Protocol I8F-MC-GPGU(f)

A Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Effect of Once-Weekly Tirzepatide on Energy Expenditure and Food Intake in Obese Subjects

NCT04081337

Approval Date: 02-Aug-2021

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A Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Effect of Once-Weekly Tirzepatide on Energy Expenditure and Food Intake in Obese Subjects

Tirzepatide (LY3298176)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 23 July 2019.
Amendment (a) Electronically Signed and Approved by Lilly: 11 September 2019
Amendment (b) Electronically Signed and Approved by Lilly: 22 October 2019
Amendment (c) Electronically Signed and Approved by Lilly: 31 January 2020
Amendment (d) Electronically Signed and Approved by Lilly: 24 February 2020
Amendment (e) Electronically Signed and Approved by Lilly: 03 August 2020
Amendment (f) Electronically Signed and Approved by Lilly on approval date provided below

Approval Date: 02-Aug-2021 GMT

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1. Protocol Synopsis

Title of Study:
A Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Effect of Once-Weekly Tirzepatide on Energy Expenditure and Food Intake in Obese Subjects

Rationale:
Tirzepatide (LY3298176) is a long-acting, 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 (BW) beyond the effect of selective GLP-1R stimulation.
Study I8F-MC-GPGU is an 18-week treatment (±1 week), 4-week post treatment follow-up, Phase 1 study designed to examine the effect of tirzepatide compared with placebo on energy expenditure (EE) and food intake in obese subjects to provide mechanistic insight to BW reduction attributable to dual GIP/GLP-1 receptor agonism.

Objectives/Endpoints:

Objectives	Endpoints
Primary To assess the effect of tirzepatide versus placebo on SMR after 18 weeks (±1 week) of treatment	• The change from baseline to Week 18 in SMR, as measured in the respiratory chamber (whole-room calorimetry)
Secondary To assess the effect of tirzepatide versus placebo after 18 weeks (±1 week) of treatment: • Appetite and food intake	• The change from baseline to Week 18 in appetite VAS • The change from baseline to Week 18 in food intake as assessed by ad libitum meal test
• Energy expenditure	• The change from baseline to Week 18 in 24-hour EE
• Substrate oxidation rates	• The change from baseline to Week 18 in 24-hour RQ • The change from baseline to Week 18 in sleep RQ • The change from baseline to Week 18 in duration of periods with RQ<0.80 • The change from baseline to Week 18 in fat, protein, and carbohydrate oxidation
• Body weight and body composition	• The change from baseline to Week 18 in BW • The change from baseline to Week 18 in body fat free mass • The change from baseline to Week 18 in body fat mass • The change from baseline to Week 18 in the percentage of body fat mass

Objectives	Endpoints
Secondary (continued) • Lipid metabolism	• The change from baseline to Week 18 in triglycerides, cholesterol, LDL, VLDL, and HDL cholesterol, FFA, glycerol, 3-hydroxybutyrate, and acylcarnitines assessed during sMMTT • The change from baseline to Week 18 in ApoB-48, ApoB-100, ApoC-III, and LPL during sMMTT • The change from baseline to Week 18 in fasting concentration of leptin, adiponectin, IGFBP 1 and 2
• Insulin sensitivity	• The change from baseline to Week 18 in fasting insulin resistance (as measured by the HOMA2 method [HOMA2-IR]) and postprandial insulin sensitivity indices (Matsuda, OGIS, and Stumvoll) assessed during sMMTT
• Glucose control	• The change from baseline to Week 18 in fasting and postmeal glucose during sMMTT • The change from baseline to Week 18 in hemoglobin A1c

Abbreviations: ApoB-48 = apolipoprotein B-48; ApoB-100 = apolipoprotein B-100; ApoC-III = apolipoprotein C-III; BW = body weight; EE = energy expenditure; FFA = free fatty acid; HDL = high-density lipoprotein; HOMA2 = Homeostatic Model Assessment of Insulin Resistance; HOMA2-IR = insulin resistance as measured by the HOMA2 method; IGFBP = insulin-like growth factor binding protein; LDL = low-density lipoprotein; LPL = lipoprotein lipase; OGIS = Oral Glucose Insulin Sensitivity; RQ = respiratory quotient; sMMTT = standardized mixed-meal tolerance test; SMR = sleep metabolic rate; VAS = visual analog scale; VLDL = very low-density lipoprotein.

Summary of Study Design:

Study I8F-MC-GPGU is a Phase 1, single-center, randomized, sponsor (study team members directly involved in study management)-, investigator- and subject-blind, placebo-controlled, parallel-arm study in obese subjects. This study is designed to assess differences in the mechanisms of action with respect to energy balance, lipid and carbohydrate metabolism, and insulin sensitivity between tirzepatide and placebo, both in combination with a low-calorie diet in non-diabetic, obese subjects.

Eligibility for this study will be assessed at screening (Visit 1) and confirmed at lead-in (Visit 2). Tirzepatide 15 mg will be attained via step-wise dose escalation to reduce the risk of gastrointestinal adverse events.

Treatment Arms and Planned Duration for an Individual Subject:

The study will consist of the following periods: 4-week screening period, 2-week lead-in period, 18-week (±1 week) treatment period, and a 4-week safety follow-up period. Subjects will be screened within 4 weeks prior to lead-in. Eligible subjects will enter lead-in (Visit 2) within 2 weeks prior to randomization. Subjects will be randomized in a 1:1 ratio to tirzepatide or placebo. Tirzepatide dosing will start at a dose of 2.5 mg once weekly (QW) for 2 weeks, followed by step-wise dose escalation to 5 mg QW for 2 weeks, and 10 mg QW for 4 weeks, until the 15-mg QW dose is reached and maintained for the remainder of the treatment period (10 weeks ±1 week). Study participants will target BW reduction of 10% (±2%) after approximately 14 weeks of treatment, followed by BW maintenance until the final on-treatment visit (Visit 20).

Number of Subjects:
Up to 56 subjects may be enrolled (randomized) to maximize the probability that approximately 46 subjects complete the study assuming a 15% discontinuation rate.

Statistical Analysis:
Pharmacodynamic (PD) analyses will be conducted on data from all subjects who receive at least 1 dose of the investigational product and have evaluable data.

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

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

The primary PD parameter for analysis is sleep metabolic rate (SMR) measured using whole-room indirect calorimetry (respiratory chamber), which will be analyzed using an analysis of covariance model (ANCOVA) to compare the effect of tirzepatide versus placebo. The dependent variable to be used in the model will be the change from baseline to 18 weeks in SMR. The independent variables will include treatment as a factor, baseline SMR and body composition parameter(s) as covariates. The primary analysis will be performed in all randomized subjects with evaluable data (modified intent-to-treat [mITT] population). Similar analysis will also be performed in subjects who reach the BW target range of -10% (±2%) at Week 18 as a sensitivity analysis.

Other PD parameters that are scheduled to be measured only once postbaseline will be analyzed using a similar ANCOVA model with baseline measurement and treatment group as covariates. For parameters that are measured in the respiratory chamber, an adjustment for body composition parameter(s) as covariates may be applied if deemed appropriate. If the response is positive for all subjects and highly skewed, a log-transformation may be considered. Other parameters that are positive and skewed may be log-transformed.

The PD parameters that are scheduled to be measured at least twice postbaseline will be analyzed using a mixed-model repeated-measure method with restricted maximum likelihood estimation. The model will include the treatment, visit, and treatment-by-visit interaction as fixed effects, baseline value of the dependent variable as a covariate, and subject as a random effect. An unstructured variance-covariance matrix will be used to model the within-subject effects.

All PD analyses will performed in the mITT population and selected analyses also in on-BW-target population. All analyses will show least squares means of each treatment and the treatment difference in the original scale as well as standard error and 95% confidence interval. All tests will be done at the 2-sided 0.05 α level unless otherwise specified.

2. Schedule of Activities

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

Procedure	Screening	Lead-In					Comments
Visit	1*	2					
Week of Treatment	-6 to -2	-2 to -1					Week of treatment should be established versus the day of randomization (end of lead-in).
Study Day	-42 to -14	Any time from Day -14 to Day-1					
		-5	-4	-3	-2	-1	
Screening Procedures							
Informed consent	X						
Medical history	X						
Lifestyle interview	X						Performed to ensure subjects understand what they will be doing and if they are capable of meeting study demands.
Drug and alcohol screen	X						Procedures may be repeated throughout the study as deemed necessary by the investigator.
Physical examination/ medical assessment	X				X		Full physical examination at screening. After screening, medical assessment is performed to include medical review and targeted examination, as appropriate.
Height	X						
Weight	X					X	See Section 9.6.2 for details.
Waist circumference	X						
Vital signs (BP/PR/body temperature)	X				X		See Section 9.4.2 for details. Vital sign measurements whose nominal times are not listed in the schedule should be taken before PK samples scheduled on the same day.
ECGs	X					X	See Section 9.4.3 for details.
Concomitant medications		X				X	
C-SSRS (baseline/ screening form) + SHSF + SHFF	X	X					The SHFF is required only if triggered by the SHSF, per instructions in the form. Day-5 C-SSRS assessment may be performed any time from Day -5 to before the first dose.
PHQ-9	X						
Review/confirm inclusion/exclusion	X						

Procedure	Screening	Lead-In					Comments
Visit	1*	2					
Week of Treatment	-6 to -2	-2 to -1					Week of treatment should be established versus the day of randomization (end of lead-in).
Study Day	-42 to -14	Any time from Day -14 to Day-1					
		-5	-4	-3	-2	-1	
criteria							
Clinical Procedures							
CRU admission		X					
Training on signs/symptoms of hypoglycemia and self-treatment		X					Training can be completed anytime during the lead-in period (prior to discharge).
AEs		X	X	X	X	X	
Randomization						X	Performed after all baseline assessments.
Laboratory Tests							
Safety laboratory tests (including hemoglobin A1c and calcitonin)	X		X				See Appendix 2 for details. Subjects will fast for at least 10 hours before all blood samples are collected. As fasting glucose is collected as part of the sMMTT procedure, glucose need not be included here.
Insulin, leptin, adiponectin, IGFBP 1, IGFBP 2			X				See Appendix 6, Table GPGU.4 for sampling details.
Glucose			X				See Appendix 6, Table GPGU.4 for sampling details.
Lipid panel: • Triglycerides, total cholesterol • LDL-C, VLDL-C, HDL-C • ApoB-48, ApoB-100, ApoC-III • LPL FFA, glycerol, 3-hydroxybutyrate, acylcarnitine			X				See Appendix 6, Table GPGU.4 for sampling details.
OGTT	X						To determine subject eligibility per requirements listed in Section 6.1 (Inclusion Criteria), OGTT will be performed (see Appendix 6 for details).
Pregnancy test	X		X				For women of childbearing potential, a serum pregnancy test will be performed at screening. Urine pregnancy test will be performed on Day -4.
Investigative Tests							

Procedure	Screening	Lead-In					Comments
Visit	1*	2					
Week of Treatment	-6 to -2	-2 to -1					Week of treatment should be established versus the day of randomization (end of lead-in).
Study Day	-42 to -14	Any time from Day -14 to Day-1					
		-5	-4	-3	-2	-1	
Appetite (VAS), ad libitum food intake test			X				See Appendix 6 for details.
Retrospective VAS				X			See Appendix 6 for details.
Food craving inventory and food preference questionnaire				X			See Appendix 6 for details.
Adipose tissue biopsy (abdominal)						X	Sample will be collected outside of the respiratory chamber. See Appendix 6 for details.
Respiratory chamber				X	X	X	Approximately 2 × 23 hours from Day -3 to Day -1. See Appendix 6 for details.
sMMTT			X				See Appendix 6 for details of the procedure and sampling schedule.
DXA scan				X			See Appendix 6 for details. The predose DXA scan may be scheduled any time from Day -5 to Day -1.

*Screening activities on Visit 1 may be performed over more than 1 day if necessary to fit subject and site scheduling.

Study Schedule Protocol I8F-MC-GPGU: Treatment Period

Procedure	Treatment															Comments
Visit	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Week of Treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Study Day	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	
Clinical Procedures																
Weight		P	P	P	P	P	P	P	P	P	P	P	P	P	P	Refer to screening and lead-in table.
Vital signs (BP/PR/body temperature)		P	P	P	P		P		P				P			Refer to screening and lead-in table.
ECGs									X							Refer to screening and lead-in table.
Concomitant medications	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	
Physical examination/ medical assessment								X								Refer to screening and lead-in table.
CRU discharge	X															CRU discharge will be ± 1 day.
C-SSRS (Since Last Visit Version) + SHSF + SHFF				X				X				X				The SHFF is required only if triggered by the SHSF, per instructions in the form. The C-SSRS since last visit version here refers to when last C-SSRS assessment was performed.
PHQ-9								X								
Outpatient		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Investigational Product																
Investigational product administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Tests																
Safety laboratory tests (including hemoglobin A1c and calcitonin)									X							
Glucose					X											Fasting sample.
Insulin, leptin, adiponectin, IGFBP 1, IGFBP 2					X				X							Fasting samples.

