CLINICAL STUDY PROTOCOL

A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Daily Administrations of the GLP-1 Analogue ROSE-010 on Appetite and Food Intake in Overweight and Obese Subjects

Investigational Product: ROSE-010

Protocol Number: RP-24-02

Sponsor:

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SIGNATURE PAGE

STUDY TITLE: A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Daily Administrations of the GLP-1 Analogue ROSE-010 on Appetite and Food Intake in Overweight and Obese Subjects

We, the undersigned, have read this Protocol and agree that it contains all necessary information required to conduct the study.

Signature
Enda Kenny
Electronically signed by: Enda Kenny
Reason: Approved
Date: Oct 17, 2024 11:45 GMT+1

Date
17-Oct-2024

Enda Kenny, PhD
CEO
Rose Pharma Inc.

Signature
Yulia Lurye
Electronically signed by: Yulia Lurye
Reason: Approved
Date: Oct 17, 2024 13:05 GMT+1

Date
17-Oct-2024

Yulia Lurye, MD
Medical Director
Medpace, Inc.

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this Protocol. I approve this document, and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this Protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this Protocol and access to all information furnished by Rose Pharma Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Rose Pharma Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Rose Pharma Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and applicable regional regulations.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Daily Administrations of the GLP-1 Analogue ROSE-010 on Appetite and Food Intake in Overweight and Obese Subjects

PROTOCOL NUMBER: RP-24-02

INVESTIGATIONAL PRODUCT: ROSE-010

PHASE: 2

INDICATION: Weight management and obesity

OBJECTIVES:

The primary objective of this study is to assess the efficacy of ROSE-010 on food intake.

The secondary objectives of this study are the following:

- To assess the efficacy of ROSE-010 on hunger;
- To assess the efficacy of ROSE-010 on satiety;
- To assess the efficacy of ROSE-010 on prospective consumption;
- To assess the efficacy of ROSE-010 on desire to eat;
- To assess the efficacy of ROSE-010 on palatability;
- To characterize the pharmacokinetics (PK) of ROSE-010 following subcutaneous (SC) administration on Day 1 and Day 7; and
- To evaluate safety and tolerability of SC administrations of ROSE-010 to overweight and obese subjects.

The exploratory objective of this study is to assess the effect of 7 days of treatment with ROSE-010 on body weight.

POPULATION:

Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Female subjects between the age of 18 and 65 years, inclusive, at Screening;
2. Body mass index ≥27 and ≤35 kg/m^2 at Screening;
3. Good health, as assessed by the Investigator, based on medical, surgical, and psychiatric history, physical examination, 12-lead electrocardiogram (ECG), vital sign assessments, and clinical laboratory evaluations at Screening and Check-In;

4. Subjects must have a negative serum pregnancy test result at Screening and at Check-In and must not be pregnant, lactating, or planning a pregnancy from the Screening Visit to 60 days after the last dose of study drug;
5. Female subjects of non-childbearing potential must be either surgically sterile (ie, had a hysterectomy, bilateral tubal ligation, bilateral salpingectomy, and/or bilateral oophorectomy at least 26 weeks prior to Screening) or postmenopausal (ie, have experienced spontaneous amenorrhea for at least 2 years, with a follicle-stimulating hormone level in the postmenopausal range at Screening based on the central laboratory's ranges);
6. Subjects of childbearing potential (ie, ovulating, premenopausal, and not permanently surgically sterile) with male partners will be included if they are either sexually inactive (complete abstinence from heterosexual activity if in line with the subject's preferred and usual lifestyle) for at least 30 days prior to the first dose of study drug and agree to continue complete abstinence for at least 60 days after the last administration of study drug, or, if sexually active, agree to use a medically accepted contraceptive regimen during their participation in the study and for at least 60 days after the last administration of study drug. Medically accepted contraceptive methods are defined as those with 90% or greater efficacy and include the following:
    - Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before Screening;
    - Intrauterine device for at least 12 weeks before Screening; or
    - Vasectomy in the male partner (as long as performed at least 6 months prior to study drug administration).

    Note: Sexual abstinence is considered an effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. In this study, abstinence is only acceptable if in line with the subject's preferred and usual lifestyle. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not acceptable methods of contraception.
7. Able to understand and willing to comply with study procedures and restrictions (including confinement to the clinical pharmacology unit [CPU], fasting and meal requirements, restrictions on physical activity, prohibition of recreational drugs or alcohol, and medication restrictions) and provide written informed consent according to institutional and regulatory guidelines.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Previous medical history or evidence of an uncontrolled intercurrent illness that, in the opinion of the Investigator and/or Medical Monitor, may compromise the safety of the subject in the study or interfere with evaluation of the study drug or compromise the subject's ability to participate in the study;
2. Personal or family history of long QT syndrome, Torsades de Pointes, or other complex ventricular arrhythmias, or family history of sudden death;

3. History of or current clinically significant arrhythmias as judged by the Investigator, including ventricular tachycardia, ventricular fibrillation, atrial fibrillation, sinus node dysfunction, or clinically significant heart block. Subjects with minor forms of ectopy (eg, premature atrial contractions) are not necessarily excluded;
4. Prolonged QTcF >470 msec based on the average of triplicate 12-lead ECGs at Screening or Check-In;
5. Resting heart rate (after the subject is seated for at least 5 minutes) <50 beats per minute or >100 beats per minute at Screening or Check-In;
6. Systolic blood pressure (after the subject is seated for at least 5 minutes) ≥150 mmHg or <90 mmHg or diastolic blood pressure ≥100 mmHg or <50 mmHg at Screening or Check-In;
7. Temperature >37.6°C (99.7°F, measured orally) at Screening or Check-In;
8. Respiratory rate <12 or >20 breaths/minute at Screening or Check-In;
9. Clinically significant or active gastric emptying abnormality (eg, gastroparesis or gastric outlet obstruction, intestinal obstruction, or any gastrointestinal [GI] motility disorders); malabsorption, including chronic constipation/diarrhea, celiac disease, inflammatory bowel disease, or bowel resection; or chronic use of drugs that directly affect GI motility (eg, anticholinergics, 5-hydroxytryptamine [serotonin] antagonists, opiates);
10. Obesity induced by other endocrinologic disorders (eg, Cushing syndrome, acromegaly, inadequately treated hypothyroidism) or diagnosed monogenic or syndromic forms of obesity (eg, melanocortin 4 receptor deficiency or Prader-Willi syndrome);
11. Thyroid disease that is not controlled (thyroid-stimulating hormone outside normal range at Screening);
12. Symptomatic gallbladder disease within the past 2 years or history of cholecystectomy;
13. History or presence of acute or chronic pancreatitis;
14. A positive response to either Question 4 or Question 5 on the Suicidal Ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) or a positive response to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS at Screening or Check-In;

