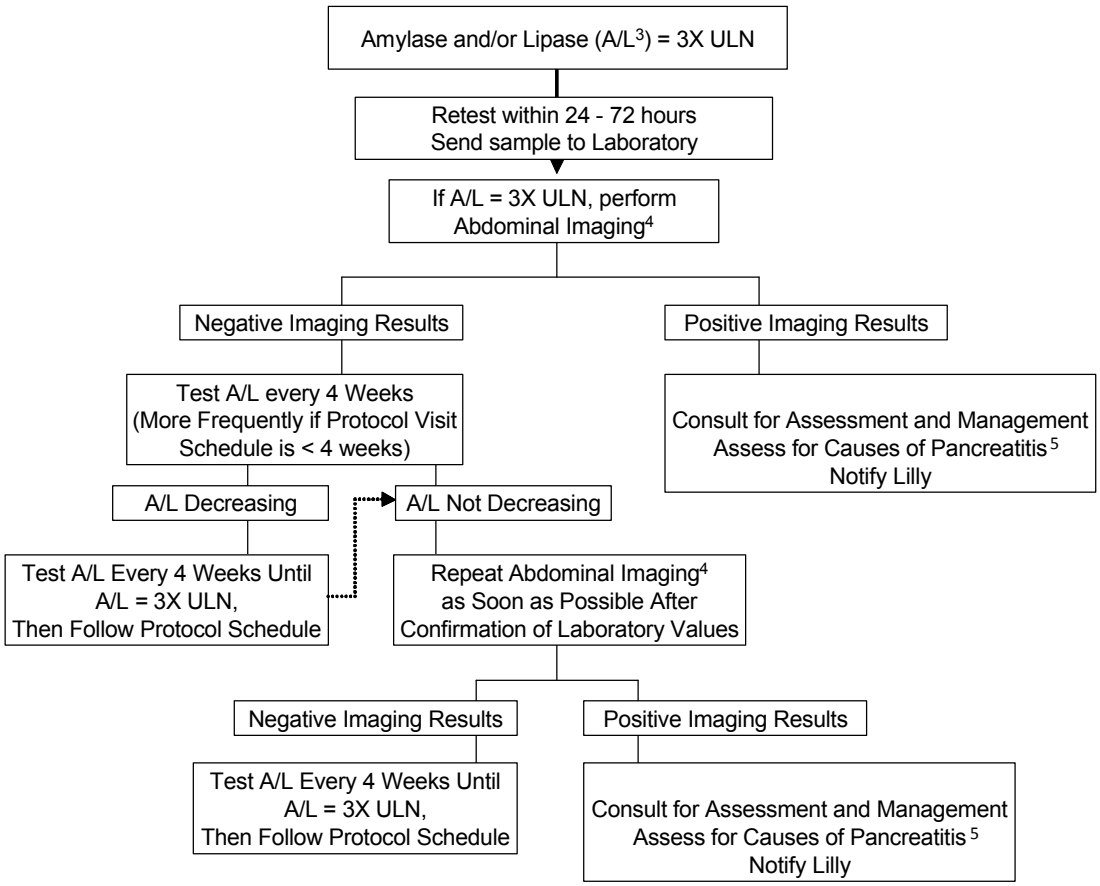
For days with indirect calorimetry, the following requirements will be applied:

- Fasting for at least 10 hours prior to baseline measurement (up to 200 mL of water are allowed);
- No strenuous exercise within the last 48 hours before the measurement;
- No protein-rich meal in the evening before;
- No consumption of alcohol, caffeine- and/or methylxanthine-containing products in the last 24 hours before the measurement (i.e., coffee, coke, black/green tea, chocolate, cacao, energy drinks);
- No smoking in the last 4 hours prior to measurement.

Appendix 7. Pancreatic Monitoring

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

Follow this algorithm when the value(s) for serum amylase and/or lipase are = 3x upper limit of normal (ULN)



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

2. If in the opinion of the investigator, the patient has symptoms of acute pancreatitis:
   (a) Stop injectable study drug
   (b) Consult for assessment and management
   (c) Assess for causes of pancreatitis
   (d) Notify Lilly

3. A/L = amylase and/or lipase. Either or both enzymes 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. At a minimum, order a CBC and a pancreatic panel (which includes LFTs, calcium and triglycerides). Record all concomitant medications.

Abbreviations: CBC = complete blood count; CT = computed tomography; LFTs = liver function tests; MRI = magnetic resonance imaging.

Patients diagnosed with pancreatitis will be discontinued from the study. Investigators will be responsible for following, through an appropriate health care 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. Highly Effective Contraceptive Methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - injectable
  - implantable[2]
- Intrauterine device[2]
- Intrauterine hormone-releasing system[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

1 Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method.

2 Contraception methods that in the context of this guidance are considered to have low user dependency.

3 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success.

4 In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

For hormonal contraception methods, caution should be taken to possible interaction with a (nonbiologic) investigational medicinal product (IMP). Interaction with the IMP leading to reduced efficacy of the hormonal contraception method can occur due to e.g. increased metabolism (enzyme induction).