Procedure	Treatment															Comments
Visit	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Week of Treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Study Day	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	
Lipid panel: • Triglycerides, total cholesterol • LDL-C, VLDL-C, HDL-C • ApoB-48, ApoB-100, ApoC-III • LPL FFA, glycerol, acylcarnitine 3-hydroxybutyrate					P				P							Fasting samples.
Investigative Tests																
Retrospective VAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Food craving inventory and food preference questionnaire								X								
Diagnostics																
PK sample	P				P				P							All samples for PK and immunogenicity must be taken predose, and time-matched as much as possible.
Immunogenicity	P				P				P							
Nonpharmacogenetic stored samples	P				P				P							Fasting samples.
Pharmacogenetic sample	P															

Study Schedule Protocol I8F-MC-GPGU: Treatment Period Continued and Follow-up/Early Termination

Procedure	Treatment								Follow-up/ET	Comments
Visit	18	19	20	20	20	20	20	20	21	
Week of Treatment	16	17	18	18	18	18	18	18	22	
Study Day	106 ±1	113 ±1	120 ±7	121	122	123	124	125	Within 4 weeks after last dose	
Clinical Procedures										
Weight	P	P	P			X	X	X	X	Refer to screening and lead-in table
Vital signs (BP/PR/body temperature)		P				X	X	X	X	Refer to screening and lead-in table.
ECGs							X			Refer to screening and lead-in table.
Concomitant medications	X	X	X					X	X	
AEs	X	X	X	X	X	X	X	X	X	
Physical examination/ medical assessment							X		X	Refer to screening and lead-in table.
Outpatient visit	X	X	X							
C-SSRS (Since Last Visit Version) + SHSF + SHFF	X								X	The SHFF is required only if triggered by the SHSF, per instructions in the form. The C-SSRS since last visit version here refers to when the last C-SSRS assessment was performed.
PHQ-9	X								X	
CRU admission				X						
CRU discharge								X		
Investigational Product										
Investigational Product administration	X	X	X							
Laboratory Tests										
Safety laboratory tests (including hemoglobin A1c and calcitonin)					X				X	Fasting sample. As fasting glucose is collected as part of the sMMTT procedure, glucose need not be included here.
Glucose					X					See Appendix 6, Table GPGU.4 for sampling details.

Procedure	Treatment								Follow-up/ET	Comments
Visit	18	19	20	20	20	20	20	20	21	
Week of Treatment	16	17	18	18	18	18	18	18	22	
Study Day	106 ±1	113 ±1	120 ±7	121	122	123	124	125	Within 4 weeks after last dose	
Insulin, leptin, adiponectin, IGFBP 1, IGFBP 2					X					See Appendix 6, Table GPGU.4 for sampling details.
Lipid panel: • Triglycerides, total cholesterol • LDL-C, VLDL-C, HDL-C • ApoB-48, ApoB-100, ApoC-III • LPL FFA, glycerol, 3-hydroxybutyrate, acylcarnitine					X					See Appendix 6, Table GPGU.4 for sampling details.
Pregnancy test					X				X	For women of childbearing potential, a urine pregnancy test will be performed on Day 122. Serum pregnancy test at follow-up.
Investigative Tests										
Appetite (VAS), ad libitum food intake test					X					
Retrospective VAS						X				
Food craving inventory and food preference questionnaire						X				
Adipose tissue biopsy (abdominal)								X		
Respiratory chamber						X	X	X		Approximately 2 × 23 hours from Days 123 to 125. See Appendix 6 for details.
sMMTT					X					See Appendix 6 for details on the procedures and sampling schedule.
DXA scan						X				See Appendix 6 for details. The postdose DXA scan may be scheduled any time from Day 123 to 125.
Diagnostics										

Procedure	Treatment								Follow-up/ET	Comments
Visit	18	19	20	20	20	20	20	20	21	
Week of Treatment	16	17	18	18	18	18	18	18	22	
Study Day	106 ±1	113 ±1	120 ±7	121	122	123	124	125	Within 4 weeks after last dose	
PK samples			P						X	Immunogenicity / PK sampling times must be time-matched as much as possible.
Immunogenicity			P						X	
Nonpharmacogenetic stored samples			P						X	Fasting samples.

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; C-SSRS = Columbia-Suicide Severity Rating Scale; DXA = dual energy X-ray absorptiometry; 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; OGTT = oral glucose tolerance test; P = predose; PD = pharmacodynamics; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetics; PR = pulse rate; SHFF = Self-Harm Follow-Up Form; SHSF = Self-Harm Supplementary Form; sMMTT = standard mixed-meal tolerance test; 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 of assessments should be used: Vital signs, ECG, PD, PK, immunogenicity, safety laboratory, storage samples.

3. Introduction

3.1. Study Rationale

Tirzepatide (LY3298176) is a long-acting, 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 (BW) beyond the effect of selective GLP-1R stimulation (Frias et al. 2018; Coskun et al. 2018). Study I8F-MC-GPGU (GPGU) is an 18-week treatment (±1 week), 4-week post treatment follow-up, Phase 1 study designed to examine the effect of tirzepatide compared with placebo on energy expenditure (EE) and food intake in obese subjects to provide mechanistic insight to BW reduction attributable to dual GIP/GLP-1 receptor agonism (GIPRA/GLP-1RA).

3.2. Background

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

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

Tirzepatide, a dual GIPRA/GLP-1RA, is a 39-amino acid synthetic peptide. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety which facilitates albumin binding. It has a chemical structure and pharmacologic profile that is distinct from the GLP-1RAs due to

the additional GIP activity. It is administered once weekly (QW) by subcutaneous (SC) injection.

Tirzepatide is being developed as a therapy to improve glycemic control in adults with type 2 diabetes mellitus (T2DM), as an adjunct to diet and exercise. Phase 3 studies are also planned for chronic weight management in obese adults and a Phase 2 study is planned for nonalcoholic steatohepatitis.

In a Phase 1 study (Coskun et al. 2018) that included single and multiple ascending dose (SAD, MAD) parts, tirzepatide has been administered as a single SC dose up to 8 mg in healthy subjects. In the MAD part, higher doses up to 10 mg were attained in healthy subjects via dose escalation. In the same study, doses up to 15 mg were achieved in patients with T2DM via dose escalation. In this study, GI adverse events (AEs) (nausea, vomiting, diarrhea, abdominal distension) and decreased appetite were the most frequently reported events by both healthy subjects and patients with T2DM and were dose related. Most AEs were mild in severity, a few were moderate, and none were reported as severe. During the SAD study, the high incidence of GI AEs, notably vomiting, were considered to be dose limiting at the 8-mg dose; therefore, the 5-mg dose was considered the maximum tolerated dose. A dose-dependent increase in heart rate was detected in 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.

Once-weekly doses of 1, 5, 10, and 15 mg have been further investigated in a Phase 2 study (Frias et al. 2018). An additional dose level of 12 mg and alternate dose escalation schemes were investigated in a 12-week Phase 2 study. Doses above 5 mg of tirzepatide were attained via step-wise dose escalation. Results from the 2 Phase 2 studies demonstrated that tirzepatide at doses between 5 and 15 mg provided clinically meaningful efficacy in both glucose- and BW-lowering. Gastrointestinal-related AEs (nausea, diarrhea, vomiting) were the most frequently reported AEs in Phase 2 studies. The majority of the treatment-emergent adverse events (TEAEs) were mild or moderate in severity. Treatment with tirzepatide was associated with treatment-emergent anti-drug antibodies (TE-ADAs) in 40.7% in the largest and longest Phase 2 study. However, the presence of anti-drug antibodies (ADAs) appeared to have no effect on pharmacokinetic (PK), safety, or efficacy of tirzepatide. There were no other clinically relevant safety observations in the Phase 1 and 2 studies.

Tirzepatide terminal half-life was estimated to be approximately 5 days, thus supporting a QW dosing regimen, with maximum observed drug concentration occurring 24 to 72 hours postdose.

The prevalence of obesity has increased worldwide resulting in an increased risk of its common comorbidities including T2DM, fatty liver disease, hypertension, and dyslipidemia as well as increased CV risk. The available obesity prevention and treatment strategies have limited success due to the complex regulation of energy homeostasis, which is the balance between energy intake and energy expenditure (EE). Diet and life-style modification are the first-line treatment in the management of obesity but these often fail to provide sustainable weight loss.

Currently, available pharmacological treatments, phenylpropanolamine (Acutrium®), liraglutide 3 mg (Saxenda®), orlistat (Xenical® or Alli™), sibutramine (Meridia®), mazindol (Sanorex®), lorcaserin (BELVIQ®), phentermine (Adipex-P®)-topiramate (Topamax®) (Qsymia™), or naltrexone-bupropion (Contrave®) for weight loss have limited efficacy due to the mechanism of action or side effect profiles (Bluher 2019; Bonamichi et al. 2018; Yanovski et al. 2014).

Glucagon-like peptide-1 receptor agonists have demonstrated efficacy in BW reduction. Liraglutide (Saxenda) is the first agent from this class that has been approved for the treatment of obesity. After 56 weeks, treatment with Saxenda resulted in BW reduction of at least 5% when compared with placebo (Saxenda package insert, 2014; Mehta et al. 2017). Studies that investigated the mechanism of action of GLP-1 RAs have shown that these agents induce weight loss by reducing appetite and energy intake, with no effect on EE (van Can et al. 2014; Blundell et al. 2017).

Several clinical trials suggest that weight loss during a dietary intervention the human body switches to a more energy efficient state by reducing energy expenditure. Such metabolic adaptation has been proposed as the main cause of BW regain following cessation of dietary intervention (Martin et al. 2007; Redman et al. 2009; Rosenbaum et al. 2016; Maclean et al. 2011). In Phase 1 and Phase 2 development, treatment with tirzepatide has shown clinically meaningful effect on BW regulation by suppressing appetite and reducing food intake, but no data are available from these studies on the effects on EE and substrate utilization. In a preclinical study, it was observed that reduced food intake may also be accompanied by increased EE in animals treated with tirzepatide, probably via more efficient substrate utilization, while GLP-1RA had no effect on EE, similar to observations in clinical trials. These results warrant further investigations of how dual GIPR/GLP-1R agonism affects regulation of energy balance in the human body (Frias et al. 2018; Coskun et al. 2018).

We hypothesized that tirzepatide may increase EE and reduce metabolic adaptation. Potential reduction in metabolic adaptation may result in a sustained and durable improvement in weight control. Study GPGU is designed to assess the effect of tirzepatide versus placebo on various aspects of EE, appetite and food intake, substrate (oxidation), and insulin sensitivity in obese, nondiabetic subjects targeting reduction in BW of 10% (±2%) by a mean of low-calorie diet. The primary objective is to compare the effect of tirzepatide and placebo on sleep metabolic rate (SMR) assessed in a respiratory chamber (whole-room indirect calorimetry) after 18 weeks of treatment. The subjects will be closely monitored during the study for general safety and special safety issues attributable to incretins. The study is expected to provide important, new information on the key mechanisms of BW-lowering associated with treatment with a dual GIP/GLP-1 receptor agonist.

3.3. Benefit/Risk Assessment

The most common safety issue with administration of tirzepatide was related to frequent reporting of decreased appetite and GI side effects, most commonly nausea, vomiting, and diarrhea. These GI events were generally mild in severity, with few moderate, and no severe events reported in Phase 1 studies. Tirzepatide triggered generation of ADAs in a subset of

patients in Phase 2 trials. The presence of tirzepatide ADA did not affect PK or pharmacodynamic (PD) parameters, and was not associated with increased incidence of local or systemic hypersensitivity AEs in Phase 1 and Phase 2 studies up to 26 weeks of exposure. Based on these results, tirzepatide ADA represents a low risk in exposed patients, but more data is needed for definitive conclusion on the frequency and severity of possible side effects. 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 studies in T2DM patients, administered QW up to 26 weeks. Findings to date indicate that the safety profile for a dual GIPRA/GLP-1RA is similar to the safety profile of the selective GLP-1RAs. Potential risks, such as GI effects, acute pancreatitis, increases in heart rate, and hypoglycemic events are consistent with the risks associated with currently available long-acting GLP-1RAs. To mitigate the risk of GI side effects, tirzepatide 15 mg will be attained via step-wise dose escalation. Details on the management of these AEs are provided in Section 7.7.1 (Management of Subjects with Gastrointestinal Symptoms). The monitoring plan for all AEs of special interest is included in this protocol, as well as treatment measures, when appropriate.

Since Study GPGU will enroll subjects without diabetes, no self-monitoring of plasma glucose (PG) is planned. Consistent with the mechanism of action of incretins, which are nonsecretagogues, severe hypoglycemia has not been reported in Phase 1 or Phase 2 trials that included healthy subjects or patients with T2DM. However, to mitigate the risk, the subjects in this study will be trained on signs and symptoms of hypoglycemia and self-treatment measures. Section 9.2.2.1 (Hypoglycemia) describes definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia. Section 7.4.1.1 (Management of Hypoglycemia) provides detailed information concerning the management of hypoglycaemia.

There are several possible AEs associated with the planned procedures in the study. The respiratory chamber will be used to obtain parameters needed to calculate respiratory quotient (RQ), EE, and substrate oxidation rates (see Appendix 6 for details). Some level of claustrophobia or discomfort may be experienced from staying in the respiratory chamber and being continuously monitored by a camera. The dual energy X-ray absorptiometry (DXA) scan will be used to measure the amount of bone, muscle, and fat in the body. Subjects may be exposed to a small amount of radiation during the procedure. The radiation dose for a DXA scan is less than 1 mrem, which is less than a chest X-ray, or equal to about 12 hours of background radiation from the sun.

Subjects in Study GPGU are not expected to have direct health-related benefits. Potential risks described above, are considered to be transient and long-term health risks are low. The majority of these risks are clinically detectable and manageable, and will be monitored during the study.