    Note: A subject should be referred to a mental health professional if she has any suicidal ideation of Type 4 or 5 on the C-SSRS at any time during the study.
15. A baseline score >15 on the Patient Health Questionnaire 9 at Screening or Check-In;
16. A history of Major Depressive Disorder within the last 2 years;
17. Any lifetime history of a suicide attempt;
18. A history of other severe psychiatric disorders (eg, schizophrenia, bipolar disorder);
19. Previous bariatric surgery, procedure for obesity, or GI surgery altering GI passage, motility, and/or nutrient absorption or recent (within 6 months of Screening) changes in body weight (≥5%) due to dieting, including commercial weight loss programs, or pharmacologic treatment;

20. Currently on or planning to participate in any weight loss regimen during the course of the study;
21. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2;
22. History of malignancy, except the following: curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colorectal polyps >5 years prior to Screening;
23. Abnormal fasting blood glucose (ie, >125 mg/dL) at Screening or Check-In and/or HbA1c (ie, >6.4%) at Screening, or prior history/diagnosis of any type of diabetes mellitus (eg, type 1, type 2, or gestational);
24. Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and/or total bilirubin above the central laboratory's upper limit of normal (ULN); fasting triglycerides >500 mg/dL; impaired renal function with estimated glomerular filtration rate <90 mL/min/1.73 m^2 at Screening or Check-In; or calcitonin above the central laboratory's ULN at Screening;
25. Any other clinical laboratory values that are meaningfully outside of normal limits (based on laboratory normal range) at Screening or Check-In in the opinion of the Investigator;
26. Positive for HIV antibody, hepatitis C virus antibody, or hepatitis B surface antigen at Screening;
27. Positive COVID-19 test at Check-In;
28. Use of any prescribed or over-the-counter (OTC) medication other than approved contraceptives (see Inclusion Criterion 6) within 14 days or 5 half-lives (whichever is longer) prior to dosing on Day 1 and throughout the study;

    Note: Following study drug administration, medications used for the treatment of adverse events (AEs) may be allowed at the discretion of the Investigator or designee.
29. Any glucagon-like peptide-1 (GLP-1) receptor agonist, GLP-1/glucose-dependent insulinotropic polypeptide dual agonist (eg, tirzepatide), or any prescription or OTC medications intended for weight loss or with a potential impact on weight and appetite regulation (eg, stimulant medications) within 6 months of Screening;
30. Positive urine drug screen or positive alcohol breath test result at Screening or Check-In;
31. Use of tobacco- or nicotine-containing products (including vaping devices) within 6 months prior to Screening and throughout the study, or positive cotinine test result at Screening or Check-In;
32. History of alcoholism or drug/chemical abuse within 12 months prior to Screening, or unwillingness to agree to abstain from alcohol and drugs throughout the study;
33. Typical consumption of ≥14 alcoholic drinks weekly;

    Note: 1 drink of alcohol is equivalent to ½ pint of beer (285 mL), 1 glass of spirits (25 mL), or 1 glass of wine (125 mL).
34. Surgical procedures within 4 weeks of Check-In or planned elective surgery during the study period;

35. Known allergy to any ingredient of ROSE-010 or any history of severe allergic reaction (including drugs, food, insect bites, or environmental allergens);
36. Inadequate venous access;
37. Blood donation ≥500 mL within 8 weeks prior to Screening, blood transfusion/severe blood loss within 3 months prior to Screening, hemoglobinopathy, or hemoglobin <11 g/dL;
38. Unwillingness or inability to refrain from strenuous exercise from 4 days prior to Day 1 until discharge from the CPU on Day 8;
39. Actively participating in an experimental therapy study; or received experimental therapy with a small molecule within 30 days of the first dose of study drug or 5 half-lives, whichever is longer; or received experimental therapy with a large molecule within 90 days of the first dose of study drug or 5 half-lives, whichever is longer;
40. Considered by the Investigator, after review of eligibility data, to be unsuitable for any other reason that may either place the subject at increased risk during participation or interfere with the interpretation of the study outcomes.

STUDY DESIGN AND DURATION:

This is a randomized, placebo-controlled, double-blind, parallel-group Phase 2 study evaluating the efficacy, safety, and PK of daily administrations of the GLP-1 analogue ROSE-010 on appetite and food intake in overweight and obese female subjects. The study is planned to include 3 parallel treatment groups, with 40 subjects randomized in a 3:3:2 ratio to receive ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo, respectively, as follows:

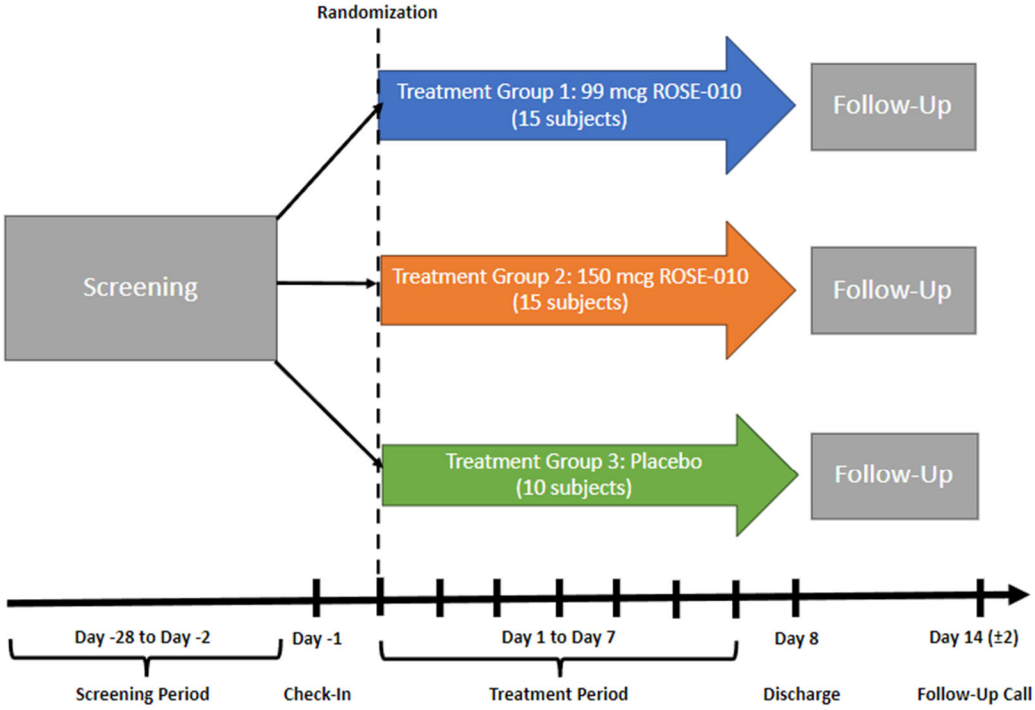
- Treatment Group 1: 99 mcg ROSE-010 (15 subjects) administered SC once daily for 7 consecutive days;
- Treatment Group 2: 150 mcg ROSE-010 (15 subjects) administered SC once daily for 7 consecutive days; and
- Treatment Group 3: Placebo (10 subjects) administered SC once daily for 7 consecutive days.

