A 6-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, TWO-ARM, PARALLEL METHODOLOGY STUDY TO ASSESS THE EFFECT OF LIRAGLUTIDE ON FOOD INTAKE IN OBESE SUBJECTS

Investigational Product Number:	Not Applicable (N/A)
Investigational Product Name:	Liraglutide
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	A9001498
Phase:	Methodology Study

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	21 November 2016	Not applicable (N/A)

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SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject. For a list of abbreviations, refer to Appendix 1: Abbreviations.

Table 1. Comprehensive Schedule of Activities

Protocol Activity	Screening	Run In	Double-Blind Randomized Dosing Period								Follow Up	
Visit (V) Number	V1	V2	V3			V4			V5		V6[a]	Phone Contact
Days Relative to Dosing on Day 1	Day -44 to -17	Day -16 (±3 days)	Day -2	Day -1 to 1	Day 2 to 18	Day 19	Day 20 to 22 (±3 days)	Day 23 to 39 (±3 days)	Day 40	Day 41 to 43 (±3 days)	10 days post last dose (±3 days)	31 days post last dose (±3 days)
Outpatient visit	X	X		Inpatient stay at study site (See Table 2 For details)			Inpatient stay at study site (See Table 2 For details)			Inpatient stay at study site (See Table 2 For details)	X	
Admission to CRU			X			X			X			
Informed consent & demography	X											
Serious and non-serious AE monitoring	X	→	→		→	→		→	→		→	X
Review inclusion/exclusion criteria	X	X	X									
Medical history including alcohol, nicotine and drug use	X		X[b]			X[b]			X[b]			
Prior/concomitant treatments	X	X	X[b]			X[b]			X[b]		X	
Review lifestyle requirements	X		X[b]			X[b]			X[b]			
Review contraceptive method	X	X	X[b]			X[b]			X[b]		X	X
C-SSRS and PHQ-9 questionnaires	X		X[b]			X[b]			X[b]		X	
Physical exam (height at V1 only)	X[c]	X[d]									X[c]	
[redacted]	C											
Single supine 12-lead ECG	X	X									X	
Single supine BP and PR	X	X									X	
Hematology, chemistry, lipid panel, UA	X										X	
Amylase, lipase, calcitonin	X										X	
Serum β-hCG[g]	X	X									X	
FSH, TSH, HbA1c, HIV, HepBsAg, HepBcAb, HCVAb	X											
Urine drug screen	X	X	X			X			X			
Blinded IP administration					→[h]	→[i]		→[h]	→[i]			

a. The procedures listed in this visit will also be performed if the subject is withdrawn from the study (See Follow-up section).

b. Timing of specified procedures on day of admission (Day -2 [V3], Day 19 [V4], Day 40 [V5]) is flexible and may also take place on the morning Day -1 [V3], Day 20 [V4], and Day 41 [V5], prior to fasting laboratory samples (V3-V5).

c. Full physical exam performed at V1 and V6 (See Physical Examinations section).

d. Limited physical exam performed at V2 (See Physical Examinations section).

[redacted]

g. At V1, serum β-hCG will be obtained in all female subjects. At all other visits (V2-V6), Serum β-hCG will be obtained in females of childbearing potential only.

h. Blinded dosing of Investigational Product (IP) will be administered on a daily basis from Day 2-18 and from Day 23-Day 39 by an unblinded administrator, either at subject's home or via outpatient clinic visit as specified in Study Treatments section.

i. For Day 19 and Day 40, blinded IP administration may occur at subject's home or at inpatient CRU by an unblinded administrator, as long as time of administration of blinded IP adheres to guidelines in the Administration section.

Table 2. List of Procedures for Inpatient Visits (V3, V4, V5)

Study Day	Day -1 (V3) Day 20 (V4) Day 41 (V5)												Day 0 (V3) Day 21 (V4) Day 42 (V5)										Day 1 (V3), Day 22 (V4) Day 43 (V5)	
Approx. Clock Time (24H)	6	7	7.5	8	8.5	9	10	12	12.5	13	14	18	6	7	8	10	12	12.5	13	14	18	22	6	7
Inpatient stay at CRU	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious and non-serious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Limited physical exam	X																							
CCI [redacted]	[redacted]												[redacted]										[redacted]	
Single supine 12-lead ECG	X																							
Single supine BP and PR	X												X	X	X	X	X				X	X	X	
Hematology, chemistry, lipid panel		X[a]																						
Amylase, lipase, calcitonin		X[a]																						
Serum β-hCG		X[b]																						
Prep D1 ***(V3 only)*** and Prep P2		X[a]																						
[redacted]		C																						
Acetaminophen PK		X[a]	X	X	X	X	X	X[c]																
[redacted]		C	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]																
Urinalysis		X																						
Breakfast (fixed kcal meal)[e]		X												X										X
Ad libitum meals[e]								X				X					X				X			
Acetaminophen administration		X[f]																						
Blinded IP administration		X[g]												X[g]										X[h]
Food intake assessment		X						X				X		X			X				X			
VAS questionnaire[i]		X	X	X		X		X	X	X	X						X	X	X	X				
[redacted] CCI [j]														X										
Discharge from CRU																								X[k]

a. Blood sampling performed ***before*** breakfast and administration of acetaminophen (V3, V4, V5) ***and prior to*** administration of IP on V4 and V5. For Prep D1 collection: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.

b. Serum β-hCG level for all female subjects of childbearing potential. Testing may also be completed on day of admission to CRU (Day -2 [V3], Day 19 [V4] and Day 40 [V5].

c. Blood sampling performed ***before*** lunch.

C [redacted]

e. Meals served at approximate clock times during inpatient stay.

f. Acetaminophen administered ***with*** breakfast.

g. Blinded IP administered at these time points on Days 20 (V4), Day 21 (V4), Day 41 (V5) and Day 42 (V5) only (***not*** Day -1 [V3] and Day 0 [V3]).

h. Blinded IP administered at this time point on Day 1 (V3) and Day 22 (V4) only (***not*** Day 43 [V5]).

i. VAS questionnaires to be performed immediately prior to meals (breakfast and lunch on Days -1, 20, and 41 and lunch only on Days 0, 21, 42), then at 30, 60, and 120 minutes following the start time of the meal.

[redacted]

k. Time of discharge is flexible but should occur after subject completes breakfast (V3, V4, V5) and receives IP (V3 and V4).

1. INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake.[1] GLP-1 activation of the GLP-1 receptor (GLP-1R) stimulates insulin release, inhibits glucagon secretion in a glucose-dependent manner, and delays gastric emptying.[2,3] Several injectable peptidic GLP-1R agonists are approved for the treatment of Type 2 diabetes mellitus. In addition, GLP-1 has been shown to increase satiety and suppress food intake, supporting the use of GLP-1R agonists for the treatment of obesity.[4] Liraglutide is a peptide GLP-1R agonist that is approved both for the treatment of obesity (known as Saxenda®)[5] and for the treatment of Type 2 diabetes (known as Victoza®).[6]

The primary purpose of this study is to assess the variability and operating characteristics of food (energy) intake in non-diabetic, obese subjects using liraglutide, an agent that has been demonstrated to result in decreased food intake. This assessment will aid in determining if food intake is an appropriate decision-making endpoint CCI [redacted]

1.1. Mechanism of Action/Indication

Liraglutide is a specific and potent GLP-1R agonist that is approved at doses up to 3.0 mg for the treatment of chronic weight management in adult subjects with body mass index (BMI) >30 kg/m^2 (obese) or >27 kg/m^2 body mass index (BMI) (overweight) with weight-related co-morbidities as adjunct with reduced calorie diet and increased physical activity,[5] or at doses up to 1.8 mg to improve glycemic control in subjects with Type 2 diabetes mellitus.[6] For this study, liraglutide is being used as a research tool to assess the performance characteristics of food intake as a primary endpoint in obese subjects.

1.2. Background

Obesity is a chronic disease that is associated with serious co-morbidities including type 2 diabetes mellitus, dyslipidemia, hypertension, atherosclerosis, obstructive sleep apnea and certain cancers.[7] Obesity is also associated with increased all-cause mortality.[8] The prevalence of obesity is estimated at greater than 35% of the United States (US) population and poses a major public health challenge.[9] First line treatment for obesity is lifestyle intervention including diet, exercise and behavioral therapy. While effective in many patients, lifestyle intervention is often not sustainable, and many patients regain weight after initial weight loss.[10] Pharmacotherapy has been approved by the Food and Drug Administration (FDA) for long-term treatment of obesity and can be a useful adjunct to lifestyle intervention that helps augment and maintain weight loss.

GLP-1 is a hormone released from the gut post-prandially that improves appetite regulation and glucose metabolism. The half-life of endogenous GLP-1 in vivo is exceptionally short at approximately 1 to 2 minutes, due to cleavage by dipeptidyl peptidase IV.[11,12] Liraglutide is a long acting GLP-1 analog with 97% amino acid homology to native GLP-1 and a half-life of approximately 13 hours,[13] making it suitable for once daily dosing.[14] Liraglutide lowers blood glucose in a glucose-dependent manner by stimulating insulin secretion and inhibiting glucagon secretion from the pancreas via activation of GLP-1Rs.[15] Liraglutide also delays

gastric emptying, reduces food intake, and suppresses appetite leading to weight loss. This anorectic action is proposed to be mediated by activation of the GLP-1R in appetite centers of the brain.[16,17,18]

Liraglutide has been evaluated in many clinical trials, in both subjects with Type 2 diabetes and non-diabetic subjects with obesity. The clinical development program for Saxenda® included 5 double-blind, placebo controlled trials in 3384 overweight or obese subjects for a mean treatment duration of 45.9 weeks (range 32 to 56 weeks duration).[5]

Two Phase 1 studies have evaluated the effect of liraglutide on food intake and appetite.[16,17] In obese subjects treated with daily doses of liraglutide 3.0 mg for 5 weeks, food intake during a test meal (ad libitum lunch) was reduced by approximately 140 kcal.[17] Liraglutide 3.0 mg treated subjects also demonstrated delayed gastric emptying, reduced appetite, and increased nausea. In subjects with Type 2 diabetes, daily doses of liraglutide 1.8 mg reduced food intake during an ad libitum lunch by approximately 200 kcal.[16] In addition, the liraglutide 1.8 mg treated subjects demonstrated reduced hunger and higher fullness ratings.[16]

In clinical trials, the most common adverse events reported with Saxenda® were nausea (in 39% of subjects), diarrhea (in 21% of subjects), constipation (in 19% of subjects), and vomiting (in 16% of subjects). The percentage of subjects reporting nausea declined as treatment continued, and most of the gastrointestinal adverse events were of mild or moderate intensity. The most common adverse reactions leading to discontinuation were nausea (2.9% versus 0.2% for Saxenda® and placebo, respectively), vomiting (1.7% versus less than 0.1%), and diarrhea (1.4% versus 0%).[5]

Additional information for liraglutide can be found in the Single Reference Safety Document (SRSD), which for this study is the Saxenda® label.[5] The SRSD for the non-investigational medicinal product acetaminophen (administered as a challenge agent) will be its label.[19]

1.3. Rationale

1.3.1. Study Rationale

This study is designed to assess the performance characteristics of energy intake as a biomarker for anorexiant agents in obese subjects. Study subjects will be randomized to receive either liraglutide dosed up to 3.0 mg daily or placebo during 6 weeks of dosing. Additional goals of this study include:

- To assess the variability and operating characteristics in study measures related to food intake, including gastric emptying, appetite, and satiety, with an agent that has been demonstrated to impact these endpoints.

- To provide a mid-point assessment at 3 weeks that will assess food intake as an early signal of efficacy CCI [redacted]

- To create an internal database for energy intake and related assessments, such as tolerability, gastric emptying, appetite, satiety [redacted]

This study will enroll non-diabetic obese subjects who may be treated for co-existing conditions, such as hyperlipidemia or hypertension, but who are otherwise clinically stable. The study population is chosen in accordance with the Saxenda® prescribing instructions,[5] and the duration of dosing allows titration to the maximum dose of 3 mg daily for 2 weeks. In addition, to increase the comparability of the data from this methodology study to published literature, inclusion criteria similar to a previously reported study, including BMI range, will be applied.[17] Nicotine use is listed in the exclusion criteria, due to its possible confounding effect on appetite and food intake. Furthermore, this study will enroll men and women who are not currently pregnant or breastfeeding and who have no intention of becoming pregnant during the study, in accordance with the Saxenda® prescribing instructions.[5]

Subjects in this study will be randomized to receive either liraglutide (administered from Saxenda® pens) or placebo (0.9% normal saline administered subcutaneously) for 6 weeks. To ensure blinded status through the study, an unblinded pharmacist will manage study medication, and study medication will be administrated via an unblinded administrator. Imperfect blinding techniques are being utilized in this study, as neither the investigator site nor the Sponsor has access to a placebo device that matches Saxenda® pens. Although an imperfect blinding approach is being utilized, blinding was deemed an essential component of the study design, as perception of appetite and satiety can be affected by external cues. Randomization will be stratified by baseline body weight to ensure that both treatment groups have similar baseline body weight, as subjects with lower baseline weight may demonstrate higher drug levels of liraglutide and greater degrees of weight loss than subjects with higher baseline body weight at the same dose of 3.0 mg daily.[20]

[redacted] To minimize the impact of the placebo effect on body weight and associated variability, subjects will complete a Run-in visit (V2) prior to the initial inpatient visit (V3) to stabilize food intake and body weight.