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

Table GPGU.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess the effect of tirzepatide versus placebo on SMR after 18 weeks (±1 week) of treatment	• The change from baseline to Week 18 in SMR, as measured in the respiratory chamber (whole-room calorimetry)
Secondary To assess the effect of tirzepatide versus placebo after 18 weeks (±1 week) of treatment: • Appetite and food intake	• The change from baseline to Week 18 in appetite VAS • The change from baseline to Week 18 in food intake as assessed by ad libitum meal test
• Energy expenditure	• The change from baseline to Week 18 in 24-hour EE
• Substrate oxidation rates	• The change from baseline to Week 18 in 24-hour RQ • The change from baseline to Week 18 in sleep RQ • The change from baseline to Week 18 in duration of periods with RQ<0.80 • The change from baseline to Week 18 in fat, protein, and carbohydrate oxidation
• Body weight and body composition	• The change from baseline to Week 18 in BW • The change from baseline to Week 18 in body fat-free mass • The change from baseline to Week 18 in body fat mass • The change from baseline to Week 18 in the percentage of body fat mass
• Lipid metabolism	• The change from baseline to Week 18 in triglycerides, cholesterol, LDL, VLDL, and HDL cholesterol, FFA, glycerol, 3-hydroxybutyrate, and acylcarnitines assessed during sMMTT • The change from baseline to Week 18 in ApoB-48, ApoB-100, ApoC-III, and LPL during sMMTT • The change from baseline to Week 18 in fasting concentration of leptin, adiponectin, IGFBP 1 and 2

Objectives	Endpoints
Secondary (continued) • Insulin sensitivity	• The change from baseline to Week 18 in fasting insulin resistance (as measured by the HOMA2 method [HOMA2-IR]) and postprandial insulin sensitivity indices (Matsuda, OGIS, and Stumvoll) assessed during sMMTT
• Glucose control	• The change from baseline to Week 18 in fasting and postmeal glucose during sMMTT • The change from baseline to Week 18 in hemoglobin A1c
Exploratory To assess the effect of tirzepatide versus placebo after 18 weeks (±1 week) of treatment: • GIPR signaling, lipid metabolism, carbohydrate metabolism, and insulin signaling pathways in subcutaneous adipose tissue	• The change from baseline to Week 18 in markers of GIPR signaling, lipid metabolism, carbohydrate metabolism, and insulin signaling pathways as measured in exploratory mRNA expression, lipidomics, metabolomics, or targeted protein assays of subcutaneous adipose tissue biopsy samples, receptor expression, signal transduction, and metabolic changes in adipose tissue
• Safety and tolerability	• Adverse events • Safety laboratory parameters • Frequency of treatment-emergent anti-tirzepatide antibodies • Treatment-emergent depression and suicidal ideation as assessed using C-SSRS and PHQ-9

Abbreviations: ApoB-48 = apolipoprotein B-48; ApoB-100 = apolipoprotein B-100; ApoC-III = apolipoprotein C-III; BW = body weight; C-SSRS = Columbia-Suicide Severity Rating Scale; EE = energy expenditure; FFA = free fatty acid; GIPR = glucose-dependent insulinotropic polypeptide receptor; HDL = high-density lipoprotein; HOMA2 = Homeostatic Model Assessment of Insulin Resistance; HOMA2-IR = insulin resistance as measured by the HOMA2 method; IGFBP = insulin-like growth factor binding protein; LDL = low-density lipoprotein; LPL = lipoprotein lipase; mRNA = messenger ribonucleic acid; OGIS = Oral Glucose Insulin Sensitivity; PHQ-9 = Patient Health Questionnaire-9; RQ = respiratory quotient; sMMTT = standardized mixed-meal tolerance test; SMR = sleep metabolic rate; VAS = visual analog scale; VLDL = very low-density lipoprotein.

5. Study Design

5.1. Overall Design

This is a Phase 1, single-center, randomized, sponsor (study team members directly involved in study management)-, investigator- and subject-blind, placebo-controlled, parallel-arm study in obese subjects. This study is designed to assess differences in the mechanisms of action with respect to energy balance, lipid and carbohydrate metabolism, and insulin sensitivity between tirzepatide and placebo, in combination with a low-calorie diet in non-diabetic, obese subjects. The primary objective of this study is to compare the 2 treatment groups for changes from baseline in sleep metabolic rate (SMR) after 18 weeks (±1 week) of treatment.

The subject will sign the informed consent form (ICF) before any study procedures are performed. Eligibility for this study will be assessed at screening (Visit 1) and confirmed at lead-in (Visit 2). Screening procedures will be performed within 4 weeks prior to lead-in, according to the Schedule of Activities (Section 2).

Eligible subjects will enter lead-in (Visit 2) within 2 weeks prior to randomization. Subjects will perform baseline assessments in the clinical research unit (CRU) prior to randomization, according to the Schedule of Activities (Section 2). After the completion of all baseline procedures, subjects will be randomized in a 1:1 ratio to tirzepatide or placebo.

Tirzepatide 15 mg will be attained via step-wise dose escalation to reduce the risk of GI AEs. Tirzepatide dosing will start at a dose of 2.5 mg QW for 2 weeks, followed by a step-wise dose escalation to 5 mg QW for 2 weeks, and 10 mg QW for 4 weeks, until the 15-mg QW dose is reached and maintained for the remainder of the treatment period (10 weeks ±1 week). Subjects will return to the CRU every week for QW dose administration for 18 weeks (±1 week).

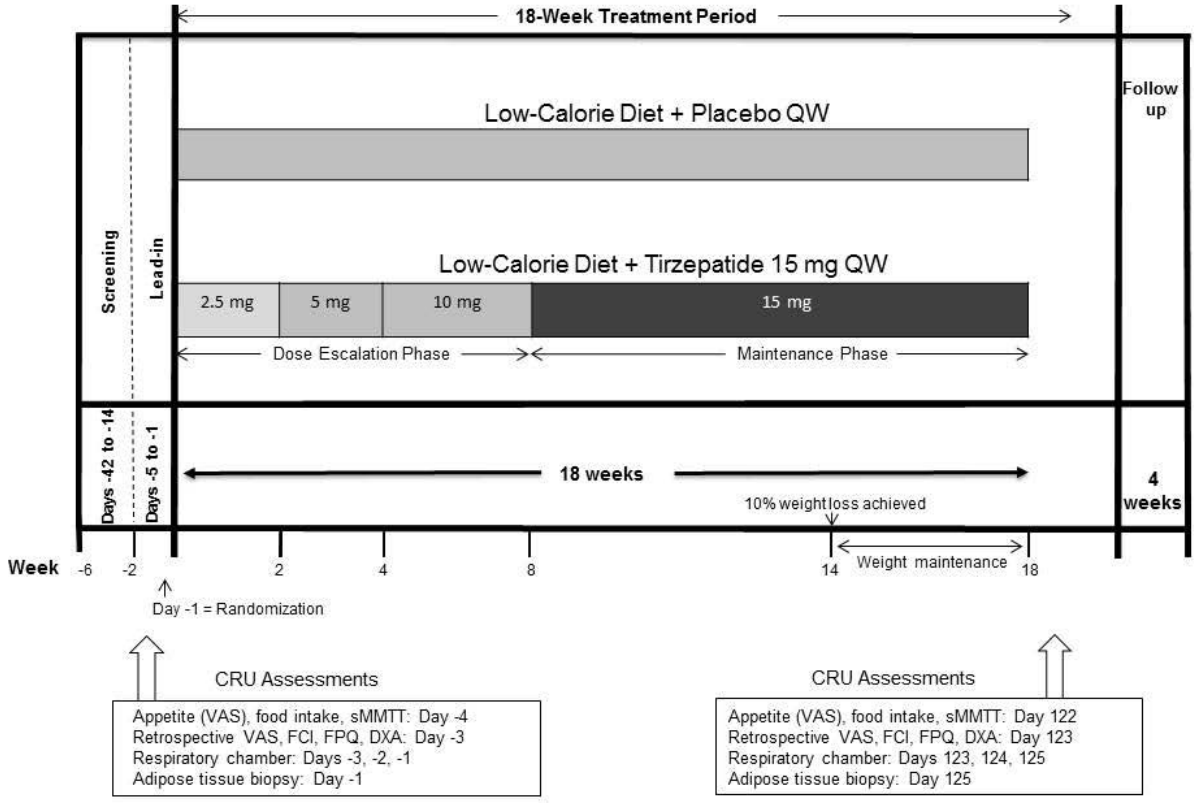
Subjects in both groups will receive a standardized dietary intervention to target a BW reduction of 10% (±2%) after approximately 14 weeks of treatment. Between Week 14 and Week 18 (±1 week), dietary intervention will shift to promoting maintenance of 10% weight loss (Section 6.3.1) within target range prior to admission to the CRU and end-of-treatment procedures to assess primary and secondary objectives. Description of these procedures is provided in Section 2 (Schedule of Activities). Subjects will be readmitted to the CRU at Week 18 (±1 week) to perform end-of-treatment CRU study procedures. These CRU study procedures will be performed in all patients, irrespective of whether they reached their BW target or not, and according to the same schedule as during the lead-in period.

Section 2 (Schedule of Activities) presents all planned visits and procedures for this study. After the completion of the treatment period, a follow-up visit will be performed within 4 weeks of the last dose to assess subject safety and subsequently complete the subject's participation.

Study governance considerations are described in detail in Appendix 3.

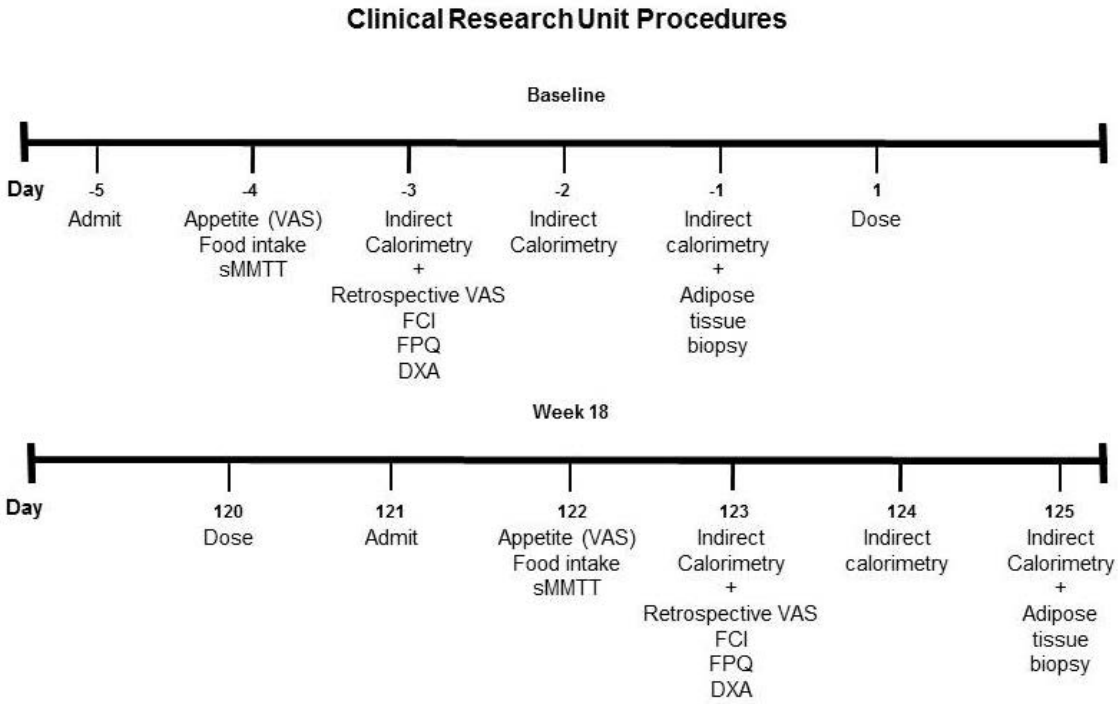
Figure GPGU.1 illustrates the study design.

Figure GPGU.2 illustrates the clinical research unit procedures.



Abbreviations: DXA = dual energy X-ray absorptiometry; FCI = Food Craving Inventory; FPQ = Food Preference Questionnaire; QW = once weekly; sMMTT = standardized mixed-meal tolerance test; VAS = visual analog scale.

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



Abbreviations: DXA = dual energy X-ray absorptiometry; FCI = Food Craving Inventory; FPQ = Food Preference Questionnaire; sMMTT = standardized mixed-meal tolerance test; VAS = visual analog scale.

Figure GPGU.2. Illustration of clinical research unit procedures.

5.2. Number of Participants

Up to 56 subjects may be enrolled (ie, randomized) to maximize the probability that approximately 46 subjects complete the study assuming a 15% discontinuation rate. For purposes of this study, a subject completes the treatment period when all scheduled procedures through Week 18 (Visit 20), as shown in Section 2 (Schedule of Activities), have been finished. A subject completes the study when all scheduled procedures through Week 22 (Visit 21) have been completed.

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 subject.

5.4. Scientific Rationale for Study Design

Study GPGU will employ a parallel-group design to minimize the confounding effects of changes in BW and, potentially, other metabolic parameters on the primary efficacy measure of SMR.

Placebo is chosen as the comparator to enable determination of the effect on parameters of energy balance (food intake and EE) attributable specifically to tirzepatide. An active GLP-1RA comparator was considered as unnecessary since the results of EE and substrate utilization studies showed no effect of selective GLP-1RAs on the outcomes of interest (van Can et al. 2014; Blundell et al. 2017).

The primary study measure SMR was chosen as the most reproducible measure of EE, since it is not influenced by activity or food intake.

The secondary study measures, such as other parameters of EE, appetite and food intake, substrate oxidation, BW and body composition, lipid metabolism, insulin sensitivity, and glucose control, are expected to provide important, additional data. All study measures and methods of assessment are well validated and fully established in the medical literature as the parameters and methods relevant for evaluation of objectives of Study GPGU. The timing of endpoint measurements (Week 18 [Visit 20]) was determined based on exposure response modeling of tirzepatide's effect on weight loss as observed in a Phase 2 clinical study (Frias et al. 2018).