For each subject, the study will consist of the following:

- Screening Period (Day -28 to -2) and Check-In (Day -1), during which subjects will be evaluated for eligibility;
- Treatment Period (Day 1 to Day 7), during which subjects will receive 7 once-daily doses of ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo, followed by discharge on Day 8; and
- Follow-up phone call, which will be completed 7 (±2) days after the final dose of study drug.

Figure S1 below provides a study schema.

Figure S1. Study Schema



Consenting subjects will be screened for eligibility according to study-specific inclusion/exclusion criteria within 28 days prior to the first administration of study drug (Day 1).

Subjects will be admitted to the clinical pharmacology unit (CPU) on Day -1 and will remain confined to the CPU until discharge on Day 8/ET. On Day 1, subjects will be randomized in a 3:3:2 ratio to receive ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo, respectively. Study drug will be administered SC once daily (30 minutes before lunch) for 7 consecutive days (Days 1 to 7). All meals served at the CPU will be standardized and controlled. Subjects will consume as much of the standardized lunch as desired, and food will be weighed prior to and after eating to assess food intake. Assessments of hunger, satiety, prospective consumption, desire to eat, palatability, and nausea will be performed. Blood samples will be collected to evaluate PK. Safety parameters will be monitored.

Subjects will be discharged on Day 8/ET. The end of study follow-up phone call will be completed 7 (±2) days after the final dose of study drug.

Unscheduled procedures or visits and/or additional follow-up may be required for subjects with clinically significant abnormal laboratory findings, unresolved treatment-emergent AEs, serious AEs that require follow-up laboratories and review, or clinically significant AEs.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Study drug (ROSE-010 [99 mcg or 150 mcg] or placebo) will be administered as a single SC injection once daily (30 minutes before lunch) for 7 consecutive days (Days 1 to 7). Study drug will be administered by blinded clinical staff who are trained, qualified, and designated by the

Investigator. All doses will be administered SC in the abdominal skin; the injection site location in the abdomen will be rotated at each administration.

ROSE-010 (300 mcg/mL) is a clear, colorless, aqueous, sterile solution for SC injection and will be provided in 2R injection vials. Each vial contains 1 mL ROSE-010 and is for single use.

Commercially available sterile normal saline (0.9% NaCl) solution for injection will be used as the placebo.

CRITERIA FOR EVALUATION:

The primary endpoint is the amount of food (weight and energy content) consumed during lunch on each day of treatment (Day 1 to Day 7) after administration of ROSE-010 at 2 dose levels (99 mcg and 150 mcg) compared to placebo.

The secondary endpoints are the following:

- Hunger score on a visual analogue scale (VAS) (0 to 100 mm) measured pre-dose; 20 minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours after study drug administration;
- Satiety score on a VAS (0 to 100 mm) measured pre-dose; 20 minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours after study drug administration;
- Prospective consumption score on a VAS (0 to 100 mm) measured pre-dose; 20 minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours after study drug administration;
- Desire to eat score on a VAS (0 to 100 mm) measured pre-dose; 20 minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours after study drug administration;
- Palatability (tastiness) score on a VAS (0 to 100 mm) measured at the start of lunch;
- Incidence and severity of nausea on a VAS (0 to 100 mm) measured pre-dose; 20 minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours after study drug administration; and
- Plasma PK analysis of ROSE-010: maximum plasma concentration (C_{max}), time to C_{max}, area under the plasma concentration-time curve, terminal phase elimination half-life, and other plasma PK parameters.

The exploratory endpoint is the effect of 7 days of treatment with ROSE-010 on body weight, measured as the relative change (ie, percent change) in body weight from baseline to Day 8.

SAFETY:

Safety assessments will include injection site reactions, incidence and severity of nausea on a VAS (0 to 100 mm), clinical laboratory parameters, blood glucose monitoring, vital signs, ECGs, physical examinations, incidence and severity of treatment-emergent AEs, and C-SSRS.

STATISTICAL METHODS:

The Per Protocol Analysis Set will include all randomized subjects who have received all doses and have evaluable efficacy data, and no major Protocol deviation that significantly affects the evaluability of the subjects in the study.

The Safety Analysis Set will include all randomized subjects who have received at least 1 dose of study drug (ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo). Subjects will be analyzed according to the treatment they actually received if this differs from that to which the subject was randomized.

The PK Analysis Set will include subjects who have received at least 1 dose of ROSE-010 99 mcg or ROSE-010 150 mcg and have at least 1 measurable post-dose plasma PK concentration.

Study data will be summarized by treatment group using descriptive statistics, figures, and/or raw data listings where appropriate.

Continuous data and change from baseline will be presented in terms of evaluable observations (n), arithmetic mean, standard deviation, median, minimum, and maximum value.

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment (ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo) and by assessment time. Individual subject data will be listed by treatment, subject number, and, where applicable, by assessment time.

All descriptive summaries and statistical analyses will be performed using SAS version 9.4 or later (SAS Institute, Inc., Cary, North Carolina).

Baseline will be defined as the last data collection point (assessment) prior to the first dose of ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo.