In addition to assessing changes in energy intake and body weight with liraglutide, this study will generate an internal dataset of endpoints relevant to liraglutide-induced weight loss, including gastric emptying (measured by acetaminophen pharmacokinetic [PK] concentrations after acetaminophen administration) and assessment of appetite and satiety (measured by Visual Analog Scale [VAS] questionnaire). [redacted] Energy intake will be measured over a period of 48 hours to assess day-to-day variability in food intake. [redacted] While published literature exists with liraglutide for many of these endpoints, gaps exist in the individual level data available in the literature, as

published studies were completed in separate, small study populations, with varying dose ranges of liraglutide explored. This study seeks to fill those gaps by creating an internal dataset CCI [redacted]

In addition to assessments of vital signs, electrocardiogram (ECG), standard safety labs and adverse events, amylase, lipase and calcitonin will be assessed at baseline and during the study in accordance with the Saxenda® prescribing instructions.[5] Assessment of Suicidal Ideation and Behavior (SIB) by Columbia Suicide Severity Rating Scale (C-SSRS)[21] and Patient Health Questionnaire-9 (PHQ-9)[22] will also be performed in accordance with the Saxenda® prescribing instructions.[5] Furthermore, in light of a prior study demonstrating increases in diastolic blood pressure with short-term liraglutide administration,[23] subjects will receive frequent blood pressure assessments at similar time points CCI [redacted]

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS may also be used in research on obesity.

Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited by local regulations or ethics committee (EC) decision.

1.3.2. Dose Rationale

Liraglutide will be administrated subcutaneously in accordance with the Saxenda® prescribing instructions for a total of 6 weeks, with an initial dose of 0.6 mg per day and increasing by 0.6 mg in weekly intervals until a dose of 3.0 mg per day is reached.[5] To ensure blinded status throughout the study, placebo (0.9% normal saline) will be administered subcutaneously via syringe in matching volume for 6 weeks.

Additionally, the non-investigational medicinal product acetaminophen 1.5 g will be administered orally as a challenge agent to assess gastric emptying during inpatient visits.[17]

Following subcutaneous administration, maximum concentrations of liraglutide are achieved at approximately 11 hours post dosing with an elimination half-life of approximately 13 hours, making liraglutide suitable for once daily administration. Liraglutide exposure increases proportionally in the dose range of 0.6 mg to 3 mg and is considered similar among three subcutaneous injection sites (upper arm, abdomen, and thigh). Liraglutide is extensively bound to plasma protein (greater than 98%), and is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.[5]

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
• To assess the effect of liraglutide on food intake during 6 weeks of administration, compared to placebo.	• Mean energy intake (in kcal) during ad libitum lunch meals.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To assess effects on safety measures and tolerability (including spontaneously reported nausea and vomiting) of liraglutide over 6 weeks of dosing. • To evaluate the effect of liraglutide on additional food intake endpoints during 6 weeks of administration, compared with placebo. • To assess the effect of liraglutide on appetite and satiety during 6 weeks of liraglutide administration, compared to placebo. • To assess the effect of liraglutide on gastric emptying during 6 weeks of liraglutide administration, compared with placebo.	• Vital sign measurements, adverse event monitoring, changes in 12-lead ECGs, and clinical laboratory testing. • 48-hour energy intake (in kcal). • Appetite and satiety scores, as assessed by VAS questionnaire. • Plasma area under the curve (AUC) of acetaminophen for 0-60 mins and 0-300 minutes after acetaminophen administration.

CCI [redacted]

3. STUDY DESIGN

3.1. Study Overview

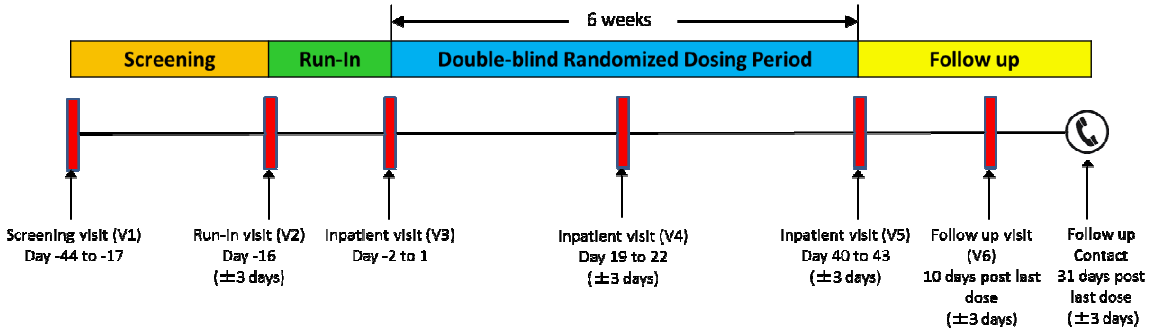
This will be a randomized, double-blind, placebo-controlled, 2-arm, parallel group, methodology study to assess the effect of 6 weeks of liraglutide administration on food intake in obese subjects. Subjects will complete screening procedures to determine eligibility and once confirmed to meet all other criteria, will proceed to a Run in visit (V2) and then to randomization at V3.

The study includes a total of six (6) visits to the site, including 3 outpatient visits (V1, V2 and V6) and 3 inpatient visits (V3, V4 and V5). Subjects will be randomized at V3 to receive 1 of 2 blinded treatment regimens for a duration of 6 weeks: liraglutide (administered subcutaneously via pen injection and titrated per Saxenda® label[5] to maximum dose of 3.0 mg/day) or placebo (0.9% saline, administered subcutaneously via syringe in matching volume). At V3, V4 and V5, subjects will be admitted for an inpatient stay and receive blinded investigation product (IP) from an unblinded administrator. Each inpatient stay consists of 4 days and 3 nights. For the study duration between V3 and V4, and also between V4 and V5, subjects will be administered blinded IP on a daily basis via an unblinded administrator, either at home or at an outpatient visit.

Total participation in the study for each subject, including Screening (V1) and investigator site Follow-up visits (V6) will be approximately 10 weeks (minimum) to 14 weeks (maximum). In addition, there will be follow up contact with the subject via a phone call, at least 28 after last dose of IP (V5). The overall study scheme is summarized in Figure 1.

Approximately 60 subjects (30 per arm) will be randomized at one or more study sites. A minimum of 50 completed subjects (approximately 25 subjects per arm) are required for the study. The 60 randomized subjects account for a projected approximate premature withdrawal rate of 15% and reflects intent not to replace subjects prematurely withdrawn after first dose of IP.

Figure 1. Study Design



3.2. Stopping Rules

Discontinuation of IP should be considered for a subject if any of the following conditions listed below occur. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not overrule the investigator's decision to discontinue IP in a particular subject.

1. Criteria for a potential Hy's law case are met (see Potential Cases of Drug-Induced Liver Injury section);
2. Subject becomes pregnant;
3. Subject answers "yes" to question 4 or question 5 on the C-SSRS, indicating active suicidal ideation, with intent to act (see Assessment of Suicidal Ideation and Behavior section).

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Female or male subjects who, at the time of screening, are between the ages of 18 and 75 years, inclusive.
2. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 28 days after the last dose of IP. Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure.

   All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

3. Body mass index (BMI) of 30.0 to 40.0 kg/m^2 at the screening visit (V1).
4. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

5. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing). However, subjects treated for hypothyroidism, hypertension and/or hyperlipidemia are permitted in this study.