To avoid the confounding effect of changes in glucose regulation on EE, the study will enroll nondiabetic, obese subjects, only. Subjects in both study groups will target same BW lowering range by means of a low-calorie diet to minimize the confounding effect of BW changes on the primary study measure. The weight loss target of 10% (±2%) was chosen as it matches expected BW change with the 15-mg dose of tirzepatide at study endpoint, based on data from Phase 2 trials.

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

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

5.5. Justification for Dose

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

The tirzepatide treatment period will consist of a step-wise dose escalation. Tirzepatide dosing will start at a low dose of 2.5 mg QW and will be escalated to 15 mg QW as described in Section 5.1 (Overall Study Design). The step-wise increments are based on cumulative understanding of safety and GI tolerability from Phase 1 and 2 studies and are expected to minimize GI tolerability concerns in this obese population by permitting adequate time for development of tolerance to GI events.

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

To minimize the incidence of GI tolerability events, this study will employ a lower starting dose of 2.5 mg to initiate the dose escalation, permitting 8 weeks of step-wise dose escalation prior to attaining a maintenance dose of 15 mg at Week 9. Steady-state exposures are expected to be

attained within 4 weeks of starting 15 mg dose of tirzepatide. Treatment will be continued for 10 weeks (±1 week) after commencing the 15-mg maintenance dose.

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. Additional information can be found in the IB.

6. Study Population

Eligibility of subjects 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 within 4 weeks prior to lead-in. Eligible subjects will enter lead-in (Visit 2) within 2 weeks prior to randomization. Subjects who are not enrolled within 6 weeks of screening may be subjected to additional medical assessment and/or clinical measurements to confirm their eligibility.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening:

Subject Characteristics

[1] Are obese (body mass index of 30 kg/m^2 to 45 kg/m^2, inclusive), and nondiabetic male or female subjects, as determined by medical history, physical examination, and laboratory assessments at screening, and have at least one of the following metabolic impairments (Alberti and Zimmet 1998; American Diabetes Association 2019; Grundy et al. 2005; Huang 2009; NIH [WWW]):

- Waist circumference ≥102 cm (40 inches) or ≥88 cm (35 inches) for males and females, respectively;
- High-density lipoprotein (HDL) cholesterol concentration <50 mg/dL for females and <40 mg/dL for males (or being on medicine to treat low HDL cholesterol);
- Serum triglycerides concentration ≥150 mg/dL or on medication to treat elevated triglycerides;
- Systolic blood pressure >130 mm Hg and/or diastolic blood pressure >85 mm Hg or already being treated with anti-hypertension medications;
- Impaired glucose tolerance defined as at least one of the following:
  - Fasting plasma glucose (PG) >100 mg/dL and <125 mg/dL;
  - Postglucose challenge PG (oral glucose tolerance test [OGTT]) ≥140 mg/dL and <200 mg/dL;
  - Hemoglobin A1c between ≥5.7% and <6.5%;

- Insulin resistance as measured by the Homeostatic Model Assessment of Insulin Resistance (HOMA2-IR) >1.8 (Matthews et al. 1985; Levy et al. 1998);

[2] Must be weight stable (no dietary weight loss/gain greater than 3 kg) in the last 1 month;

[3] Have safety laboratory test results within normal reference range or with abnormalities deemed clinically insignificant by the investigator;

[4] Have venous access sufficient to allow for blood sampling as per the protocol;

[5] Male or female subjects between the ages of 18 to 60 years, inclusive;

[5a] Male subjects:

- 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 method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted however that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined).
    - Periodic abstinence (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 investigational product (IP).

- Men who are in exclusively same-sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

[5b] Female subjects:

- 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 IP administration for 30 days.
    - Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 48 hours prior to exposure and at other times as specified in Section 2 (Schedule of Activities).
    - Two forms of effective contraception, where at least 1 form is highly effective (less than 1% failure rate, such as combination oral contraceptives, implanted contraceptives or intrauterine devices) will be used. Effective contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide). It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
- Women who are not of childbearing potential may participate and include those who are:
    - Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis, or

- Postmenopausal – defined as either
  - i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either
    - a) cessation of menses for at least 1 year, or
    - b) at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or
  - ii. A woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
  - iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Informed Consent

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

[7] Are willing and able to participate in the dietary intervention part of the study, in the opinion of the investigator;

[8] Have given written informed consent approved by Eli Lilly and Company (Lilly) and the institutional review board (IRB) governing the site.

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions - General

[9] Have a history or current CV (for example, myocardial infarction, congestive heart failure, cerebrovascular accident, venous thromboembolism, etc), respiratory, hepatic, renal, GI, endocrine, hematological (including history of thrombocytopenia), or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; or constituting a risk when taking the IP; or may interfere with the interpretation of data;

[10] Have acute or chronic pancreatitis or a history of acute idiopathic pancreatitis; or have other GI disorders (for example, relevant esophageal reflux or gall bladder disease) that could be aggravated by GLP-1 analogs; subjects who had cholecystolithiasis (removal of gall stones) and/or cholecystectomy (removal of gall bladder) in the past, with no long-term complications, are eligible for participation;

[11] Have a known clinically significant gastric emptying abnormality (eg, gastric outlet obstruction) or have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (eg, Lap-Band®);

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

[13] Are currently diagnosed with any form of diabetes; or have fasting and/or postglucose challenge PG (OGTT) compatible with diabetes, and/or hemoglobin A1c value ≥6.5% at screening (Visit 1); subjects with borderline glucose intolerance are eligible (see Section 6.1 Inclusion Criteria [1]);

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

[15] Have blood pressure of >160/90 mm Hg and/or pulse rate of <50 or >100 bpm (sitting) at screening with or without stable doses [at least 3 months prior to screening] of anti-hypertension medications;

[16] 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;

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

[18] Have evidence of hepatitis B or positive hepatitis B surface antigen and/or evidence of hepatitis C virus (HCV) or hepatitis C antibody with confirmed presence of hepatitis C virus ribonucleic acid (RNA) at screening (a positive HCV antibody at screening will need an additional HCV RNA assay – detectable HCV RNA means a subject will meet exclusion criteria). Subjects 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.

Subjects 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.

[19] Have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5X the upper limit of normal (ULN) or total bilirubin (TBL) >1.5X ULN; subjects with nonalcoholic fatty liver disease are allowed to participate;

[20] 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;

[21] Have a history of drug or alcohol abuse or a positive drug screen (unless the positive testing is due to a drug prescribed to the subject by a health care professional); and/or smoke >10 cigarettes per day or the equivalent; or are unable or unwilling to refrain from nicotine use during CRU admission;

[22] 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;

[23] 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;

[24] Have any lifetime history of a suicide attempt;

[25] Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more at screening;

[26] On the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening:

- a "yes" answer to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or
- a "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS, or
- a "yes" answer to any of the suicide-related behaviors (Actual Attempt, Interrupted Attempt, Aborted Attempt, Preparatory Act or Behavior) on the "Suicidal Behavior" portion of the C-SSRS, and
- the ideation or behavior occurred within the past month

[27] Have a history of atopy or clinically significant multiple or severe drug allergies, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).

Prior/Concomitant Therapy - General

[28] Have been treated with prescription drugs that promote weight loss (eg, sibutramine, mazindol, phentermine, phentermine-topiramate combination, lorcaserin, phenylpropanolamine, naltrexone/bupropion, liraglutide) or similar other BW loss medications, including over-the-counter medications (eg, Alli®) within 6 months prior to screening or between screening and randomization;

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

[30] Have been treated with any glucose-lowering agent during the last 3 months prior to screening (Visit 1) or between screening and randomization (Visit 2);

[31] Have received treatment with a drug that has not received regulatory approval for any indication within 3 months or 5 half-lives (whichever is longer) of screening.

[32] Use of other medications not listed above may result in exclusion of the subject at the discretion of the investigator in consultation with the sponsor;

Prior/Concurrent Clinical Trial Experience

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

[34] Have previous exposure to tirzepatide or known allergies to tirzepatide or GLP-1 receptor agonists;

[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 employees;

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

6.3. Lifestyle and Dietary Requirements

Throughout the study, subjects may undergo medical assessments and review of compliance with requirements before continuing in the study.

All subjects, regardless of the group to which they are randomized, will receive a comprehensive dietary intervention to produce 10% (±2%) weight loss by Week 14, at which time the focus of the intervention will shift to promoting weight maintenance until the end of treatment period at Week 18 (±1 week), when end-of-treatment assessments in the CRU will be performed.

This weight goal should be achieved by providing each subject with a personalized energy intake target that, if adhered to, should result in weight loss of 10% (±2%) over 14 weeks. The weight goal should be achieved by promoting energy restriction, not by increasing physical activity. Subjects will be instructed to maintain their current activity levels.

The personalized energy intake targets will be generated with mathematical models of energy balance (Thomas et al. 2009; Thomas et al. 2010; Thomas et al. 2011). The models avoid the problems associated with the static 3,500 kcal/pound rule (Thomas et al. 2013) and are well validated (Thomas et al. 2009; Thomas et al. 2010; Thomas et al. 2011; Pieper et al. 2011).

Subjects will receive structured meal plans that reflect their energy intake target and include an abundance of portion-controlled foods and meal replacements, including nutrition shakes and bars, and frozen or shelf-stable entrees. The meal plans will be consistent with dietary guidelines (ie, approximately 55% carbohydrate, 15% protein, and 30% fat [USDA 2015, WWW]), and include lean sources of protein (poultry, seafood) and whole grains.

In addition to providing personalized energy intake targets and meal plans, the models will be used to help subjects adhere to their diet and achieve their weight loss goal. This will be accomplished by using the models to generate personalized weight graphs or weight loss nomograms that display subjects' predicted weight over time assuming adherence to the energy intake target. An upper and lower limit to the weight loss goal that reflects approximately 8% and 12% weight loss will also be graphed, thus providing a zone of acceptable weights. Subjects' actual weights will be graphed against this zone and adherence to the energy intake target will be demarcated by subjects' actual weights being in the zone (Thomas et al. 2015; Martin et al. 2015; Martin et al. 2016). Subjects will be provided with their personalized weight graph and a BodyTrace© scale that automatically transmits weights to the internet, where the weights can be retrieved by the subject and the interventionist at the site. Subjects will be instructed to weigh daily at the same time and plot their weight on their weight graph. They will also be told that the interventionist will track their weight using the same method at the site. Should a subject have difficulty following the meal plan and adhering to the energy intake target, his/her actual weights will be out of the zone and the interventionist will offer supportive strategies, described below, to help the subject adhere to the diet and achieve the desired 10% (±2%) weight loss goal.

Subjects will meet weekly with their interventionist at the site to receive support to foster adherence to the energy intake target and weight loss goal. Subjects will be instructed on the use of strategies that have been found to promote weight loss, including self-monitoring of food intake, stimulus control, use of portion-controlled foods and meal replacements, and meal planning (Rickman et al. 2011). The interventionist will also conduct remote sessions via phone, for example, if subjects need additional support in meeting their goal.

6.3.1. Meals and Dietary Restrictions

Subjects shall fast for at least 10 hours overnight prior to each outpatient visit where fasting samples are drawn or weight measurements taken. Subjects will fast for at least 10 hours prior to dosing, after which subjects will receive a meal or snack. For outpatient visits that require fasting, a snack (eg, granola bar, juice, or coffee) will be provided. During inpatient visits and long days at the CRU, a meal will be provided. Water can be consumed freely. Subjects will only consume meals provided by the CRU during inpatient stays. While not resident in the CRU, subjects will be required to follow the plan described in Section 6.3 (Lifestyle and Dietary Requirements).

6.3.2. Caffeine, Alcohol, and Tobacco

No alcohol, caffeine, and/or methylxanthine-containing products will be allowed at least 12 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). Subjects will not be allowed to use tobacco products in the CRU.

6.3.3. Activity

Subjects will be advised to maintain their regular levels of physical activity/exercise during the study. No intense physical activity will be allowed for at least 48 hours before each CRU admission. When certain study procedures are in progress at the CRU, subjects may be required to remain recumbent or sitting. While in the respiratory chamber, the intensity of any physical activity can be no higher than walking around the chamber or stretching (no push-ups or sit-ups).

6.4. Screen Failures

Screening tests such as clinical laboratory tests and vital signs/ECGs may be repeated at the discretion of the investigator. Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened up to 1 time. The interval between re-screenings should be at least 2 weeks. Each time re-screening is performed, the individual must sign a new ICF and will be assigned a new site screening number. Subject numbers/enrollment numbers are assigned on Day -1 of the lead-in period to ensure only eligible subjects enter the study.

7. Treatment

7.1. Treatment Administered

Subjects will receive tirzepatide or placebo administered SC QW for 18 weeks (±1 week).

Table GPGU.2 shows the study treatments and dose escalation for tirzepatide and placebo.

Table GPGU.2. Study Treatments and Dose Escalation

Dose Escalation Schemes (dose in mg)				
Treatment	**Week 1-2[a]**	**Week 3-4 [a]**	**Week 5-8 [a]**	**Week 9-18 [a]**
Tirzepatide	1 × 2.5-mg PFS	1 × 5-mg PFS	1 × 10-mg PFS	1 × 15-mg PFS
Placebo	1 × PFS	1 × PFS	1 × PFS	1 × PFS

Abbreviation: PFS = prefilled syringe

[a] Interval may change based on visit window.

All treatments will be administered QW at the CRU. Dosing will occur at approximately the same time of day and day of the week every week in all groups. The actual time of dosing will be recorded in the subject's electronic case report form (eCRF). 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.

Whenever possible, IP administration should be carried out by the same personnel. Additional details are provided in Section 7.3 (Blinding). The personnel who dispenses or administers IP will be unblinded to IP. Any unblinded staff will not be performing any study assessments with subjects.