SAMPLE SIZE DETERMINATION:

Approximately 40 subjects will be enrolled.

No formal sample size calculation was performed. Given the exploratory nature of this study, the proposed sample size is considered sufficient to provide adequate information for the study objectives.

SITE: 1 site in the United States

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
21 CFR	Title 21 of the Code of Federal Regulations
AE	Adverse event
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration
BMI	Body mass index
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus Disease 2019
CPU	Clinical pharmacology unit
CRA	Clinical Research Associate
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated hemoglobin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome-constipation
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
NOAEL	No observable adverse effect level
OTC	Over-the-counter
PD	Pharmacodynamic(s)
PHQ-9	Patient Health Questionnaire 9
PK	Pharmacokinetic(s)
QTcF	Heart-rate corrected QT interval using Fridericia's formula
SAE	Serious adverse event

Abbreviation	Definition
SC	Subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Terminal phase elimination half-life
T2DM	Type 2 diabetes mellitus
T_{max}	Time to maximum plasma concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

Rose Pharma Inc. (hereinafter referred to as Rose Pharma) is developing ROSE-010, a glucagon-like peptide-1 (GLP-1) analogue, for weight management and obesity. This is a Phase 2 study to evaluate the efficacy, safety, and pharmacokinetics (PK) of ROSE-010 in overweight and obese female subjects.

1.1 Background

ROSE-010 is a 31 amino acid peptide identical to native GLP-1 (7-37) but position 8 has been substituted by valine, which renders the molecule resistant to dipeptidyl peptidase IV degradation. This amino acid substitution results in a prolonged circulating half-life of approximately 1 hour in the human following subcutaneous (SC) injection. ROSE-010 is identical to LY307161, a product previously under development by Eli Lilly and Company for the treatment of type 2 diabetes mellitus (T2DM).

Following the launch of the first GLP-1 drugs to treat diabetes it became clear that they had a significant effect on weight loss. As obesity and overweight are risk factors for T2DM, this was seen as a positive outcome. The effect on weight loss is due to appetite reduction and not due to increase in energy output. These clinical observations in diabetes patients, backed up by clinical studies in obese patients, led to approvals of GLP-1 drugs for weight loss in 2021.

The main side effects of all GLP-1 drugs are nausea and vomiting, and the continuous exposure to GLP-1 activity in order to maintain the weight target gives rise to continuous side effects.[1] Rose Pharma believes that ROSE-010 may be an attractive option for overweight or obese patients who discontinue use of the longer acting versions due to persistent and continuous gastric side effects such as nausea.

ROSE-010 is fast acting and starts to exert its effects within 30 minutes with a plasma half-life of about 1 hour and its effects diminish within a few hours, making it ideally suited for administration around the main meal of the day.

ROSE-010 is being developed for indications where GLP-1 is implicated in the underlying physiology such as weight management, obesity, and gastrointestinal (GI) disturbances including irritable bowel syndrome (IBS).

Rose Pharma is now initiating clinical studies with ROSE-010 to investigate the preliminary efficacy on appetite and food intake in overweight and obese subjects.

1.2 Non-Clinical Summary

In in vitro pharmacology studies, ROSE-010 and LY307161 exhibited comparable potency to each other and were both of similar potency to GLP-1 when assayed utilizing the Millipore GPCRProfiler® Service. LY307161 binds and activates the rat and human GLP-1 receptors with lower affinity than the naturally occurring peptide. From these results, it appears that the increase in activity of the peptide compared to native GLP-1 observed in vivo is not due to an increase in the intrinsic activity of the peptide, but rather to the prolonged preservation of its activity compared to native GLP-1, by virtue of its resistance to proteolytic degradation in vivo.

ROSE-010 and LY307161 have activity in in vivo animal models similar to native GLP-1, including decreasing the GI transit rate in mice. ROSE-010 at all doses had a prompt inhibitory effect on the migrating myoelectric complex, similar to GLP-1 in all animals. The action of

ROSE-010 was inhibited in the presence of Exendin(9-39)amide (a GLP-1 receptor blocker), indicating that ROSE-010 mediates the migrating myoelectric complex effect through the GLP-1 receptor.

The PK profiles of ROSE-010 were determined following SC administrations in rats and dogs. PK parameters were linear and proportional to dose. Absorption of ROSE-010 following SC administration was rapid in both rats and dogs, with time to peak concentration values of 0.25 hours in rats and <1 hour in dogs. After SC administration, ROSE-010 had a plasma half-life ranging from 0.24 to 1.68 hours at Day 91. No sexual dimorphism in PK parameters was detected in rats or dogs. There was no apparent accumulation of ROSE-010 in plasma following repeated daily SC administration.

Single and repeated SC doses of ROSE-010 were well tolerated in both rats and dogs, and no animals died as a result of the test article at any dose tested up to 0.3 mg/kg/day and 0.9 mg/kg/day in rats and dogs, respectively. In rats, clinical findings included decreases in body weight gain, decreases in red blood cells in females, decrease in total cholesterol, and increases in adrenal weight in conjunction with minor hypertrophy in the zona glomerulosa at 0.3 mg/kg/day. In repeated dose studies in dogs, clinical findings included occasional soft or liquid feces, a decrease in creatine kinase levels in females, lower relative prostate weights, and lower testes/epididymides weights at 0.9 mg/kg/day. All findings were at least partially reversed at 1 month after the last dose, except the decrease in creatine kinase in dogs, which persisted at 1 month. The no observable adverse effect level (NOAEL) was considered to be 0.085 mg/kg/day and 0.9 mg/kg/day for rats and dogs, respectively. The mean systemic exposure (area under the serum concentration time curve from time 0 to time t) at the NOAEL was 6.023 h*ng/mL (rats) and 387 h*ng/mL (dogs), males and females, Days 42 and 91 combined.

Effects of ROSE-010 on heart rate were evaluated in a 13-week SC multiple-dose toxicity study in the dog. Heart rates were variable but there appeared to be a modest, but not dose-related, reduction of heart rate in male groups treated with the test article in Week 12.

Nonclinical toxicology studies of LY307161 have demonstrated minimal evidence of target organ toxicity. LY307161 has been demonstrated to produce systemic effects in animals typical of the extended pharmacodynamic (PD) effects of native GLP-1, including reductions in food consumption and body weight or body weight gain. There were no indications of local tolerability issues with LY307161.