2. Any condition possibly affecting drug absorption (eg, gastrectomy).

3. A positive urine drug test.

4. History of regular alcohol consumption exceeding 7 drinks/week for female subjects or 14 drinks/week for male subjects (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before screening.

5. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product (whichever is longer).

6. Screening supine blood pressure (BP) ≥150 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥150 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the subject's eligibility.

7. Screening supine 12-lead ECG demonstrating a corrected QT (QTc) interval >450 msec or a QRS interval >120 msec. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the subject's eligibility.

8. Subjects with **ANY** of the following abnormalities in clinical laboratory tests at screening (V1), as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - Aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level ≥2 × upper limit of normal (ULN);

    - Total bilirubin level ≥1.5 × ULN; subjects with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;

- Serum calcitonin ≥50 ng/L;
- Amylase > ULN **or** lipase > ULN;
- Thyroid stimulating hormone (TSH) outside of the laboratory reference range.

9. Pregnant or breastfeeding female subjects.
10. Use of prescription or nonprescription drugs and dietary supplements within 28 days prior to the first dose of investigational product, except as noted in the Concomitant Treatments section.
11. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
12. History of sensitivity to heparin or heparin-induced thrombocytopenia.
13. History of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb), or hepatitis C antibody (HCVAb).
14. Unwilling or unable to comply with the criteria in the Lifestyle Requirements section of this protocol.
15. Subjects who are investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
16. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
17. Use of tobacco- or nicotine-containing products.
18. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2), or patients with suspected MTC per the investigator's judgment.
19. Allergy or intolerance to liraglutide or other GLP-1R agonists.
20. Acute pancreatitis, history of chronic pancreatitis.
21. Acute gallbladder disease.

22. Renal impairment with a creatinine clearance <60 mL/min as determined by the Cockcroft-Gault equation at V1.

23. Patients with current or prior diagnosis of type 1 or type 2 diabetes mellitus.

24. Use of any insulin/anti-diabetic therapy during within 24 weeks prior to V1.

25. Glycosylated hemoglobin (HbA1c) ≥6.5% at V1.

26. Change in body weight ≥5 kg within 12 weeks prior to V1.

27. Use of GLP-1R agonists (including liraglutide, exenatide or other similar medications) within 24 weeks prior to V1.

28. Use of weight-modifying medications, including prescription or over-the-counter medications, herbal supplements, or marijuana within 12 weeks prior to V1.

29. Current or prior treatment with medications that may cause significant weight gain within 12 weeks prior to V1, including systemic corticosteroids (except for a short course of treatment, ie, <5 days), tricyclic antidepressants, atypical antipsychotic and mood stabilizers (eg, imipramine, amitriptyline, mirtazapine, paroxetine, phenelzine, chlorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium).

30. Current or previous treatment within 12 weeks prior to V1 with any of the following medications that may affect glycemic measures: coumadin-type anticoagulants or other anticoagulants (eg, dabigatran, enoxaparin), anticonvulsants, antiarrhythmics, β-blockers, thiazide diuretics >25 mg per day, and sympathomimetic agents.

31. Medical history or characteristics suggestive of genetic or syndromatic obesity or obesity induced by other endocrinologic disorders (eg, Cushing Syndrome).

32. History of major depressive disorder or history of other severe psychiatric disorders (eg, schizophrenia or bipolar disorder) within the last 2 years.

33. A Patient Health Questionnaire (PHQ-9) score ≥15 obtained at V1 (see Assessment of Suicidal Ideation and Behavior section).

34. Subjects with any lifetime history of a suicide attempt.

35. Response of "yes" to question 1 of C-SSRS at V1, indicating a history of suicidal ideation (see Assessment of Suicidal Ideation and Behavior section).

36. Intolerance to acetaminophen use.

37. Intolerance or aversion to any components of the meals administered in the clinical research unit (CRU) for food intake and satiety assessments (eg, lactose intolerance, gluten intolerance or celiac disease).

4.3. Randomization Criteria

Subjects will be randomized into the study prior to dosing of IP on Day 1 (V3), provided they have satisfied all subject eligibility criteria outlined in the Inclusion Criteria and Exclusion Criteria sections of this protocol.

Eligible subjects will be randomized prior to the first dose of IP to either liraglutide or placebo in a 1:1 ratio. A computer-generated randomization schedule will be used to assign subjects to the treatment groups using the 1:1 allocation ratio stratified by body weight at V3 (≥100 kg or <100 kg). An attempt will be made to balance the number of subjects assigned to receive liraglutide and placebo within each stratum.

4.4. Lifestyle Requirements

4.4.1. Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 8, but preferably 10 hours, prior to any fasting blood sample collections for clinical laboratory tests, glucose, and insulin assessments.

- Water may be consumed as desired.

- CCI [redacted]

- For the food intake assessment, the menus for each meal during the 48 hour period comprising the assessment will be identical across all assessments in the study.

- During inpatient visits, the total daily nutritional composition should be approximately 50% carbohydrate, 35% fat and 15% protein.

- During run in period (between V2 and V3) and home dosing (ie between V3 and V4 and between V4 and V5), subjects will be instructed to maintain usual dietary intake.

4.4.1.1. Breakfast (Fixed Kilocalorie) Meal

An identical fixed kcal breakfast (approximately 500 kcal) will be provided to study subjects at the time points listed in the Schedule of Activities. The breakfast meal is standardized to minimize any variability in food intake assessment of the succeeding ad libitum lunch and dinner meals and CCI [redacted]. Breakfast will be timed so that subjects start the meal at approximately 07:00 hours. On study Days -1, 20 and 41, the breakfast meal will serve as the stimulus for CCI [redacted] and the gastric emptying assessment. Subjects will be instructed to complete the meal over a period of 20 minutes. If a subject is unable to do so, this will be recorded as a protocol deviation.

4.4.1.2. Ad Libitum Meals

Ad libitum meals will be served to study subjects for lunch and dinner at the time points listed in the Schedule of Activities. Subjects will be instructed to consume their meals within 30 minutes with a reminder notification at 25 minutes after initiation of meal ingestion.

Meals will be consumed until subjects reach satiety, stopping at will, without distractions such as reading materials, television, cell phones or computer.

4.4.2. Alcohol, Caffeine, and Tobacco

- Intake of alcohol is permitted outside of inpatient study visits (V3, V4, V5) in moderation as defined in the Exclusion Criteria.

- Subjects will abstain from alcohol for 24 hours prior to admission to the clinical research unit (CRU) and continue abstaining from alcohol until collection of the final PK sample of each inpatient stay. Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Caffeine containing products will be permitted during the study with the following restrictions: caffeine containing products may not be consumed within 2 hours prior to measuring blood pressure, pulse rate, or ECGs.

- Use of tobacco and nicotine-containing products is not permitted in this study.

4.4.3. Activity

- Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

- During run in period (between V2 and V3) and home dosing (ie, between V3 and V4 and between V4 and V5), subjects will be instructed to maintain usual physical activity.