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

7.1.1. Packaging and Labeling

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

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

7.2. Method of Treatment Assignment

Subjects who meet all criteria for enrollment will be randomized in a 1:1 ratio to receive tirzepatide or placebo. Assignment to treatment will be determined by a randomization table with treatment codes.

7.2.1. Selection and Timing of Doses

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

7.3. Blinding

This study is a sponsor (study team members directly involved in study management)-, investigator-, and subject-blind study. Blinding will be maintained throughout the conduct of the study as described in the separate Blinding and Unblinding Plan. To preserve the blinding of the study for treatment allocation, all study site personnel, except site staff who dispense and administer study medication, will be blinded to treatment allocation. Tirzepatide and placebo will be dispensed by the site pharmacy in accordance to the randomization table. The site staff will take the necessary steps to ensure that subjects will remain blinded to the treatment administration.

If a subject's study treatment assignment is unblinded, the subject 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 subject to continue in the study. During the study, emergency unblinding should occur only by accessing the subject's emergency code.

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

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

7.4. Dose Modification

The subject should follow the planned dosing regimen. In the case of poor tolerability during the study, dosing can be interrupted temporarily following the guidance provided in Section 8.1.2 (Temporary Interruption of IP).

7.4.1. Special Treatment Considerations

7.4.1.1. Management of Hypoglycemia

Tirzepatide is an incretin which acts on the pancreatic β cell as a nonsecretagogue, therefore, the risk of hypoglycemia is very low. If hypoglycemia occurs, each episode should 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. For hypoglycemia reporting see Section 9.2.2.1 (Hypoglycemia).

7.5. Preparation/Handling/Storage/Accountability

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

Only subjects 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. Subjects will be considered compliant if they received at least 75% of their scheduled doses for each dosing interval (Weeks 1 to 2, Weeks 3 to 4, Weeks 5 to 8, and Weeks 9 to endpoint) 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 IP) will be taken into consideration. Subjects who are repeatedly (2 or more episodes) noncompliant with the maintenance dose will be reviewed by the investigator and sponsor to determine if the subject should continue treatment or be discontinued from the study.

7.7. Concomitant Therapy

Section 6.2 (Exclusion Criteria) provides excluded medications in this study prior to randomization (glucose-lowering and weight-lowering agents, systemic glucocorticoids). These medications are also not allowed during the treatment period. Erroneous use of excluded medications for up to 14 days would not qualify for discontinuation. If used for >14 days during the entire treatment period or for any duration during the final 4 weeks of the treatment period, these subjects will discontinue treatment immediately and will be discontinued from the study after performing the early termination (ET) and safety follow-up visits. Subjects who use any of the medications from these classes for <14 days any time prior to the final 4 weeks of the

treatment period will be requested to stop these treatments and will be allowed to continue in the study.

Subjects on stable concomitant medication at the time of study entry, other than those that are prohibited, should continue their regular, unchanged dose throughout the study. These medications include hormone replacement therapy (stable for at least 3 months), blood pressure medication, and statins.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. Acetaminophen (1 g, maximum 3 g/24 hours) may be administered at the discretion of the investigator for treatment of headaches or other conditions associated with pain. If the need for concomitant medication, other than acetaminophen arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly CP or CRP. Any medication used during the course of the study must be documented in source documents and transcribed into the eCRF.

7.7.1. Management of Subjects with Gastrointestinal Symptoms

The tirzepatide dose escalation schemes have been designed to minimize the development of intolerable GI symptoms. The dose escalation period for tirzepatide is considered to be 8 weeks to reach the 15-mg maintenance dose. Steady-state exposures are expected to be attained within 4 weeks of starting the 15-mg dose of tirzepatide. Treatment will be continued for 10 weeks (±1 week) after commencing the 15-mg maintenance dose. During the dose escalation period, every effort should be made by the investigator to be able to escalate and maintain subjects on the corresponding IP drug dosage.

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

- Advise subjects 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 subject needs.
- Temporarily interrupt study per guidance provided in Section 8.1.2 (Temporary Interruption of IP).

7.8. Treatment after the End of the Study

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

8. Discontinuation Criteria

Subjects discontinuing from the study prematurely for any reason should complete the ET visit and safety follow-up visit procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of IP:

- The subject requests to discontinue IP
- If a subject is inadvertently enrolled and it is determined that continued treatment with IP would not be medically appropriate (Section 8.1.3 Discontinuation of Inadvertently Enrolled Subjects)
- If a subject is diagnosed with acute or chronic pancreatitis after randomization
- If a subject is diagnosed with MTC after randomization
- If a subject 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 subject is diagnosed with a significant IP-related hypersensitivity reaction
- If a subject is diagnosed with any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent IP discontinuation is the appropriate measure to be taken
- If female subject becomes pregnant

Discontinuation of the IP for abnormal liver tests **should be considered** by the investigator when a subject meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or AST >8X ULN for healthy subjects
- ALT or AST >5X ULN 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 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>2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

- Drug-related vomiting requiring intravenous (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 IP (Section 8.1.2 Temporary Interruption of IP).

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

8.1.2. Temporary Interruption of Investigational Product

In certain situations after randomization, for example, if GI tolerability AEs occur, the investigator may need to temporarily interrupt IP. Temporary interruptions are allowed during the dose escalation period (ie, while the dose is lower than 15 mg) and not during the maintenance phase of dosing with 15 mg. Investigators should immediately inform the sponsor, that IP 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 subjects on IP and to restart IP after temporary interruption, as soon as it is assessed as safe to do so. The subject should resume study treatment administration at the scheduled dose level, per protocol. If 2 or more episodes of study interruptions occur in the same subject, these cases will be reviewed by the investigator (or his/her designee) and Lilly to assess the feasibility of the subject's further participation in the study. If IP 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 Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CP/CRP and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CP/CRP to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with IP.

8.2. Discontinuation from the Study

In addition to the situations that result in IP discontinuation described in Section 8.1.1 (Permanent Discontinuation from Study Treatment), subjects 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 subject should be discontinued from the study
  - if the subject, 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

- Subject Decision
  - the subject, or legal representative, requests to be withdrawn from the study.

8.3. Subjects Lost to Follow-up

A subject 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 subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the 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 approximate number and volume of invasive samples, for all sampling, during the study.

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

Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

In this study, the measures used to assess mechanisms of action of study treatments with respect to energy balance, lipid and carbohydrate metabolism, and insulin sensitivity are considered efficacy measures. The planned assessments will be performed at baseline and at the end of the treatment period at 18 weeks (±1 week).

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

9.1.1. Primary Efficacy Assessment and Procedure

The primary efficacy measure in the study is the change from baseline to Week 18 (Visit 20) in SMR for comparison of tirzepatide with placebo. The change in SMR will be measured in the respiratory chamber (whole-room calorimetry).

The SMR extrapolated to 24 hours will be calculated:

- SMR = average SMR*1440, where average SMR is the average minute by minute EE for the sleep time period.

9.1.2. Secondary Efficacy Assessments and Procedures

The change from baseline to Week 18 (Visit 20) for the following secondary efficacy measures will be used for secondary objectives to compare tirzepatide with placebo.

Secondary efficacy measure to assess the effect of study treatment on appetite, measured by visual analog scale (VAS), and food intake:

- appetite (VAS) for hunger, fullness, satiety, prospective food consumption, desire for specific foods, and the overall appetite score, assessed at fasting and during standardized mixed-meal tolerance test (sMMTT) (van Can et al. 2014; Flint et al. 2000; Flint et al. 2013);
- food intake assessed by ad libitum meal test (see Appendix 6, Section 6.5 for description of parameters);

Secondary efficacy measure to assess the effect of study treatment on EE:

- 24-hour EE, defined as the total EE for the 23-hour measurement period in the respiratory chamber extrapolated to 24 hours;

  EE = 3.941*total oxygen consumption [VO_2] + 1.106*total carbon dioxide production [VCO_2] – 2.17*[urinary nitrogen] (Weir JB deV 1949);

Secondary efficacy measure to assess the effect of study treatment on substrate oxidation rates:

- 24-hour respiratory quotient (RQ), defined as the ratio of VCO_2 to VO_2 during the 23-hour measurement period in the respiratory chamber and extrapolated to 24 hours;

  RQ = VCO_2/VO_2;

- sleep RQ, defined as the ratio of VCO_2 to VO_2 during sleep time points;
- RQ<0.80, defined as the cut point for high lipid oxidation of RQ; lipid oxidation will be calculated and corrected for protein oxidation; the total number of minutes with RQ <0.80, termed “lipid oxidation duration,” during each 23-hour measurement period will be recorded; protein oxidation will be determined from urine nitrogen that will be collected during 2 periods for each calorimeter day;

- substrate oxidation for fat, protein, and carbohydrates (Frayn 1983; Jéquier et al. 1987);

  Protein Oxidation = 6.25*[urinary nitrogen]

  Fat Oxidation = 1.689*[VO_2] – 1.689*[VCO_2] – 0.324*[protein oxidation]

  Carbohydrate Oxidation = 4.113*[VCO_2] – 2.907*[VO_2] – 0.375*[protein oxidation]

Secondary efficacy measure to assess the effect of study treatment on BW and body composition:

- BW (kg)
- body fat-free mass (kg) measured by the difference between BW and body fat mass
- body fat mass (kg) measured using DXA
- Percentage of body fat mass measured using DXA

Secondary efficacy measure to assess the effect of study treatment on lipid metabolism:

- triglycerides, cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and HDL cholesterol, free fatty acid (FFA), glycerol, 3-hydroxybutyrate, and acylcarnitines assessed during sMMTT;
- apolipoprotein B-48 (ApoB-48), apolipoprotein B-100 (ApoB-100), apolipoprotein C-III (ApoC-III), and lipoprotein lipase (LPL) during sMMTT.
- leptin, adiponectin, insulin-like growth factor binding protein (IGFBP) 1 and 2 at fasting

Secondary efficacy measure to assess the effect of study treatment on insulin sensitivity:

- fasting insulin resistance as measured by the HOMA2 method (HOMA2-IR) (Hill et al. 2013) and postprandial insulin sensitivity indices (Matsuda [Matsuda and DeFronzo 1999], Oral Glucose Insulin Sensitivity [OGIS] Index [Mari et al. 2001], and Stumvoll Index [Stumvoll et al. 2000]); assessed during sMMTT (Hill et al. 2013);

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

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

9.1.3. Exploratory Efficacy Assessments and Procedures

The change from baseline to Week 18 (Visit 20) for following exploratory efficacy measures will be used for exploratory objectives to compare tirzepatide with placebo.

Exploratory efficacy measure to assess the effect of study treatment on GIPR signaling, lipid metabolism, carbohydrate metabolism, and insulin signaling pathways in SC adipose tissue:

- markers of GIPR signaling, lipid metabolism, carbohydrate metabolism, and insulin signaling pathways as measured in exploratory messenger ribonucleic acid (mRNA) expression, lipidomics, metabolomics, or targeted protein assays of SC adipose tissue biopsy samples, receptor expression, signal transduction, and metabolic changes in adipose tissue.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects 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 subject.

The investigator is responsible for the appropriate medical care of subjects 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 subject to discontinue the IP before completing the study. The subject should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

The investigator will record all AE/SAE information in the eCRF. After the ICF is signed, study site personnel will record, via eCRF, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

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

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

If a subject'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 subject 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 subject 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 subjects once they have discontinued from and/or completed the study (the subject summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/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

Subjects will be trained during Visit 2 about signs and symptoms of hypoglycemia and how to treat hypoglycemia.

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 subject 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 subject 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 eCRF and reported to Lilly as an SAE.

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

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

9.2.2.2. Pancreatitis

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

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

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the local laboratory. Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the subject must discontinue IP, and will be discontinued from the study after completing all ET and follow-up procedures. A review of the subject'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 IP.

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

9.2.2.3. 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 ≥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.

Subjects 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 subject 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. Subjects 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. Investigational product should be discontinued in situations when post randomization calcitonin value is ≥35 pg/mL. If the calcitonin value decrease below 35 pg/mL on repeat tests, IP 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 subject 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 subjects who require additional endocrine assessment because of increased calcitonin concentration per criteria provided in this section, data from the additional assessment will be collected in the specific section of the eCRF.

9.2.2.4. Major Adverse Cardiovascular Events

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

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

9.2.2.5. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders should be further evaluated. Subjects 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.

9.2.2.6. 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 IP via a eCRF created for this purpose. Additional serum samples should also be collected as outlined in Section 9.6.1 (Immunogenicity Assessments). IP should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to IP. IP may be restarted when/if it is safe to do so, in the opinion of the investigator. If IP is permanently discontinued, the subject will receive another glucose-lowering treatment, judged by the investigator to be appropriate based on the subject's clinical status, and will be discontinued from the study (Section 8.1.1 Permanent Discontinuation from Study Treatment).

9.2.2.7. Injection-Site Reactions

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

- an AE from a subject, or
- a clinical observation from an investigator.

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

- edema
- erythema
- induration
- itching
- pain

Injection-site reactions will be collected on the eCRF created for these events. At the time of AE occurrence, unscheduled samples may be collected for measurement of tirzepatide ADA and tirzepatide concentration if the event is suspected to be immune related by the investigator.

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

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

9.2.2.8. 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.

9.2.2.9. Severe Gastrointestinal Adverse Events

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

9.2.2.10. 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. Subjects 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. Subjects should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

9.2.2.11. Major Depressive Disorder/Suicidal Ideation Monitoring Using the C-SSRS and PHQ-9 Questionnaires

Overweight and obese patients are at an increased risk of depression (Luppino et al. 2010). Depression can increase the risk of suicidal ideation and behavior. Therefore, study subjects will be screened at trial entry and monitored during the study for depression, and suicidal ideation and behavior.