1.3 Clinical Summary

The recombinant version of ROSE-010 (LY307161) has been tested in 3 clinical studies. Two Phase 1 clinical studies were conducted to evaluate safety and PK; 1 in healthy subjects, and 1 in T2DM patients. A Phase 2a efficacy study (GL61-001) for the treatment of pain of IBS has been performed in Europe.

LY307161 was generally safe and well tolerated when administered SC in early human clinical studies. Nausea and vomiting were observed as the consistent dose-related side effects of LY307161. Although the majority of subjects tolerated all doses, doses of 500 mcg and greater produced nausea and/or vomiting in the majority of subjects. The maximum tolerated dose was therefore determined to be 400 mcg.

The most frequent adverse events (AEs) in single and multiple dose studies were nausea and vomiting, which occurred at time to peak concentration. These AEs were considered to be dose-related and were of short duration, suggesting a direct pharmacological action of LY307161.

In one study in diabetic patients (H5N-EW-GFFB), a dose-related rise in both supine systolic and supine diastolic blood pressure was observed, which was maximal at 15/11 mm Hg at 450 mcg of LY307161. No rise was demonstrated in standing systolic or standing diastolic blood pressure, and supine blood pressure returned to baseline in approximately 2 hours.

Measurements of antibody titers to LY307161 in diabetic subjects (H5N-EW-GFFB) and IBS patients (GL61-001) prior to exposure to LY307161 and 30 days after the last exposure showed no clinically significant antibody response to LY307161.

Study RP-09-01 was a single-center, randomized, parallel-group, double-blind, placebo-controlled, dose response, PD, and PK study evaluating the effects of ROSE-010 on gastric, intestinal, and colonic transit and gastric volumes in female patients with IBS-constipation (IBS-C). Doses of 30, 100, or 300 mcg ROSE-010 or matching placebo were administered via abdominal SC injection once daily for 3 consecutive days and 1 final day 2 to 10 days later, over a 13-day interval. The results of this study showed that ROSE-010 actually accelerated colonic transit at 48 hours and did not retard colonic transit at the primary colonic transit endpoint at 24 hours. There was no exacerbation of IBS-C bowel symptoms and no significant effect on stool frequency or consistency.

Overall, in the IBS patient populations studied to date there have been no exacerbations of constipation.

Study RP-23-01 was a randomized, placebo-controlled, double-blinded, 3-treatment, 3-period cross-over study with the primary aim to assess the effect of a SC administration of 2 dose levels of ROSE-010 on ad libitum food intake. Fourteen male and female subjects were randomized to receive a sequence of placebo, 100 mcg ROSE-010, and 150 mcg ROSE-010. Eleven subjects completed all 3 treatment periods. There was a signal indicating a possible dose dependency in amount of food consumed, suggesting that ROSE-010 may have a role in weight management and obesity. No safety concerns were raised.

1.3.1 General Safety of Glucagon-Like Peptide-1 Receptor Agonists

There are 2 GLP-1 receptor agonists approved for weight loss in overweight and obese subjects in the United States, namely liraglutide and semaglutide, marketed under the brand names of SAXENDA® and WEGOVY®, respectively. These were both initially developed for treatment of type 2 diabetes. There is an extensive history of use of these and other GLP-1 agonists which is instructive as to the general safety and risks of the class in general based on the mechanism of action. A summary of the prescribing information for SAXENDA and WEGOVY (United States) is provided in the Investigator's Brochure.[2]

1.4 Rationale

Although GLP-1 agonists are already available for weight management and obesity, ROSE-010 may be an attractive option for overweight or obese patients who discontinue use of the longer-acting versions due to persistent and continuous gastric side effects such as nausea. Indications of a possible effect on amount of food consumed, suggesting that ROSE-010 may have

a role in weight management and obesity, were seen in a Phase 1 study in overweight and obese subjects.[3]

The aim of this Phase 2 clinical study of ROSE-010 given SC to generally healthy subjects with a body mass index (BMI) of ≥27 and ≤35 kg/m^2 is to generate safety, preliminary efficacy (appetite and food intake), and PK data to support further clinical development of ROSE-010 in weight management and obesity.

1.5 Risk/Benefit

Although obesity was originally considered to be the result of lifestyle choices, increased medical understanding of the metabolic and psychological processes underlying the condition have led it to be classified as a chronic medical condition.[4] Globally, more than 890 million people are considered to be clinically obese,[5] and the consequences for the health system in terms of associated illness (diabetes, cardiovascular disease, sleep apnea) are immeasurable.

The main side effects of all GLP-1 drugs are nausea and vomiting and the continuous exposure to GLP-1 activity in order to maintain the weight target gives rise to continuous side effects.[1] In a real-world setting, outside the tightly controlled environment of clinical studies, a large number of patients discontinue treatment. A United Kingdom study[6] reported that up to 65% of T2DM patients with obesity and overweight discontinue GLP-1 treatment within 2 years. Interestingly, more people discontinue the once weekly version, which may reflect the higher incidence of nausea and vomiting with the once weekly version than the once daily version.

ROSE-010 is being developed for indications where GLP-1 is implicated in the underlying physiology, such as weight management, obesity, and gastrointestinal disturbances including IBS, and its primary mode of action is related to effects on gastric emptying. It is fast acting and starts to exert its effects within 30 minutes. ROSE-010 has a plasma half-life of about 1 hour and its effects diminish within a few hours, making it ideally suited for administration around the main meal of the day.

Rose Pharma believes that ROSE-010 may be an attractive option for some overweight or obese patients who discontinue use of the longer-acting versions due to persistent and continuous gastric side effects such as nausea. In a Phase 1 study in overweight and obesity there was a signal indicating a possible dose dependency in amount of food consumed, suggesting that ROSE-010 may have a role in weight management. Future studies are warranted to further investigate efficacy and safety in this population.

The combined safety data with ROSE-010 from the pre-clinical and clinical studies have not revealed any safety issues that would outweigh the expected value of the study.

The healthy subjects participating in this study will have no medical benefit from participation and their safety and wellbeing are of outmost importance.

All study subjects will remain at the study site from the day before the first dose (Day -1) until discharge on Day 8/Early Termination (ET). During the confinement to the clinic, all subjects will be closely monitored by medical staff.