4.4.4. Contraception

In this study, fertile male subjects and female subjects who are of childbearing potential will receive placebo or liraglutide, which has been associated with demonstrated teratogenicity/fetotoxicity in nonclinical studies.[5] Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm the subject has selected 2 appropriate methods of contraception for the individual subject and his or her partner(s) from the list of permitted contraception methods (see below) and will confirm that the subject has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical study, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are:

- Liraglutide, administered subcutaneously via pen injection with dose titration to 3.0 mg daily per Saxenda® prescribing instructions;[5]

- Placebo, 0.9% weight/volume (w/v) sodium chloride, United States Pharmacopeia (USP), administered subcutaneously via syringe injection with matching volume to liraglutide dose.

In addition, during each of the inpatient study visits (V3, V4, V5), a non-investigational medicinal product (acetaminophen 1.5 g) will be administered as a challenge agent for the assessment of gastric emptying (see Gastric Emptying section).

5.1. Allocation to Treatment

The investigator will assign subject numbers to the subjects as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the subject will receive the study treatment regimen assigned to the corresponding randomization number.

Subjects will be stratified into the study according to body weight at V3. Once stratified, subjects will be randomized in a 1:1 ratio to receive liraglutide or placebo according to the randomization schedule generated by the sponsor. With the exception of the study site pharmacist and the unblinded administrator(s), study site and sponsor personnel who are directly involved in the study conduct will be blinded to the randomization schedule. The only exception will be in the event of an emerging safety issue which requires breaking the blind (see Breaking the Blind section).

5.2. Breaking the Blind

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be either a manual or an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.3. Subject Compliance

Blinded IP will be administered by an unblinded administrator during all inpatient visits (V3, V4, and V5) and during dosing at home or via daily onsite visits for dosing (ie, dosing between V3 and V4 and between V4 and V5).

5.4. Investigational Product Supplies

5.4.1. Dosage Form and Packaging

Liraglutide 6.0 mg/mL, 3 mL (Saxenda® pen) and accompanying 31 gauge pen needles will be provided by the study site.

The study site will also provide placebo, which is a 0.9% w/v sodium chloride, USP, and accompanying syringe and 31 gauge syringe needles for subcutaneous injection.

In addition, the study site will provide a dose of 1.5 g acetaminophen (45 mL of liquid form for oral administration with concentration of 500 mg/15 mL),[19] which will be administered orally as a challenge agent to assess gastric emptying during inpatient visits. Acetaminophen will be drawn into a syringe by the site pharmacist and dispensed to the inpatient CRU for administration to subject.

5.4.2. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a subject in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Liraglutide and placebo will be prepared by qualified unblinded site personnel according to the IP manual and administered in blinded fashion to the subject. IP should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Doses of liraglutide will be dispensed from a pre-filled, multi-dose 6.0 mg/mL, 3 mL Saxenda® pen. Placebo will be dispensed from a multi-dose vial of 0.9% w/v sodium chloride, USP. Liraglutide pens, pen needles, placebo vial and accompanying syringes will be overseen by a qualified pharmacist who is unblinded in order to prepare the IP according to the randomization treatment assignments.

5.5. Administration

Designated and trained study staff administering blinded IP to subjects will be unblinded and will be separate from the study team who will be blinded. Liraglutide will be administered from a 3 mL Saxenda® pen.[24] Dosing with the Saxenda® pen is controlled by turning the dose selector until the dose indicator shows the relevant dose (10, 20, 30, 40, 50 clicks). One click equals 0.06 mg.

Daily subcutaneous injections of placebo or liraglutide will be administered in the abdomen, thigh or upper arm by an unblinded administrator at home or via onsite daily visits (for dosing periods between V3 and V4 and between V4 and V5) and in the CRU during inpatient study visits (V3, V4 and V5, as detailed in the Schedule of Activities). For Day 19 and Day 40, blinded IP administration may occur at a subject's home or at inpatient CRU by an unblinded administrator. The site of subcutaneous injection may vary during the study but should be administered at one of the sites listed above and according to the Saxenda medication guide.[24] A 31 gauge pen needle will be used with the Saxenda® pen, and a 31 gauge insulin syringe will be used to administer placebo.[24] The unblinded administrator will be instructed to perform an air shot before the first injection with the Saxenda® pen[24] or placebo syringe and will prepare the dose of blinded IP in a separate location away from the subject. Subjects will be blindfolded during administration to maintain blinding to the IP.

As per the Saxenda® label,[5] and in order to reduce the number of side effects, liraglutide will be initiated at a dose of 0.6 mg daily and escalated by 0.6 mg weekly up to a maximum of 3 mg. The dose titration schedule is shown in Table 3. For subjects randomized to placebo injections, the volume of saline administered for a specific week of dosing will match the volume specified in the "Volume Administered" column in Table 3. If a subject does not tolerate the next dose level during dose escalation, as determined by the Investigator, dose escalation to the next higher dose will be delayed by one week. All subjects who are able to tolerate a minimum dose of liraglutide 1.8 mg daily for at least 2 weeks prior to Day 40 will progress to V5.

Table 3. Liraglutide Dose Titration during Study

Week of Dosing	Daily Dose Administered	Number of Pen Clicks	Volume Administered
1	0.6 mg	10	0.1 mL
2	1.2 mg	20	0.2 mL
3	1.8 mg	30	0.3 mL
4	2.4 mg	40	0.4 mL
5	3.0 mg	50	0.5 mL
6	3.0 mg	50	0.5 mL

5.5.1. Timing of Administration during Inpatient Visits (V3, V4, V5)

During the inpatient visits to the CRU (V3, V4, and V5), subjects will receive IP at approximately 07:00 hours (plus or minus 60 minutes). Designated unblinded investigator site personnel will administer IP and will be separate from the study team who will be blinded.

5.5.2. Timing of Home Administration (between V3 and V4, and between V4 and V5)

To allow for additional flexibility in the timing of IP administration at home between V3 and V4 and between V4 and V5, the time chosen for daily administration of IP may be determined by the subject and designated unblinded administrator. Once this time is chosen, doses of IP should be administered by a designated unblinded administrator at approximately the same time each day (plus or minus 2 hours) without regard to the timing of meals.

5.6. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product-label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatments

Subjects in this study will be allowed to take certain concomitant medications to treat coexisting conditions such as hyperlipidemia and hypertension. Attempts must be made **not** to alter the doses and regimens of chronic background medications after randomization and for the duration of participation in this study. All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatments at each study visit, and any changes must be captured in the CRF.

Treatments taken within 28 days before the first dose of IP will be documented as a prior treatment. Treatments taken after the first dose of IP will be documented as concomitant treatments.

5.8.1. Anti-Hypertensive Medications

Use of background antihypertensive agent(s) is permitted (unless noted in Exclusion Criteria). Doses of antihypertensive agents should be stable for at least 4 weeks prior to V2. Changes to therapy or doses during the duration of the study should be avoided, if possible.

5.8.2. Lipid-Modifying Medications

Use of lipid-modifying agent(s) is permitted (unless noted below in Exclusion Criteria). Doses of lipid-modifying agents should be stable for at least 4 weeks prior to V2. Changes to therapy or doses should be avoided during the study, if possible.