Baseline and treatment-emergent assessment of depression, suicidal ideation, and behavior will be monitored during the study using the C-SSRS and PHQ-9 as specified in the Schedule of Activities (Section 2). Before administering the C-SSRS or the PHQ-9, study site personnel will question the participant about any change in the preexisting condition(s) and the occurrence and nature of any AEs. These questionnaires should be administered after assessment of AEs. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

Nonserious AEs obtained through the questionnaire are recorded and analyzed separately. Only *serious* AEs elicited through the C-SSRS or PHQ-9 are to be recorded as AEs via the eCRF and reported to Lilly or its designee within 24 hours as SAEs.

The C-SSRS (Columbia Lighthouse Project [WWW]) is a scale that captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The tool was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events.

The PHQ-9 is a validated self-report screening tool that assesses the presence and intensity of depressive symptoms. The PHQ-9, which incorporates the 9 Diagnostic and Statistical Manual-IV depression criteria as “0” (not at all) to “3” (nearly every day), was developed for use in primary care settings (Kroenke et al. 2001).

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.

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

9.3. Treatment of Overdose

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

9.4. Safety

9.4.1. Laboratory Tests

For each subject, laboratory tests to assess PD and safety of study treatment will be performed throughout the study according to Section 2 (Schedule of Activities). A detailed list of laboratory analytes is provided in Appendix 2. Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the subject receives the first dose of the IP should be reported to Lilly, or its designee, as an AE via eCRF.

9.4.2. Vital Signs

Vital sign measurements should be taken before obtaining an ECG tracing, at visits where required (see Section 2, Schedule of Activities), and before collection of blood samples for laboratory testing. For each parameter, 2 measurements will be taken using the same arm. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of blood pressure measurements. The arm used for the blood pressure measurement should be supported at heart level. Each measurement of sitting heart rate and blood pressure is to be recorded in the eCRF. Any AE related to changes in blood pressure and heart rate should be reported, per requirements provided in Section 9.2.

9.4.3. Electrocardiograms

For each subject, 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. Subjects must be supine for approximately 5 to 10 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 subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject 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 subject can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in subject 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 subject receives the first dose of the IP 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:

- trends in safety data
- safety laboratory analytes including glucose, amylase, and lipase
- serious and nonserious AEs, including AEs of interest (GI events, hypoglycemia, injection-site reactions, hypersensitivity reactions) and reported and adjudicated pancreatitis

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 subject 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. 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 two 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 a SAE

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), 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 subjects are not planned.

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

9.6. Pharmacodynamics

The sample(s) will be stored for up to a maximum of 1 year after the last subject visit for the study at a facility selected by the sponsor.

Briefly, PD assessments will include parameters of energy expenditure, appetite (appetite sensations and desire for specific foods) and food intake, substrate utilization (oxidation), metabolic flexibility, and insulin sensitivity. A detailed description of PD efficacy measures is provided in Section 9.1 (Efficacy Assessments). A description of procedures for obtaining the samples for PD parameters is detailed in Appendix 6.

9.6.1. Immunogenicity Assessments

For immunogenicity testing, venous blood samples of approximately 10 mL will be collected from each subject 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 where relevant. Detailed instructions on the sample collections will be provided by Lilly or its designee. The actual date and 24-hour clock time of each sampling will be recorded.

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

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

Subjects who have clinically significant TE-ADA at early discontinuation or at the safety follow-up visit, may be asked to return for additional follow-up testing.

A clinically significant TE-ADA will be defined as any TE-ADA with:

- a high titer (≥1280) or an increasing titer from last measured value, and/or
- an association with a moderate-to-severe injection site reaction or systemic hypersensitivity AE

Every attempt should be made to contact subjects for the follow-up immunogenicity assessment; however, if subjects 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 subject visit, or for a shorter period if local regulations and IRBs 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 will be measured according to the schedule provided in Section 2 (Schedule of Activities). Subjects 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. Weight will be measured twice on each scheduled occasion, with the subject stepping off the scale between measurements. A third measurement will be made if the first 2 measurements are >0.5 kg apart. The 2 closest measurements will be recorded. Wherever possible, the same scale will be used for all weight measurements throughout the study, and the scale will not be moved or recalibrated. Weight measurements will be recorded in the source document and the eCRF.

Waist circumference will be measured at the midpoint between the inferior border of the rib cage and the superior aspect of the iliac crest. The subject will stand in a straight, upright position with feet together and arms at the side. The area measured will be cleared of all clothing other than undergarments. The measurement should be taken at the end of normal expiration. Two separate measures will be taken and steps are repeated until 2 measurements are obtained within 0.5 cm of each other.

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 type 2 diabetes, obesity, and/or diabetic complications. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or IRBs 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 subject response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

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

Samples will be used for research on the drug target, disease process, variable response to tirzepatide, pathways associated with T2DM, obesity, and/or diabetic complications, mechanism of action of tirzepatide, and/or research method, or for validating diagnostic tools or assay(s) related to type 2 diabetes, obesity, or diabetic complications.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or IRBs 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

Up to 56 subjects are planned to be randomized so that approximately 46 subjects complete the study assuming 15% discontinuation rate. These 56 subjects will be randomized to QW tirzepatide or placebo in a 1:1 ratio. The estimated variability of the change in SMR from baseline is 117 kcal/day (Heilbronn et al. 2006). With an expected treatment difference of 100 kcal/day, this provides at least 80% power for the comparison of tirzepatide versus placebo based on 2 sample t-test using 2-sided test at alpha level of 0.05, and at least 85% power for the sensitivity analysis where only patients who achieve the target weight loss and are considered at least 90% compliant will be included for the assessment of the primary endpoint.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A summary of subject disposition will be provided at the end of the study. All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation from study will be given.

10.2.2. Study Participant Characteristics

Demographic and baseline characteristics will be summarized by treatment group. These data will be summarized using standard descriptive statistics.

10.2.3. Treatment Compliance

Treatment compliance will be listed and summarized using standard descriptive statistics.

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 subjects who receive at least 1 dose of the IP and have evaluable data. Sensitivity analyses may be performed as deemed necessary.

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

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

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

The incidence of AEs for each treatment will be presented by severity and by association with IP as perceived by the investigator. Adverse events reported to occur prior to study entry will be

distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

All AEs and SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters (including tirzepatide ADA), vital signs, TEAEs (including TEAEs of special interest), and SAEs. Summary statistics will be presented by treatment for the safety measures. Additionally, analyses may be performed if warranted upon review of the data.

Vital signs will be summarized with respect to observed values and change from baseline by treatment at each time point using descriptive statistics. The analysis details will be provided in SAP.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Sparse PK samples will be collected across the 18-week (±1 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 based on historical understanding. Additional tirzepatide PK parameters will not be derived.

10.3.2.2. Pharmacokinetic Statistical Inference

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

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

The following parameters will be measured at baseline and Week 18 (Visit 20), respectively, to assess the effect of study treatments on energy balance:

Measures of energy expenditure:

- SMR
- 24-hour EE

Measures of substrate oxidation (fat, protein, and carbohydrates):

- 24-hour RQ
- Sleep RQ
- Duration of periods with RQ<0.80
- Fat, protein, and carbohydrates oxidation rates

Measures of appetite and 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.
- Food intake assessed by ad libitum meal test

For other PD parameter estimations, please see Section 9.1. Further details will be described in the SAP.

10.3.3.2. Pharmacodynamic Statistical Inference

The primary endpoint (SMR) will be analyzed using an analysis of covariance model (ANCOVA) to compare the effect of tirzepatide versus placebo. The dependent variable to be used in the model will be the change from baseline to 18 weeks in SMR. The independent variables will include treatment as a factor, baseline SMR and body composition parameter(s) as covariates. The primary analysis will be performed in all randomized subjects with evaluable data (modified intent-to-treat [mITT] population). Similar analysis will also be performed in subjects who reach the BW target range of −10% (±2%) at Week 18 as a sensitivity analysis.

Other PD parameters that are scheduled to be measured only once postbaseline will be analyzed using a similar ANCOVA model with baseline measurement and treatment group as covariates. For parameters that are measured in the respiratory chamber, an adjustment for body composition parameter(s) as covariates may be applied if deemed appropriate. If the response is positive for all subjects and highly skewed, a log-transformation may be considered. Other parameters that are positive and skewed may be log-transformed.

The PD parameters that are scheduled to be measured at least twice postbaseline will be analyzed using a mixed-model repeated-measure method with restricted maximum likelihood estimation. The model will include the treatment, visit, and treatment-by-visit interaction as fixed effects, baseline value of the dependent variable as a covariate, and subject as a random effect. An unstructured variance-covariance matrix will be used to model the within-subject effects.

All PD analyses will performed in the mITT population and selected analyses also on-BW-target population. All analyses will show least squares means of each treatment and the treatment difference in the original scale as well as standard error and 95% confidence interval. All tests will be done at the 2-sided 0.05 α level unless otherwise specified.

10.3.4. Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting ADA and with TE-ADA+ to tirzepatide will be tabulated. Treatment-emergent ADA are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution (1:10) if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE-ADA+

subjects, the distribution of maximum titers will be described. The frequency of neutralizing antibodies if performed, will be tabulated for TE-ADA+ subjects. If cross-reactivity to native GLP-1 and GIP or neutralizing antibodies against native GLP-1 and GIP assays are performed, the frequency of each will be reported.

10.3.5. Interim Analyses

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

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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 subject 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
ANCOVA	analysis of covariance model
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
$AUC_{0-240min}$	area under the concentration versus time curve from time zero to 240 minutes after start of the meal
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 subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
CO_2	carbon dioxide
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	Clinical Pharmacologist
CRP	Clinical Research Physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CV	Cardiovascular
DXA	dual energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	electronic case report form
EE	energy expenditure
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ET	early termination
FFA	free fatty acid
GCP	good clinical practice
GI	Gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIPR	glucose-dependent insulinotropic polypeptide receptor
GIPRA	glucose-dependent insulinotropic polypeptide receptor agonism
GLP-1	glucagon-like peptide 1
GLP-1R	glucagon-like peptide 1 receptor
GLP-1RA	glucagon-like peptide 1 receptor agonism

HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
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
ICH	International Council for Harmonization
IGFBP	insulin-like growth factor binding protein
informed consent	A process by which a subject 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 subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB	institutional review board
IV	Intravenous
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
LDL-C	low-density lipoprotein cholesterol
LPL	lipoprotein lipase
MAD	multiple-ascending dose
MEN 2	multiple endocrine neoplasia syndrome type 2
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

MTC	medullary thyroid carcinoma
PFS	prefilled syringes
PG	plasma glucose
PHQ-9	Patient Health Questionnaire-9
PK/PD	pharmacokinetic/pharmacodynamics
PR	pulse rate
QT	QT interval
QTc	QT interval corrected for heart rate
QW	once weekly
randomize	the process of assigning subjects to an experimental group on a random basis
RMR	resting metabolic rate
RQ	respiratory quotient
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.
sMMTT	standardized mixed-meal tolerance test
SMR	sleep metabolic rate
SUSARs	suspected unexpected serious adverse reactions
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
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
VCO_2	total CO_2 production
VO_2	total oxygen consumption
VLDL-C	very low-density lipoprotein cholesterol
WOCBP	woman of childbearing potential

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
  - Absolute counts of:
    - Neutrophils
    - Lymphocytes
    - Monocytes
    - Eosinophils
    - Basophils
    - Platelets

Urinalysis
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Leukocytes
- Microscopy[a]

Clinical Chemistry
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Phosphorus
- Glucose (fasting)
- Blood urea nitrogen
- Uric acid
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Creatinine
- Lipase (fasting)
- Amylase
- Triglyceride[b]
- Total cholesterol[b]
- Hemoglobin A1c

Endocrine
- Follicle-stimulating hormone[a]
- Calcitonin

Serology[c]
- Hepatitis B surface antigen
- Hepatitis C antibody, hepatitis C RNA[d]
- HIV antibody

- Pregnancy test (urine, serum)[e]
- Drug and alcohol screen[f]

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

Note: Results of these assays will be validated by the 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 as a protocol violation.

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

[b] Triglyceride and total cholesterol concentrations in the safety panel will not be required on the days that the lipid panel is performed.

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

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

[e] Pregnancy tests will be performed for women of childbearing potential. Serum pregnancy test is done at screening and follow-up and urine pregnancy is performed on Day -4 and Day 122.

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

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the subject 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 subject 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 subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject'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 subjects. 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 institutional review board (IRB) was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

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

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

Data Quality Assurance

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

- provide instructional material to the study site, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the electronic case report form (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 subject 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 IRBs 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 subject personal information collected will be provided in a written document to the subject by the sponsor.

Study and Site Closure

Discontinuation of Study Site

Study site participation may be discontinued if Lilly or its designee, the investigator, or the IRB 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 subjects in consultation with Lilly or its designee Clinical Research Physician.