The study will be performed at a specialized research clinic with extended experience from early phase studies and adequate procedures in place to handle unexpected and expected adverse reactions in the study subjects. The Investigator will ascertain that adequate facilities and procedures are available to handle emergency situations should they occur during the study.

The excipients of the study drug formulation to be used are all well-known and accepted for use in injectable formulations.

Risks and discomfort related to medical devices used in the study (eg, blood pressure measuring devices) are considered low and ethically justifiable since these devices are used in routine medical care.

While keeping the identified risk factors at a minimum level in order to not expose the study subjects to risks that would not be ethically justifiable, the planned study assessments are considered sufficient to meet the scientific and medical goals for the study. It is therefore concluded that the potential benefits from the study will outweigh the potential risks for the treated subjects.

As ROSE-010 is an experimental medicine, it is possible that unforeseen, unknown, or unanticipated drug reactions and toxicities may occur. However, this study Protocol is designed to mitigate risks to subjects through a detailed plan for careful safety monitoring; systematic review of AEs, serious AEs (SAEs), and PK; and active pharmacovigilance review to assess for safety signals or trends.

These considerations indicate the risk/benefit ratio for ROSE-010 in this study to be favorable.

Refer to the Investigator's Brochure for additional information.[2]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the efficacy of ROSE-010 on food intake.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess the efficacy of ROSE-010 on hunger;
- To assess the efficacy of ROSE-010 on satiety;
- To assess the efficacy of ROSE-010 on prospective consumption;
- To assess the efficacy of ROSE-010 on desire to eat;
- To assess the efficacy of ROSE-010 on palatability;
- To characterize the PK of ROSE-010 following SC administration on Day 1 and Day 7; and
- To evaluate safety and tolerability of SC administrations of ROSE-010 to overweight and obese subjects.

2.3 Exploratory Objective

The exploratory objective of this study is to assess the effect of 7 days of treatment with ROSE-010 on body weight.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a randomized, placebo-controlled, double-blind, parallel-group Phase 2 study evaluating the efficacy, safety, and PK of daily administrations of the GLP-1 analogue ROSE-010 on appetite and food intake in overweight and obese female subjects. The study is planned to include 3 parallel treatment groups, with 40 subjects randomized in a 3:3:2 ratio to receive ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo, respectively, as follows:

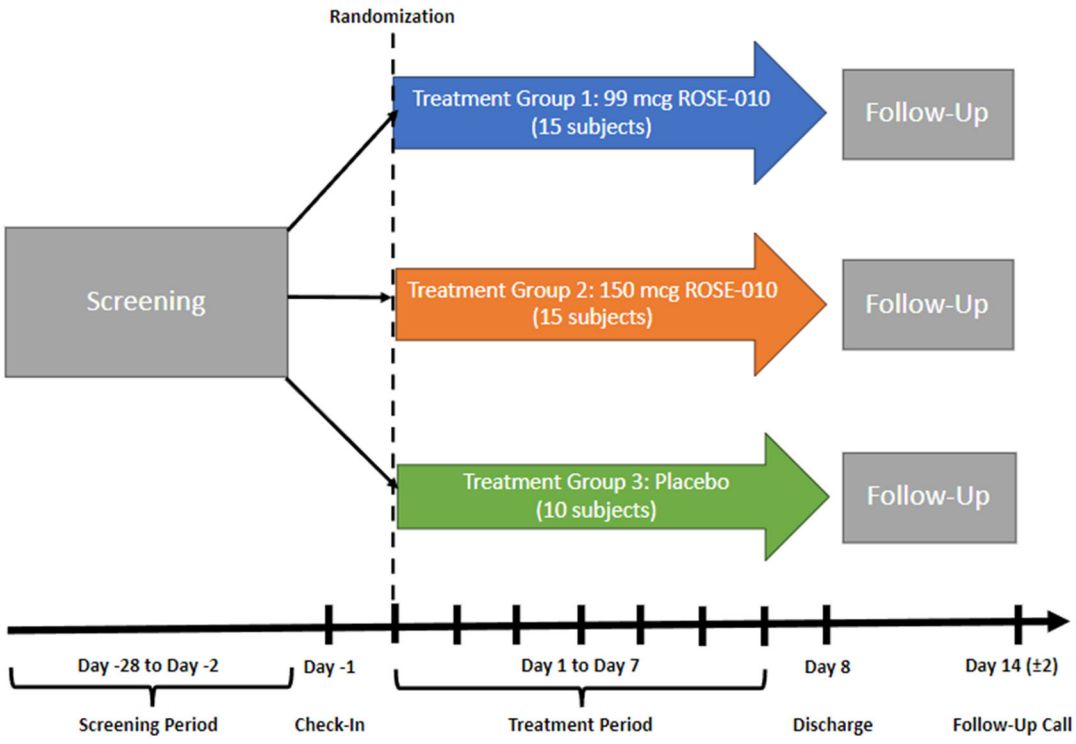
- Treatment Group 1: 99 mcg ROSE-010 (15 subjects) administered SC once daily for 7 consecutive days;
- Treatment Group 2: 150 mcg ROSE-010 (15 subjects) administered SC once daily for 7 consecutive days; and
- Treatment Group 3: Placebo (10 subjects) administered SC once daily for 7 consecutive days.

For each subject, the study will consist of the following:

- Screening Period (Day -28 to -2) and Check-In (Day -1), during which subjects will be evaluated for eligibility;
- Treatment Period (Day 1 to Day 7), during which subjects will receive 7 once-daily doses of ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo, followed by discharge on Day 8; and
- Follow-up phone call, which will be completed 7 (±2) days after the final dose of study drug.

Figure 1 below provides a study schema.

Figure 1. Study Schema



Consenting subjects will be screened for eligibility according to study-specific inclusion/exclusion criteria within 28 days prior to the first administration of study drug (Day 1).

Subjects will be admitted to the clinical pharmacology unit (CPU) on Day -1 and will remain confined to the CPU until discharge on Day 8/ET. On Day 1, subjects will be randomized in a 3:3:2 ratio to receive ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo, respectively. Study drug will be administered SC once daily (30 minutes before lunch) for 7 consecutive days (Days 1 to 7). All meals served at the CPU will be standardized and controlled. Subjects will consume as much of the standardized lunch as desired, and food will be weighed prior to and after eating to assess food intake. Assessments of hunger, satiety, prospective consumption, desire to eat, palatability, and nausea will be performed. Blood samples will be collected to evaluate PK. Safety parameters will be monitored.