5.8.3. Other Acceptable Concomitant Medications

Subjects on the following list of medications must be on stable doses (ie, at least 4 weeks prior to V2) and for the duration of participation in the study through V6:

- Inhaled and topical corticosteroids.
- Thyroid replacement therapy.
- Hormonal contraception, including oral contraceptive pills (OCPs), transdermal contraceptive patches and intrauterine devices.
- Postmenopausal hormone therapy.

Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

- Acetaminophen may be used at doses of ≤2 g/day. Acetaminophen should not be taken for 12 hours prior to **and** 12 hours after acetaminophen administration at 07:00 hours on Day -1 (V3), Day 20 (V4), and Day 41 (V5) (see Schedule of Activities).

6. STUDY PROCEDURES

6.1. Chronology of Procedures

During the inpatient visits (V3, V4, and V5), for the procedures described below, where multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, ***where possible***:

- 12-lead ECG: obtain prior to vital sign measurements and as close as possible to the scheduled time, but prior to blood specimen collection (refer to Electrocardiogram section);
- Blood pressure and pulse rate: obtain as close as possible to the scheduled time, but prior to blood specimen collection (refer to Blood Pressure and Pulse Rate section);
- *If* an intravenous catheter is placed for serial blood sample collections, ECGs and vital sign (pulse rate, BP) assessments should be collected *either* prior to the insertion of the catheter *or* after sufficient rest period after catheter insertion to minimize impact of catheter placement on these assessments;
- Fasting blood samples for clinical laboratory tests: after assessment of 12-lead ECG and blood pressure and pulse rate but *prior to* start of meal and/or dosing of IP (refer to Laboratory Tests section);
- Fasting sample for acetaminophen PK should occur *prior to* start of meal, dosing of acetaminophen and dosing of IP;
- [redacted]
- If the blood collection nominal time coincides with the nominal time of a meal, these blood samples should be collected *prior to* start of the meal.
- Dosing (refer to Administration section): should occur as close as possible to the scheduled nominal time with or without a meal;
- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

6.2. Screening (V1)

Refer to Schedule of Activities Table 1 for the study procedures to be completed at the Screening visit.

Subjects will be screened **within 28 days** prior to V2 to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section. If the time between screening and V2 exceeds 28 days as a result of unexpected delays, then subjects do not require rescreening if the Day -1 (V3) laboratory results meet the eligibility criteria.

To prepare for study participation, subjects will be instructed on the information in the Lifestyle Requirements and Concomitant Treatments sections of this protocol.

6.3. Run In Visit (V2)

Refer to the Schedule of Activities Table 1 for the study procedures to be completed at V2.
CCI [redacted]

6.4. Dosing Period

6.4.1. Inpatient Visits (V3, V4, V5)

Refer to Schedule of Activities Table 1 and Table 2 for the study procedures to be completed at V3, V4 and V5. At V3 only, collect a genomic banked biospecimen. If missed, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Clinical Research Unit until such abnormalities are deemed not clinically significant, or it is safe for outpatient Follow-up. If the subject is unable or unwilling to remain in the CRU and/or when outpatient Follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange Follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.4.2. Daily Dosing from Days 2 to 19 and Days 23 to 40

- Refer to Schedule of Activities Table 1 for the study procedures to be completed from Days 2 to 19 and Day 23 to 40. Blinded IP will be administered on a daily basis by an unblinded administrator either at the subject's home or at an outpatient visit per dose titration schedule listed in the Administration section. CCI [redacted]

[redacted]

6.5. Follow-Up (V6 and Phone Contact)

In this study, there are two Follow-up visits, as follows:

- **The first is an on-site visit** where the subjects will return to the investigator site **10 ±3 days** following the last dose of investigational product;
- **The second is a telephone contact** to occur **31 ±3 days** following the last dose of investigational product;
- Refer to Schedule of Activities Table 1 for the study procedures to be completed at each of the two Follow-up visits.

6.6. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given investigator site. The early termination visit applies only to subjects who are randomized, receive at least one dose of IP and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject twice. After 2 attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the assessments to be performed at the onsite Follow up visit (see Table 1 of Schedule of Activities).

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

Withdrawal of Consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to Follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

7. ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety

7.1.1. Laboratory Tests

The following clinical laboratory tests will be performed at times defined in the Schedule of Activities section of this protocol and will be performed by the study site laboratory. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 4. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Blood Urea Nitrogen (BUN) Creatinine Glucose Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	Serum β-hCG[b] Lipid panel: total cholesterol, HDL-C, LDL-C, triglycerides Amylase Lipase Calcitonin CCI [redacted] Urine drug screen **<u>At V1, only:</u>** FSH TSH HbA1c Human Immunodeficiency Virus (HIV) Hepatitis Panel: HepBsAg, HepBcAb, HCVAb
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. Serum β-hCG for all female subjects at V1. At V2-V6, serum β-hCG for women of childbearing potential ***<u>only</u>***.

- The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.

- Subjects will complete urine drug testing during each inpatient stay per the Schedule of Activities. Additional unscheduled urine drug testing may be performed at the discretion of the investigator. Drug testing conducted prior to dosing must be negative during each inpatient stay for subjects to continue dosing with investigational product.

- Blood samples CCI [redacted] at the pre-specified nominal time points outlined in Table 2 of the Schedule of Activities and analyzed at the study site. Samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) relative to baseline laboratory samples will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/DCT).

Any remaining serum/plasma from samples collected for clinical laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the clinical study report (CSR). Samples to be used for this purpose will be shipped to either a Pfizer-approved Biospecimen Banking System (BBS) facility or other designated laboratory and retained for up to 1 year following the completion of the study.

7.1.2. Pregnancy Testing

All serum pregnancy tests used in this study must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female subjects of childbearing potential, 2 negative pregnancy tests are required before receiving investigational product (1 negative pregnancy test at screening [V1] and 1 at the baseline visit immediately before investigational product administration [V3]). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit and within 5 days after the first day of the menstrual period (counting the first day of the menstrual period as Day 1) before the subject may receive the investigational product. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be performed at V2, V3, V4, V5 and at the end of the study (V6) to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of IP and from the study.

7.1.3. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes,

and gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

CCI

[redacted]

7.1.5. Blood Pressure and Pulse Rate

BP and PR will be measured at times specified in the Schedule of Activities section of this protocol. Additional collection times, or changes to collection times, of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. If an intravenous catheter is used for blood collection, BP should not be taken from the arm with an intravenous catheter. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and PR is acceptable; however, when done manually, PR will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection.

7.1.6. Electrocardiogram

12-Lead ECGs should be collected at times specified in the Schedule of Activities section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTc interval is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2 to 4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (ie, is ≥45 msec from the baseline, or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

7.2. Pharmacokinetics

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Samples will be analyzed using a validated analytical method in compliance with vendor standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

PK samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for any other internal exploratory purposes. These data will not be included in the CSR.