Hepatic Monitoring Tests

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

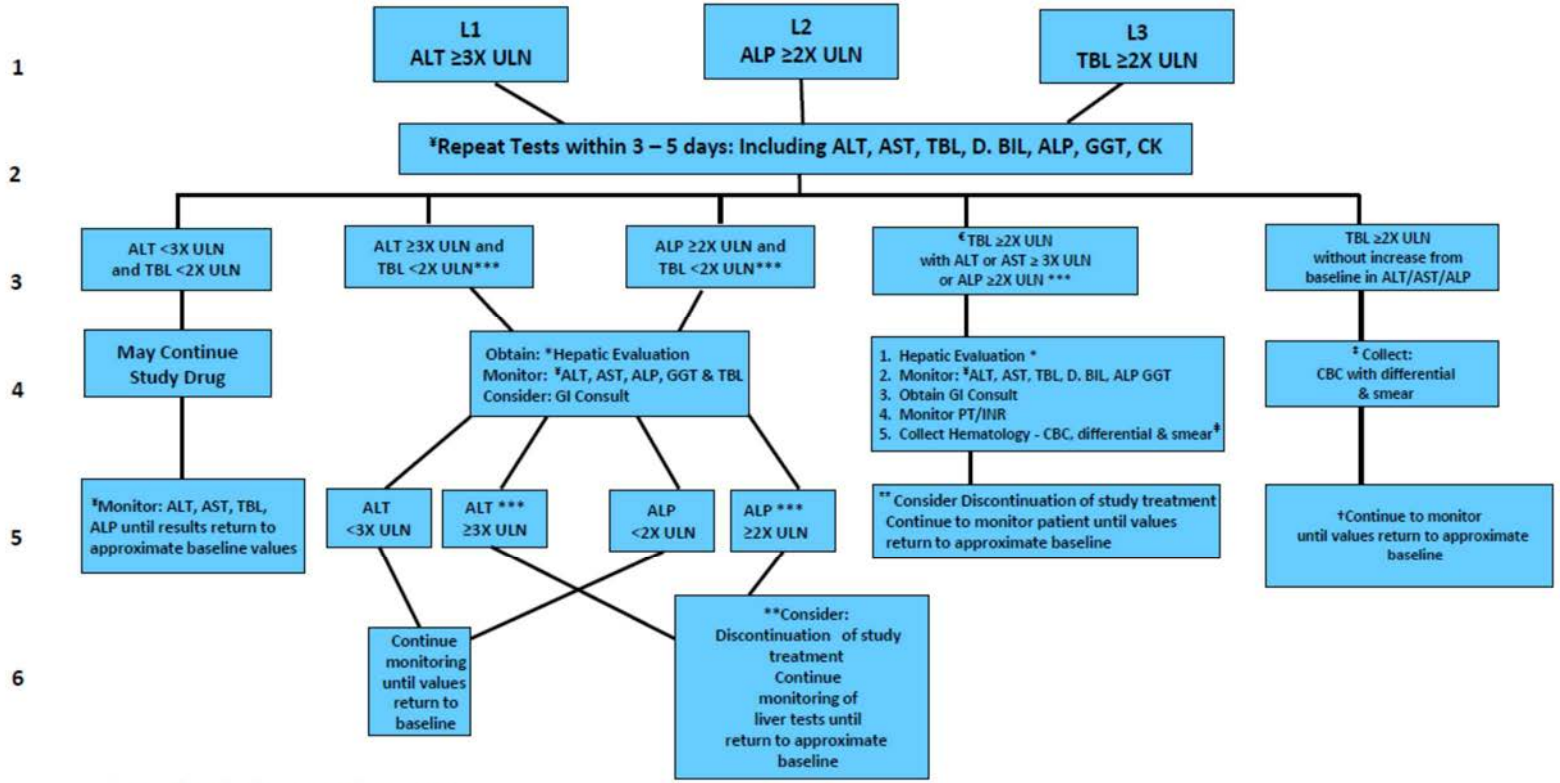
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[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-GPGU Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a,b]	24	1	24
Safety laboratory tests (including hemoglobin A1c and calcitonin)[a,b]	15	5	75
Tirzepatide pharmacokinetics[c]	3	5 (+3)	24
Pharmacodynamics[c]			
3-hydroxybutyrate (fasted)	2	2	4
3-hydroxybutyrate (fasted) during sMMTT	2	6 × 2	24
Acylcarnitine (fasted)	5	2	10
Acylcarnitine (fasted) during sMMTT	5	6 × 2	60
Adiponectin (fasted)	2	2	4
Adiponectin (fasted) during sMMTT	2	1 × 2	4
Free fatty acid (fasted)	2	2	4
Free fatty acid (fasted)during sMMTT	2	6 × 2	24
Glucose (fasted)	2	2	4
Glucose (fasted) during sMMTT	2	11 × 2	44
Glycerol	2	2	4
Glycerol during sMMTT	2	6 × 2	24
IGFBP 1 and 2 (fasted)	5	2	10
IGFBP 1 and 2 (fasted) during sMMTT	5	1 × 2	10
Insulin (fasted)	2.5	2	5
Insulin (fasted) during sMMTT	2.5	9 × 2	45
Leptin (fasted)	2	2	4
Leptin (fasted) during sMMTT	2	1 × 2	4
Lipid panel (fasted): TG, total cholesterol, LDL-C, VLDL-C, HDL-C	7.5	2	15
Lipid panel (fasted): TG, total cholesterol, LDL-C, VLDL-C, HDL-C during sMMTT	7.5	6 × 2	90
Lipid panel (fasted): ApoB-48, ApoB-100, ApoC-III	3.5	2	7
Lipid panel (fasted): ApoB-48, ApoB-100, ApoC-III during sMMTT	3.5	6 × 2	42
Lipid panel: LPL	2.5	2	5
Lipid panel: LPL during sMMTT	2.5	6 × 2	30
OGTT at screening – glucose (2 mL) and Insulin (2.5 mL)[b]	4.5	2	9

continued

Protocol I8F-MC-GPGU Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Immunogenicity[c]	10	5 (+3)	80
Pharmacogenetics[c]	10	1	10
Nonpharmacogenetic stored sample[c] (fasted)	11	5	55
Total			754
Total for clinical purposes [rounded up to nearest 10 mL]			760

Abbreviations: ApoB-48 = apolipoprotein B-48; ApoB-100 = apolipoprotein B-100; ApoC-III = apolipoprotein C-III; HDL-C = high-density lipoprotein cholesterol; IGFBP = insulin-like growth factor-binding protein; LDL-C = low-density lipoprotein cholesterol; LPL = lipoprotein lipase; OGTT = oral glucose tolerance test; 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. Triglycerides and total cholesterol will be excluded on study days where a lipid panel pharmacodynamics sample is collected.

[b] Performed on site or in a local laboratory.

[c] Performed at a central or referral laboratory, including for storage.

Appendix 6. Efficacy Assessments

6.1. Appetite Visual Analog Scale

The aim of the appetite visual analog 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 9.1.2 (Secondary Efficacy Assessments and Procedures).

Subjects will be asked to rate their feelings of hunger, satiety, fullness, prospective food consumption, and desire for specific foods on a 10-cm (100-mm) line, or a 100 unit line represented on a computer screen; anchored by verbal descriptors, usually "not at all" and "extremely." 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?

Subjects will see the line on a validated electronic device that will record the subject's rating on the respective lines, ranging from 0 ("not at all") to 100 ("extremely"). In the case of technology failure, pen-and-paper VAS will be used and will include a 10-cm line. Only provided or printed (not copied) paper VAS can be used, as copying them alters the length line. For assessment of postprandial appetite sensations and desire for specific foods during standardized mixed-meal tolerance test (sMMTT), the scores will be obtained immediately prior to the start of the meal (time point -10), 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).

6.2. Retrospective Visual Analog Score

Visual analog score will be used to measure average ratings of appetite that subjects experienced over the past week. This method of collecting VAS data has been found to be consistent with daily assessments of satiety (Womble et al. 2003). These VAS items will be identical to those that are collected on the day of food intake testing, though the instructions to the subjects will be modified, as detailed here:

- How hungry did you feel over the past week?
- How satisfied did you feel over the past week?
- How full did you feel over the past week?
- How much food did you think you could eat over the past week?

6.3. Food Craving Inventory

The 33-item food craving inventory (FCI) (White et al. 2002) will be used to measure cravings for specific food groups. The measure consists of 5 empirically derived factors: high fats, sweets, carbohydrates/starches, fast food fats, and fruits and vegetables. The FCI is scaled in a frequency format assessing the frequency of cravings for particular foods. All items are scored in the following manner:

- Never = 1
- Rarely = 2
- Sometimes = 3
- Often = 4
- Always = 5

It is noted that the fruits/vegetables scale was not included in the White et al. paper (White et al. 2002), though support for the scale was obtained and will be included in the study.

6.4. Food Preference Questionnaire

The Food Preference Questionnaire (FPQ) (Geiselman et al. 1998) assesses preferences for 72 foods in a 2 (high-fat, low-fat) by 3 (high-simple sugar, high-complex carbohydrate, low-carbohydrate/high-protein) matrix. Subjects rate each food hedonically on a 9-point Likert scale by rating how much they like each food, with 1 = dislike extremely, 5 = neither like nor dislike, and 9 = like extremely. The FPQ has established reliability and validity (Geiselman et al. 1998).

6.5. Ad Libitum Food Intake Test

Efforts will be made to schedule the baseline and follow-up food intake tests during the luteal phase of female subjects' menstrual cycle, as assessed by the Menstrual Cycle Questionnaire.

Ad libitum intake will be recorded at lunch and dinner on Day -4 prior to entering the respiratory chamber. Subjects will complete a test lunch at 1200 hours. The test lunch will consist of ad libitum sandwiches, potato chips, cookies, water, and a choice of a sugar and artificially sweetened soda or tea. Dinner will occur at 1830 hours and will consist of the Macronutrient Self-Selection Paradigm (MSSP) (Geiselman et al. 1998). The MSSP provides subjects with a buffet meal that consists of 18 foods that vary in a 2 (High-Fat, Low-Fat) by 3 (High-Simple Sugar, High-Complex Carbohydrate, Low-Carbohydrate/High-Protein) matrix, similar to the FPQ. Subjects will not be allowed to eat between test meals but can drink water.

Subjects will be instructed that they can eat as much or as little as they wish and that they should alert a site staff member when they are finished eating, at which time the subject will leave the test meal. Site staff will check on the subject after 25 minutes and terminate the session after 40 minutes if the subject does not end the session.

Food intake will be quantified by precisely weighing foods before and after the test meals. Energy and nutrient intake will be calculated by linking each food to a match in the United States Department of Agriculture (USDA) Food and Nutrient Database for Dietary Studies (USDA 2018) or data from the food producer/manufacturer.

Food intake will be quantified separately for lunch and dinner, and combined for lunch and dinner. The primary food intake variables are: 1) energy (kcal) intake, and 2) gram intake. Secondary food intake variables are: 1) grams of carbohydrate, protein, and fat (saturated and unsaturated) consumed, and 2) percent of energy (kcal) from carbohydrate, protein, and fat (saturated and unsaturated) consumed.

6.6. Whole Room Calorimetry

Total carbon dioxide (CO_2) production (VCO_2) and total oxygen consumption (VO_2) will be sampled and measured at 1-minute intervals over 23 hours in a respiratory chamber (whole-room calorimeter) as shown in Table GPGU.3.

This will be used to calculate respiratory quotient (RQ), energy expenditure (EE), and substrate oxidation rates. The chamber is a room approximately 27 000 liters with 2 windows, a bed, a desk and chair, a computer with internet access, a TV/DVD, a telephone, toilet facilities, a motion sensor, and a video camera. Subjects will be able to contact the nursing or chamber personnel at any time using the intercom or telephone, and will be monitored for safety and compliance using the video camera.

After entering the respiratory chamber at approximately 0800 hours, subjects will be instructed to rest awake on the bed for the first 30 minutes in the chamber, after which breakfast will be provided (approximately 0835 hours). Subjects will then be allowed approximately 4 hours of free time, after which lunch will be provided (approximately 1230 hours). Lunch will be followed by approximately 6.5 hours of free time until dinner is served at approximately 1900 hours. The 3 meals will be ingested over a maximum 30-minute period. During periods of free time, subjects will not be allowed to sleep, and the intensity of any physical activity can be no higher than walking around the chamber or stretching (no push-ups or sit-ups). After dinner,

subjects will be given more free time until "lights out" at approximately 2230 hours. Urine will be collected during the entire stay (2 times in 23 hours) in the respiratory chamber. Subjects will be awakened at approximately 0615 hour and instructed to void their bladder and then return to the bed. Subjects will then be instructed to rest awake on the bed for approximately 30 minutes. At the end of the 23-hour measurement period, the subjects will be removed from the chamber.

On the first day of the 2-day stay, approximate energy balance will be maintained by the calculation of the average EE of the first 7 hours in the chamber and used to predict 24 hour EE using previously determined equations (Lam et al. 2014). Calories provided with the dinner meal will be adjusted so that energy intake equals predicted 24-hour EE, rounded to the nearest 100 calories. On the second day in the chamber, subjects will be fed the exact amount of calories they spent on the first day.

Activity counts will be recorded using a motion detector for the entire 23-hour measurement period and will be used to determine activity driven effects on EE and RQ. Average EE and RQ will be calculated for rest periods, sleep, and the entire 23-hour measurement.

Table GPGU.3. Whole-Room Calorimeter Respiratory Quotient Measurements

Approx. Hour[a]	Nominal Timing[a] (hour)	Procedure: Activity	VCO_2 and VO_2	Activity Monitoring	Urine Collection[b]
0800	0	Start of RQ measurement: resting on bed no sleep	Sampled at 1 minute intervals	Continuous activity monitoring	Entrance and exit into whole-room calorimeter
0835	0.5	End of bed rest: breakfast start			
0900	1	Breakfast end: free time start[c]			
1230	4.5	End of free time: lunch start			
1300	5	Lunch end: free time start[c]			
1900	11	End of free time: dinner start			
1930	11.5	Dinner end: free time start[c]			
2230	14.5	End of free time: lights out and bedtime			
0000	16	Sleep RQ measurement start			
0615	22.25	Sleep RQ measurement end Subjects woken: void bladder			
0630	22.5	Resting on bed no sleep			
0700	23	End of bed rest. End of RQ measurement.			

Abbreviations: RQ = respiratory quotient; VCO_2 = carbon dioxide production; VO_2 = oxygen consumption.

[a] Subjects will enter the whole-room calorimeter in the morning at approximately 0800 hours after an approximately 10-hour overnight fast. The actual times given are approximate as the timing depends on the start time of the laboratory procedure.