Subjects will be discharged on Day 8/ET. The end of study follow-up phone call will be completed 7 (±2) days after the final dose of study drug.

Unscheduled procedures or visits and/or additional follow-up may be required for subjects with clinically significant abnormal laboratory findings, unresolved treatment-emergent AEs, SAEs that require follow-up laboratories and review, or clinically significant AEs.

3.2 Study Stopping Rules

The clinical study will be suspended or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This includes the occurrence of AEs that are unknown to date in respect of their nature, severity, duration, or frequency, compared to the current established safety profile. In addition, any data deriving from other clinical studies or toxicology studies that negatively influence the risk/benefit assessment will cause discontinuation or termination of the study.

3.3 Study Indication

The proposed indication for ROSE-010 is weight management and obesity.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

Screening procedures, including vital sign assessments and abnormal laboratory tests, may be repeated no more than 1 time for eligibility purposes.

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Female subjects between the age of 18 and 65 years, inclusive, at Screening;
2. BMI ≥27 and ≤35 kg/m^2 at Screening;
3. Good health, as assessed by the Investigator, based on medical, surgical, and psychiatric history, physical examination, 12-lead electrocardiogram (ECG), vital sign assessments, and clinical laboratory evaluations at Screening and Check-In;
4. Subjects must have a negative serum pregnancy test result at Screening and at Check-In and must not be pregnant, lactating, or planning a pregnancy from the Screening Visit to 60 days after the last dose of study drug;
5. Female subjects of non-childbearing potential must be either surgically sterile (ie, had a hysterectomy, bilateral tubal ligation, bilateral salpingectomy, and/or bilateral oophorectomy at least 26 weeks prior to Screening) or postmenopausal (ie, have experienced spontaneous amenorrhea for at least 2 years, with a follicle-stimulating hormone [FSH] level in the postmenopausal range at Screening based on the central laboratory's ranges);
6. Subjects of childbearing potential (ie, ovulating, premenopausal, and not permanently surgically sterile) with male partners will be included if they are either sexually inactive (complete abstinence from heterosexual activity if in line with the subject's preferred and usual lifestyle) for at least 30 days prior to the first dose of study drug and agree to continue complete abstinence for at least 60 days after the last administration of study drug, or, if sexually active, agree to use a medically accepted contraceptive regimen during their participation in the study and for at least 60 days after the last administration of study drug. Medically accepted contraceptive methods are defined as those with 90% or greater efficacy and include the following:
   - Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before Screening;
   - Intrauterine device for at least 12 weeks before Screening; or
   - Vasectomy in the male partner (as long as performed at least 6 months prior to study drug administration).

   Note: Sexual abstinence is considered an effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. In this study, abstinence is only acceptable if in line with the subject's preferred and usual lifestyle. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not acceptable methods of contraception.
7. Able to understand and willing to comply with study procedures and restrictions (including confinement to the CPU, fasting and meal requirements, restrictions on physical activity,

prohibition of recreational drugs or alcohol, and medication restrictions) and provide written informed consent according to institutional and regulatory guidelines.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Previous medical history or evidence of an uncontrolled intercurrent illness that, in the opinion of the Investigator and/or Medical Monitor, may compromise the safety of the subject in the study or interfere with evaluation of the study drug or compromise the subject's ability to participate in the study;
2. Personal or family history of long QT syndrome, Torsades de Pointes, or other complex ventricular arrhythmias, or family history of sudden death;
3. History of or current clinically significant arrhythmias as judged by the Investigator, including ventricular tachycardia, ventricular fibrillation, atrial fibrillation, sinus node dysfunction, or clinically significant heart block. Subjects with minor forms of ectopy (eg, premature atrial contractions) are not necessarily excluded;
4. Prolonged QTcF >470 msec based on the average of triplicate 12-lead ECGs at Screening or Check-In;
5. Resting heart rate (after the subject is seated for at least 5 minutes) <50 beats per minute or >100 beats per minute at Screening or Check-In;
6. Systolic blood pressure (after the subject is seated for at least 5 minutes) ≥150 mmHg or <90 mmHg or diastolic blood pressure ≥100 mmHg or <50 mmHg at Screening or Check-In;
7. Temperature >37.6°C (99.7°F, measured orally) at Screening or Check-In;
8. Respiratory rate <12 or >20 breaths/minute at Screening or Check-In;
9. Clinically significant or active gastric emptying abnormality (eg, gastroparesis or gastric outlet obstruction, intestinal obstruction, or any GI motility disorders); malabsorption, including chronic constipation/diarrhea, celiac disease, inflammatory bowel disease, or bowel resection; or chronic use of drugs that directly affect GI motility (eg, anticholinergics, 5-hydroxytryptamine [serotonin] antagonists, opiates);
10. Obesity induced by other endocrinologic disorders (eg, Cushing syndrome, acromegaly, inadequately treated hypothyroidism) or diagnosed monogenic or syndromic forms of obesity (eg, melanocortin 4 receptor deficiency or Prader-Willi syndrome);
11. Thyroid disease that is not controlled (thyroid-stimulating hormone [TSH] outside normal range at Screening);
12. Symptomatic gallbladder disease within the past 2 years or history of cholecystectomy;
13. History or presence of acute or chronic pancreatitis;

14. A positive response to either Question 4 or Question 5 on the Suicidal Ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) or a positive response to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS at Screening or Check-In;

    Note: A subject should be referred to a mental health professional if she has any suicidal ideation of Type 4 or 5 on the C-SSRS at any time during the study.