7.2.1. Analysis of Acetaminophen Pharmacokinetics

During all study periods, blood samples (4 mL) to provide approximately 1.5 mL plasma for pharmacokinetic (PK) analysis of acetaminophen will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the Schedule of Activities section of the protocol.

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7.3. Banked Biospecimens

Banked biospecimens will be collected from subjects for exploratory research relating to the drug response and disease/condition under study. These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each subject's privacy and confidentiality. Banked biospecimens will be assigned the subject's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the subject's ID and the subject's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also post-marketing research. Subjects may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen **Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis)** will be collected at the time specified in the Schedule of Activities section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response and disease/condition under study. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

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The banked biospecimens will be collected from all subjects unless prohibited by local regulations or IRB/EC decision.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document that they will not be compensated in this event.

7.3.1. Additional Research

Unless prohibited by local regulations or IRB/EC decision, subjects will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Banked Biospecimens section will be used. Subjects may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.4. Food Intake Assessment

Food intake will be assessed at the times listed in Table 2 of the Schedule of Activities.

All meals will be prepared at the study site while the subject is inpatient. For every ad libitum meal, each portion will be weighed and recorded before and after each meal. The following parameters will be measured: total kcal consumed per day, total kcal of each macronutrient consumed per day, total kcal consumed per meal and total kcal of each macronutrient consumed per meal. The total daily nutritional composition offered in the inpatient meals will be approximately 50% carbohydrates, 35% fat and 15% protein.

Observed food intake will be measured as the total number of calories consumed during the specified time period, calculated (to the nearest 50 kcal) as the difference of the total number of calories provided minus the total number of calories remaining after meals.

7.5. Visual Analog Scale (VAS) Questionnaire

Appetite, satiety, fullness, hunger, and prospective consumption will be measured at the study site using a validated VAS questionnaire.[25] The VAS questionnaire will be completed by the subject at each of 4 time points: immediately prior to administration of the meal, 30, 60 and 120 minutes after start time of the specified meals, per the Schedule of Activities.

The VAS is an assessment in which subjects place a vertical line across a 100 millimeter (mm) line to rank their response to various questions. The 100 mm line is anchored by responses such as “Not At All Full” and “Totally Full” at either end. Scoring will consist of measuring the distance of the vertical line from the response at the left end and will be used to explore the relationships between subjective reports of appetite and other VAS measures immediately prior to and following administration of the meal.

Questionnaires will be provided to the subjects showing one question at a time (eg, one question on each page). Study staff will instruct the subjects to complete their responses to all VAS questions by placing a mark at the point on the 100 mm line which corresponds to how the subjects are feeling. Subjects will be instructed not to discuss or compare their ratings with other subjects during this assessment. Subjects will not be able to refer to their previous ratings when marking the VAS at each time point. The measurement will be scored by study staff who will measure, in millimeters, the distance from the left end of the line to the mark made by subjects using a standardized ruler. This value in millimeters will be entered into the CRF for each question at each time point.

Deviations in collection time for VAS questionnaires of ≥5 minutes of the nominal time pre- and post-test meal collection time will be recorded as a protocol deviation.

The volume of water consumed with the meal and for the entire 1.5 hour VAS assessment period following the meal will be measured and recorded in the CRF.

7.6. Gastric Emptying

Gastric emptying will be assessed using plasma acetaminophen concentrations over 5 hours as indicated in Table 2 of the Schedule of Activities. After fasting blood sampling on Day -1, Day 20 and Day 41, subjects will receive liquid oral acetaminophen 1.5 g with a fixed breakfast meal consisting of approximately 500 kcal, which must be consumed within 20 minutes. The blood sampling for determining acetaminophen concentrations will be performed at each of the pre-defined 7 nominal time points outlined in the Schedule of Activities: prior to breakfast and at 30, 60, 90, 120, 180 and 300 minutes after intake of the acetaminophen with breakfast. The last blood sampling at 300 minutes should be completed before the ad libitum lunch. Deviations in blood sampling time for gastric emptying >10% of the nominal time (eg, more than 6 minutes of a 60-minute sample) will be recorded as a protocol deviation.

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7.8. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 530 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

7.9. Assessment of Suicidal Ideation and Behavior

7.9.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is an interview based rating scale to systematically assess suicidal ideation and suicidal behavior.[21] The "baseline/lifetime" version of the C-SSRS will be administered at the Screening visit (V1). Subjects who respond "yes" to Question 1 will not be permitted in the study (see Exclusion Criteria). The "since last evaluation" version of the C-SSRS will be administered on V3, V4, V5 and V6 as listed in Table 1 of the Schedule of Activities. The C-SSRS will be administered by study site staff who have completed training in its administration.

7.9.2. Patient Health Questionnaire-9 (PHQ-9)

The Patient Health Questionnaire-9 Items (PHQ-9) is a 9-item self-report scale for the assessment of depressive symptoms.[22] The PHQ-9 will be completed by subjects and reviewed by appropriately trained site staff at the pre-defined time points outlined in the Schedule of Activities. A PHQ-9 score of ≥15 at V1 indicates clinically significant depression and serves as an exclusion criterion for this study (see Exclusion Criteria).

The study site will ensure access to and evaluation by a qualified mental health professional (MHP) for any subjects demonstrating suicidal ideation and behavior. A qualified MHP should have one of the following backgrounds:

- Psychiatry (board certified or board eligible);
- Clinical psychology (PsyD or PhD degree);
- Licensed clinical social worker (LCSW) with master's level training;
- Psychiatric nurse practitioner (PNP).

7.10. Rater Qualifications

For specific rating assessments (C-SSRS), only qualified raters will be allowed to evaluate and/or rate subjects in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in a guidance document provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not a waiver may be issued. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location, and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a

subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

  Or that is considered to be:

  - An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the Medical Device Complaint Reporting Requirements section). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

  Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);

- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury

(DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.2.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

  An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.5. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be recorded on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The sample size is based on the primary endpoint, change in mean energy intake from baseline to Week 6 (in kcal) for ad libitum lunch meals. The standard deviation (SD) for the change from baseline in energy intake (EI) for an ad libitum lunch meal was estimated to be approximately 261 kcal. The standard deviation of mean change from baseline in EI was estimated from literature sources[26,27] which were randomized, double-blind, placebo-controlled studies with endpoints and experimental conditions similar to the current protocol.

The null hypothesis to be tested is that the difference between liraglutide and placebo is greater than or equal to 0 after 6 weeks of dosing vs. the alternative hypothesis that the difference between liraglutide and placebo is less than 0 after 6 weeks of dosing. Using a between-group comparison at Week 6, 25 completers in each arm provides approximately 85% power to detect a true mean change from baseline in energy intake equal to 200 kcal. This assumes a type 1 error equal to 5% (one-sided). Keeping remaining assumptions the same, for a higher estimated SD of approximately 283 kcal, the power would reduce to 79%. This estimate is for a test conducted at a one-sided level of significance of 5%. Assuming a 15% average drop-out in the study, the sample size would be approximately 30 randomized subjects per arm for a total sample size of 60 randomized subjects, yielding 50 completers.