A potential human teratogen needs to be studied in vivo for effects on contraceptive steroids if the drug is intended for use in fertile women, regardless on the in vitro induction study results. For the purpose of this guidance, an IMP with demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy is a potential human teratogen. For these IMPs,

data from a clinical pharmacokinetic interaction study between the IMP and contraceptive steroids, if available, allow to conclude whether the efficacy of hormonal contraception is reduced. In the absence of such a clinical pharmacokinetic interaction study, any recommendation for use of hormonal contraceptives should be thoroughly justified by the sponsor.

For all other IMPs, recommendations should take into account both the evidence of the nonclinical reproductive toxicity data and available information related to the potential risk for interaction, e.g. in vitro enzyme induction results, signs of autoinduction and results from clinical interaction studies.

As a general rule, use of hormonal contraception is not recommended if a clinically relevant interaction with contraceptive steroids has been observed or is suspected. If an interaction with contraceptive steroids has been observed or is suspected, but the effect is considered to be of limited clinical significance, the hormonal contraception method must be supplemented with a barrier method (preferably male condom).

An assessment of the potential for interaction between the IMP and hormonal contraceptives should be provided in the Investigator's Brochure (IB), including a scientific rationale for the use of hormonal contraception methods with or without a supplementary barrier method (preferably male condom).

Appendix 9. Protocol Amendment I8F-MC-GPGT(d) Summary The Effect of Tirzepatide on α and β Cell Function and Insulin Sensitivity in Patients with Type 2 Diabetes Mellitus

Overview

Protocol I8F-MC-GPGT(c) The Effect of Tirzepatide on α and β Cell Function and Insulin Sensitivity in Patients with Type 2 Diabetes Mellitus has been amended in response to queries and feedback raised by the Ethics Committee (EC). 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 amendment is considered a non-substantial protocol amendment, since enrolment criteria has been tightened.

The overall changes and rationale for the changes made to this protocol are as follows:

- Provided additional clarity for Inclusion Criterion [2] that patients on a second OAM must be on stable, unchanged doses for at least 3 months.
- Changed Inclusion Criterion [3] to set the HbA1c upper limit as ≤9.5% for patients on metformin only as requested by the EC.
- Deleted ISI as an exploratory endpoint as it was considered redundant.
- Clarified Section 10.3.3.2 that primary endpoint is change from baseline in cDI instead of cDI as a standalone measure. Additional details describing the statistical analysis had been included.
- Minor formatting and editorial changes have been performed but these may not be reflected in the section below.

Revised Protocol Sections

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

6.1. Inclusion Criteria

[2] Treated with diet and exercise and stable dose(s) of metformin, with or without 1 additional stable dose of OAM other than metformin, 3 months prior to study entry; doses of metformin will be considered stable if all prescribed doses for this period were ±850 mg from the most commonly prescribed dose; allowed OAMs, in combination with metformin, are dipeptidyl peptidase-4 (DPP-IV) inhibitors, SGLT-2 inhibitors, acarbose, and sulfonylureas; the second OAM dose will be considered stable if the prescribed dose is unchanged for at least 3 months prior to study entry.

[3] Have a hemoglobin A1c value at screening (Visit 1) of ≥7.0% and ≤9.5~~10.0~~% if on metformin only; or ≥6.5% and ≤9.0% if on metformin in combination with OAMs other than metformin;

7.7. Concomitant Therapy

Paragraph 2

Patients treated with other OAMs at study entry, in addition to metformin, are allowed to participate in the study (refer to Inclusion Criteria [2] and [3] for details) but must discontinue OAMs other than metformin as soon as their eligibility is confirmed, and must complete a 4-week washout period prior to the lead-in period and randomization. Once the 4-week washout period is completed, patients can be enrolled in the study. The allowed OAMs, in combination with metformin, are DPP-IV inhibitors, SGLT-2 inhibitors, acarbose, and sulfonylureas.

9.1.3 Exploratory Efficacy Assessments and Procedures

Exploratory efficacy measures to assess the effect of study treatments on insulin sensitivity:

- ~~insulin sensitivity index (ISI) from hyperinsulinemic euglycemic clamp, defined as MCR/Imean (Imean is average steady state plasma insulin response; MCR is metabolic clearance rate of glucose) (De Fronzo et al. 1979);~~
- hyperinsulinemic euglycemic M/I value, defined as the M-value divided by total insulin over the same time period (+150 to +180 minutes).

10.3.3.1 Pharmacodynamic Parameter Estimation

Insulin sensitivity:

- ~~ISI for the clamp portion is calculated from the M value during the hyperinsulinemic euglycemic clamp test.~~ M-value from hyperinsulinemic euglycemic clamp is the measure

of insulin sensitivity; M-value is defined as the GIR over the last 30 minutes of the clamp (+150 to +180 minutes) minus a correction factor for non constant glucose level divided by body weight (DeFronzo et al. 1979).

10.3.3.2. Pharmacodynamic Statistical Inference

The primary endpoint (change from baseline in cDI ~~for tirzepatide versus placebo~~) will be calculated by first log-transforming the data then computing the change from baseline. The primary analysis will be ~~ed and then~~ analyzed using an analysis of covariance model which has effects for treatment and baseline of the parameter measured to compare tirzepatide versus placebo.

CCI [redacted]

Approver: PPD

Approval Date & Time: 10-Jun-2020 15:18:29 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 10-Jun-2020 15:28:03 GMT

Signature meaning: Approved