[b] Urine to be collected over 2 periods for each calorimeter day over 23 hours from entrance to exit. Start and end times of urine collections must be recorded, together with total volume of urine produced in each period. A 15 mL aliquot will be retained for analysis of urinary nitrogen.

[c] In "free time," subjects will not be allowed to sleep, and the intensity of any physical activity can be no higher than walking around the chamber or stretching (no push-ups or sit-ups), until lights-out.

6.7. Oral Glucose Tolerance Test

An oral glucose tolerance test (OGTT) will be performed during screening according to the Schedule of Activities (Section 2).

Subjects shall maintain adequate carbohydrate intake 3 days before the scheduled OGTT. Subjects shall fast for at least 10 hours overnight before administration of the glucose. A 75-g glucose dose will be given orally. Subjects should consume the glucose load within 5 minutes. Blood samples will be drawn for assessment of glucose and insulin at 0 hours (ie, prior to the oral glucose) and 2 hours after the initiation of the glucose load.

6.8. Body Composition Measurements

Body composition will be determined using dual energy X-ray absorptiometry (DXA) scans (GE iDXA™ whole-body scanner). Dual energy X-ray absorptiometry allows the noninvasive assessment of soft tissue composition by region with a precision of 1% to 3%. Subjects will lie in a supine position on the densitometer table in a hospital gown while the scanner emits low energy X-rays and a detector passes along the body. Two distinct energies are used to determine body mineral and soft tissue content. An attenuation ratio is determined from a known tissue content. Variations of the attenuation ratio determine the fat content of the tissue at each pixel thereby calculating the percentage body fat. The scans are analyzed with enCORE Windows-based user interface. The coefficient of variation for the body composition measurements of total body lean mass, fat mass, and percentage body fat is 0.5%, 0.8%, and 0.8%, respectively. The DXA scan will also be used to estimate muscle mass (Kim et al. 2004). The scan takes 7 to 13 minutes and the radiation dose is less than 1 mrem, which is less than a chest X-ray, or equal to about 12 hours of background radiation from the sun. The DXA scan will be performed in duplicate at each scheduled time point. The average value from the 2 tests will be used in parameter estimation and statistical analyses.

6.9. Standard Mixed-Meal Tolerance Test

The key objectives of the sMMTT are to assess α and β cell function and indirectly insulin sensitivity under physiological conditions. The parameters that will be obtained are listed in Section 9.1.2 (Secondary Efficacy Assessments and Procedures). The measurements that will be collected during the test and then used for parameter calculations are provided in Table GPGU.4.

Subjects will fast overnight for at least 10 hours before the start of the sMMTT.

Before the start of sMMTT, an intravenous (IV) cannulas (catheter) will be inserted in one of the subject's arm for serial blood sampling.

The sMMTT will be initiated between 0700 to 0730 hours with the subject in a seated position. The start of the meal will be defined as time point 0 (zero). The first blood sample collection time point will be at -10 minutes. Immediately after the second blood sample (-1 minute), subjects will consume a fixed nutrient ratio mixed meal (approximately 23% fat, 33% protein, and 47% carbohydrate) consisting of High Protein Boost® over a 5-minute period maximum. The remaining blood samples will be collected over the next 4 hours for measurement of the

parameters of interest per schedule provided in Table GPGU.4. Sampling times may be adjusted as necessary.

During the baseline assessment, the individual subjects' characteristics (weight, height, age, and gender) will be used for the calculation of sedentary 24-hour energy expenditure based on the Lam equation (Lam et al. 2014). A standard physical activity level (PAL) of 1.2 (20%) will be added to the calculated 24-hour sedentary energy expenditure to estimate daily energy requirement. The sMMTT will account for 35% of the estimated daily energy requirement.

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

The subject 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.

After the end of the meal test procedure, the subject will be served a meal. All calculations and analyses are described in Section 9.1.2 (Secondary Efficacy Assessments and Procedures) and Section 10.3 (Statistical Analyses) and in the statistical analysis plan.

Table GPGU.4. Standardized Mixed-Meal Tolerance Test

Nominal Timing (Minutes)	Meal	Sampling for Analysis					VAS
		Blood Glucose	Insulin	3-hydroxybutyrate, Acylcarnitines, FFA, Glycerol	Leptin, Adiponectin, IGFBP 1 and 2	Lipid Panel[a]	
-10		X	X	X	X	X	X
-1		X	X				
0	Start						
5	Stop						
15		X	X				
30		X	X				
60		X	X	X		X	X
90		X	X	X		X	
120		X	X	X		X	X
150		X					
180		X	X	X		X	X
210		X					
240		X	X	X		X	X

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

[a] 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.

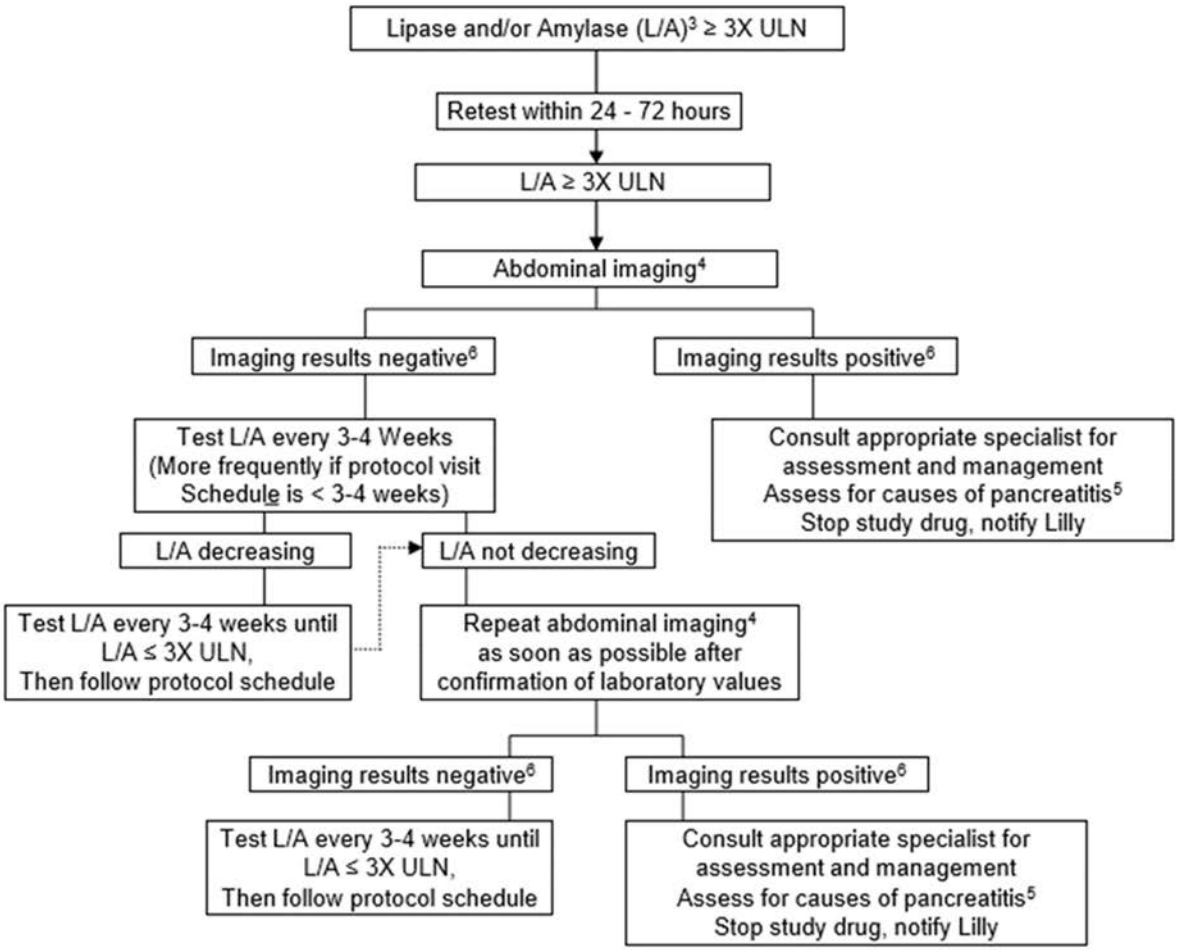
6.10. Adipose Tissue Biopsy

Two grams of adipose tissue will be collected with the Mercedes lipoaspirate technique under sterile conditions and local anesthesia. After cleansing the skin with povidone-iodine solution and placing a sterile drape, topical anesthesia containing 50%/50% ratio of lidocaine 2%/bupivacaine 0.5% will be administered. Samples will be taken from the subcutaneous abdominal region. The tissue will be divided into 4 aliquots and each aliquot will be immediately placed in sterile tubes for processing. Adipose tissue will be frozen upon collection using liquid nitrogen. Two grams of adipose tissue will allow for the assessment of tirzepatide effects on changes in markers of glucose-dependent insulinotropic polypeptide receptor signaling, lipid metabolism, carbohydrate metabolism, and insulin signaling pathways in exploratory assays.

Appendix 7. Pancreatic Monitoring

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

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



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

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

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

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

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

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

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

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

Appendix 8. Protocol Amendment I8F-MC-GPGU(f) Summary - A Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Effect of Once-Weekly Tirzepatide on Energy Expenditure and Food Intake in Obese Subjects

Overview

Protocol I8F-MC-GPGU(e), A Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Effect of Once-Weekly Tirzepatide on Energy Expenditure and Food Intake in Obese Subjects, has been amended. The new protocol is indicated by Amendment (f) and will be used to conduct the study in place of any preceding version of the protocol. This amendment is not considered to be substantial. The overall change and rationale for the change made to this protocol:

- To clarify that subjects with current diagnosis of any form of diabetes will be excluded from the study.
- The primary efficacy analysis was corrected and clarified regarding adjustment for body composition.

Revised Protocol Sections

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

1 Protocol Synopsis

Statistical Analysis:
The primary PD parameter for analysis is sleep metabolic rate (SMR) measured using whole-room indirect calorimetry (respiratory chamber), which will be analyzed using an analysis of covariance model (ANCOVA) to compare the effect of tirzepatide versus placebo. The dependent variable to be used in the model will be the change from baseline to 18 weeks in SMR~~adjusted for body composition~~. The independent variables will include treatment as a factor, ~~and~~ baseline SMR and body composition parameter(s) as covariates. The primary analysis will be performed in all randomized subjects with evaluable data (modified intent-to-treat [mITT] population). Similar analysis will also be performed in subjects who reach the BW target range of -10% (±2%) at Week 18 as a sensitivity analysis.

Other PD parameters that are scheduled to be measured only once postbaseline will be analyzed using a similar ANCOVA model with baseline measurement and treatment group as covariates. For parameters that are measured in the respiratory chamber, an adjustment for body composition parameter(s) as covariates may be applied if deemed appropriate. If the response is positive for all subjects and highly skewed, a log-transformation may be considered. Other parameters that are positive and skewed may be log-transformed.

6.2 Exclusion Criteria

[13] Are currently diagnosed with any form of diabetes~~prior to entry~~; or have fasting and/or postglucose challenge PG (OGTT) compatible with diabetes, and/or hemoglobin A1c value ≥6.5% at screening (Visit 1); subjects with borderline glucose intolerance are eligible (see Section 6.1 Inclusion Criteria [1]).

9.1.1. Primary Efficacy Assessment and Procedure

The primary efficacy measure in the study is the change from baseline to Week 18 (Visit 20) in SMR for comparison of tirzepatide with placebo. The change in SMR will be measured in the respiratory chamber (whole-room calorimetry).

The SMR extrapolated to 24 hours~~and adjusted for body composition~~ will be calculated:

- SMR = average SMR*1440, where average SMR is the average minute by minute EE for the sleep time period.

10.1. Sample Size Determination

Up to 56 subjects are planned to be randomized so that approximately 46 subjects complete the study assuming 15% discontinuation rate. These 56 subjects will be randomized to QW tirzepatide or placebo in a 1:1 ratio. The estimated variability of the change in SMR from baseline is 117 kcal/day~~, when adjusted for body composition~~ (Heilbronn et al. 2006). With an expected treatment difference of 100 kcal/day, this provides at least 80% power for the comparison of tirzepatide versus placebo based on 2 sample t-test using 2-sided test at alpha level of 0.05, and at least 85% power for the sensitivity analysis where only patients who achieve the target weight loss and are considered at least 90% compliant will be included for the assessment of the primary endpoint.

10.3.3.2. Pharmacodynamic Statistical Inference

The primary endpoint (SMR) will be analyzed using an analysis of covariance model (ANCOVA) to compare the effect of tirzepatide versus placebo. The dependent variable to be used in the model will be the change from baseline to 18 weeks in SMR~~ adjusted for body composition~~. The independent variables will include treatment as a factor~~ and~~, baseline SMR and body composition parameter(s) as covariates. The primary analysis will be performed in all randomized subjects with evaluable data (modified intent-to-treat [mITT] population). Similar analysis will also be performed in subjects who reach the BW target range of −10% (±2%) at Week 18 as a sensitivity analysis.

Other PD parameters that are scheduled to be measured only once postbaseline will be analyzed using a similar ANCOVA model with baseline measurement and treatment group as covariates. For parameters that are measured in the respiratory chamber, an adjustment for body composition parameter(s) as covariates may be applied if deemed appropriate. If the response is positive for all subjects and highly skewed, a log-transformation may be considered. Other parameters that are positive and skewed may be log-transformed.

Leo Document ID = 15303357-90ad-4847-89ed-9779ba255116

Approver: PPD

Approval Date & Time: 02-Aug-2021 01:42:40 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 02-Aug-2021 22:30:47 GMT

Signature meaning: Approved