9.2. Efficacy Analysis

All subjects who meet all of the following criteria will be included in the efficacy analysis:

- Completed baseline assessment of food intake;
- Received at least one dose of randomized, blinded IP; AND
- Completed at least one post-baseline measurement (after taking randomized IP).

Subjects who withdraw prior to tolerating liraglutide 1.8 mg daily for 2 weeks will not be included in the efficacy analysis.

9.2.1. Analysis of the Primary Endpoint

The primary endpoint is change from baseline in mean energy intake, measured in Kcal, during ad libitum lunch test meals. Mean energy intake will be calculated from ad libitum lunch test meals on Day -1 and Day 0 for V3, Day 20 and Day 21 for V4, and Day 41 and Day 42 for V5. Mean change from baseline will be calculated using V3 as baseline. The data from V4 and V5 will be incorporated in the same statistical model. This longitudinal modelling technique provides robust estimates and allows assessment of the effect at Weeks 3 and 6 in the same model. The primary time point for calculation of mean change from baseline at V3 is Week 6 (V5). All other collection time points will be considered secondary.

CCI [redacted]

Supplemental analyses of the primary variable will be performed to support the robustness of the conclusions drawn from the primary analysis described above such as, verifying assumptions of normality. Details of these supplemental analyses will be included in the SAP.

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be provided for the baseline and change from baseline values by treatment group and visit.

9.2.2. Analysis of Secondary Endpoints

The secondary efficacy endpoint for food intake is change from baseline in 48-hour energy intake. The analysis method will be similar to the analysis method for the primary endpoint.

Detailed description of analyses for other secondary endpoints will be outlined in the SAP. Continuous and discrete modelling techniques will be applied whenever applicable.

CCI [redacted]

9.3. Pharmacokinetic Analysis

9.3.1. Acetaminophen

The acetaminophen concentration population is defined as all enrolled subjects who received at least one dose of acetaminophen at the in-patient visit and in whom at least one concentration value is reported.

Similar to previously published studies,[17,28] the following parameters will be assessed: maximum acetaminophen concentration (C_{max}); time to maximum acetaminophen concentration (T_{max}); area under acetaminophen concentration curve from 0 to 60 minutes ($AUC_{0–60\ min}$); area under acetaminophen concentration curve from 0 to 300 minutes ($AUC_{0\text{-}300\ min}$) and relative acetaminophen exposure during the first postprandial hour ($AUC_{0\text{-}60\ min}/AUC_{0–300\ min}$). PK concentrations will be summarized and presented with summary statistics and data permitting, additional pharmacokinetic parameters may be estimated.

CCI [redacted]

9.4. Analysis of Other Endpoints

Pharmacogenomic data (Prep D1.5 samples), CCI [redacted] When these samples are analyzed, the results will be reported separately and not part of the clinical study report.

9.5. Safety Analysis

AEs, ECGs, BP, PR, and safety laboratory data will be reviewed and summarized, and any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical

examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

The safety analysis set will include all subjects who have received at least one dose of blinded IP. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. Categorical outcomes (eg, AEs) will be summarized by subject counts and percentage. Continuous outcome (eg, BP, heart rate, etc) will be summarized using N, mean, median, standard deviation, etc. Change from baseline in laboratory data, ECGs and vital signs will also be summarized. Subject listings will be produced for these safety endpoints accordingly.

Data relevant to the assessment of suicidality will be mapped to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes. Baseline and post-baseline C-SSRS data (mapped to C-CASA scores) will be summarized descriptively by treatment group at baseline and each post-baseline visit.

The safety analyses will be carried out in the safety population, detailed analyses will be described in the SAP.

9.5.1. Electrocardiogram Analysis

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS interval will be summarized by treatment and time.

The number (%) of subjects with maximum post dose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment

	Borderline (msec)	Prolonged (msec)
Absolute value	≥450 - <480	≥480
Absolute change	30-<60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

9.6. Interim Analysis

This study will not be utilizing an interim analysis.

9.7. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs[data collection tool (DCTs)] are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer investigator sites, it is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in the United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual patients have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
AE	adverse event
ALT	alanine aminotransferase
$AUC_{0–60\ min}$	area under acetaminophen concentration curve from T = 0 - 1 h
$AUC_{0–300\ min}$	area under acetaminophen concentration curve from T = 0 - 5 h
$AUC_{0–60\ min}$ /$AUC_{0–300\ min}$	relative acetaminophen exposure during the first postprandial hour
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BBS	Biospecimen Banking System
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
C-CASA	Columbia Classification Algorithm of Suicide Assessment
C-SSRS	Columbia Suicide Severity Rating Scale
CK	creatine kinase
C_{max}	maximum acetaminophen concentration
CO2	carbon dioxide
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
DCT	data collection tool
CCI [redacted]	[redacted]
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EI	energy intake
EIA	enzyme immunoassay
EU	European Union
EudraCT	European Clinical Trials Database
f/u	follow up
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation	Term
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1R	GLP-1 receptor
HbA1c	glycosylated hemoglobin
hCG	human chorionic gonadotropin
HCl	hydrochloric acid
HCVAb	hepatitis C antibody
HDL-C	High-density lipoprotein cholesterol
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
ICD	informed consent document
ICH	International Conference on Harmonisation
ICF	informed consent form
ID	identification code
IND	investigational new drug
INR	international normalized ratio
IP	Investigational product
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LCSW	licensed clinical social worker
LDL-C	low-density lipoprotein cholesterol
LFT	Liver function test
LSLV	last subject last visit
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MEN2	multiple endocrine neoplasia syndrome type 2
MHP	mental health professional
CCI [redacted]	[redacted]
MRI	magnetic resonance spectroscopy
MTC	medullary thyroid carcinoma
N/A	not applicable
OCPs	oral contraceptive pills
PCD	Primary completion date
PHQ-9	Patient Health Questionnaire-9
PI	principal investigator
PK	Pharmacokinetics
PGx	pharmacogenomics
PNP	psychiatric nurse practitioner
PR	pulse rate
PT	prothrombin time

Abbreviation	Term
PYY	pancreatic peptide YY3-36
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SIB	Suicidal Ideation and Behavior
SOP	standard operating procedures
SPA	spontaneous physical activity
SRSD	single reference safety document
TA	therapeutic area
TBili	total bilirubin
THC	tetrahydrocannabinol
Tmax	time to maximum paracetamol concentration
TSH	thyroid stimulating hormone
UA	urinalysis
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
V	visit
VAS	visual analog scale
WBC	white blood cell
CCI [redacted]	[redacted]

Appendix 2. Questions Listed in the Visual Analog Scale (VAS)

I am not hungry at all	How hungry do you feel?	I have never been more hungry
I am completely empty	How satisfied do you feel?	I can not eat another bite
Not at all full	How full do you feel?	Totally full
Nothing at all	How much do you think you can eat?	A lot
Yes, very much	Would you like to eat something sweet?	No, not at all
Yes, very much	Would you like to eat something salty?	No, not at all
Yes, very much	Would you like to eat something savoury?	No, not at all
Yes, very much	Would you like to eat something fatty?	No, not at all