15. A baseline score >15 on the Patient Health Questionnaire 9 (PHQ-9) at Screening or Check-In;
16. A history of Major Depressive Disorder within the last 2 years;
17. Any lifetime history of a suicide attempt;
18. A history of other severe psychiatric disorders (eg, schizophrenia, bipolar disorder);
19. Previous bariatric surgery, procedure for obesity, or GI surgery altering GI passage, motility, and/or nutrient absorption or recent (within 6 months of Screening) changes in body weight (≥5%) due to dieting, including commercial weight loss programs, or pharmacologic treatment;
20. Currently on or planning to participate in any weight loss regimen during the course of the study;
21. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2;
22. History of malignancy, except the following: curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colorectal polyps >5 years prior to Screening;
23. Abnormal fasting blood glucose (ie, >125 mg/dL) at Screening or Check-In and/or glycated hemoglobin (HbA1c) (ie, >6.4%) at Screening, or prior history/diagnosis of any type of diabetes mellitus (eg, type 1, type 2, or gestational);
24. Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and/or total bilirubin above the central laboratory's upper limit of normal (ULN); fasting triglycerides >500 mg/dL; impaired renal function with estimated glomerular filtration rate <90 mL/min/1.73 m^2 at Screening or Check-In; or calcitonin above the central laboratory's ULN at Screening;
25. Any other clinical laboratory values that are meaningfully outside of normal limits (based on laboratory normal range) at Screening or Check-In in the opinion of the Investigator;
26. Positive for HIV antibody, hepatitis C virus (HCV) antibody, or hepatitis B surface antigen at Screening;
27. Positive COVID-19 test at Check-In;
28. Use of any prescribed or over-the-counter (OTC) medication other than approved contraceptives (see Inclusion Criterion 6) within 14 days or 5 half-lives (whichever is longer) prior to dosing on Day 1 and throughout the study;

    Note: Following study drug administration, medications used for the treatment of AEs may be allowed at the discretion of the Investigator or designee.

29. Any GLP-1 receptor agonist, GLP-1/glucose-dependent insulinotropic polypeptide dual agonist (eg, tirzepatide), or any prescription or OTC medications intended for weight loss or with a potential impact on weight and appetite regulation (eg, stimulant medications) within 6 months of Screening;
30. Positive urine drug screen or positive alcohol breath test result at Screening or Check-In;
31. Use of tobacco- or nicotine-containing products (including vaping devices) within 6 months prior to Screening and throughout the study, or positive cotinine test result at Screening or Check-In;
32. History of alcoholism or drug/chemical abuse within 12 months prior to Screening, or unwillingness to agree to abstain from alcohol and drugs throughout the study;
33. Typical consumption of ≥14 alcoholic drinks weekly;

    Note: 1 drink of alcohol is equivalent to ½ pint of beer (285 mL), 1 glass of spirits (25 mL), or 1 glass of wine (125 mL).
34. Surgical procedures within 4 weeks of Check-In or planned elective surgery during the study period;
35. Known allergy to any ingredient of ROSE-010 or any history of severe allergic reaction (including drugs, food, insect bites, or environmental allergens);
36. Inadequate venous access;
37. Blood donation ≥500 mL within 8 weeks prior to Screening, blood transfusion/severe blood loss within 3 months prior to Screening, hemoglobinopathy, or hemoglobin <11 g/dL;
38. Unwillingness or inability to refrain from strenuous exercise from 4 days prior to Day 1 until discharge from the CPU on Day 8;
39. Actively participating in an experimental therapy study; or received experimental therapy with a small molecule within 30 days of the first dose of study drug or 5 half-lives, whichever is longer; or received experimental therapy with a large molecule within 90 days of the first dose of study drug or 5 half-lives, whichever is longer;
40. Considered by the Investigator, after review of eligibility data, to be unsuitable for any other reason that may either place the subject at increased risk during participation or interfere with the interpretation of the study outcomes.

4.3 Withdrawal Criteria

A subject may prematurely discontinue study drug and/or withdraw from the study at any time. A distinction must be made between premature discontinuation of study drug and withdrawal from the study. A subject may prematurely discontinue study drug and still continue his/her participation in the study. Subjects who prematurely discontinue study drug dosing will be encouraged to continue in the study and complete visits and procedures as per Protocol.

The reasons for premature discontinuation of study drug and for withdrawal from the study must be documented in the electronic case report form (eCRF). Reasons include, but are not limited to, the following:

- Withdrawal of consent;
- Any event, laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject;
- Pregnancy;
- Subject failure to comply with Protocol requirements or study-related procedures;
- Termination of the study by the Sponsor or regulatory authority;
- Initiation of any prohibited medication(s) as described in Section 5.6.1;
- Severe allergic reactions to the study drug; or
- Any stopping rule as described in Section 3.2.

If a subject withdraws prematurely from the study for any reason, study staff should make every effort to complete the full panel of assessments scheduled for Day 8/ET. The reason for subject withdrawal must be documented in the eCRF.

In the case of a subject lost to follow-up, attempts to contact the subject must be made and documented in the subject's records.

Withdrawn subjects may be replaced at the discretion of the Sponsor. Subjects who discontinue for study drug-related safety or tolerability reasons will not be replaced.

4.4 Reserve Subjects

The population for this study is healthy subjects. Additional subjects will be screened as reserve subjects for each treatment group. Reserve subjects who are eligible for enrollment will also be admitted to the CPU to ensure enough eligible subjects are available to fill the treatment group. Results of study admission procedures from Day -1 are not required to be repeated, provided the subject remains domiciled, and Protocol restrictions are monitored and followed.

Reserve subjects who fall outside of the Screening Period window will be allowed to rescreen. In addition, subjects who fail to qualify at Screening due to use of a prohibited medication may be permitted to rescreen if medication usage changes. Subject eligibility may also be reassessed if there is a change in eligibility procedures or criteria.

5 STUDY TREATMENTS

5.1 Treatment Groups

The study is planned to include 3 parallel treatment groups, with 40 subjects randomized in a 3:3:2 ratio to receive ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo, respectively, as follows:

- Treatment Group 1: 99 mcg ROSE-010 (15 subjects) administered SC once daily for 7 consecutive days;
- Treatment Group 2: 150 mcg ROSE-010 (15 subjects) administered SC once daily for 7 consecutive days; and
- Treatment Group 3: Placebo (10 subjects) administered SC once daily for 7 consecutive days.

5.2 Rationale for Dosing

The rationale for selection of the ROSE-010 dose levels (99 mcg and 150 mcg) is based on the results of Clinical Studies GL61-001, RP-09-01, and RP-23-01 (see Section 1.3 and the ROSE-010 Investigator's Brochure[2]).

The results from Study RP-09-01 showed that 300 mcg and 100 mcg have observable effects on gastric emptying relative to placebo which is known to be directly related to appetite reduction. Nausea and vomiting, known side-effects of GLP-1 treatment, were more frequently reported with the higher dose (300 mcg). The dose selection was confirmed as relevant by the results from the RP-23-01 study. In this study, a trend in dose dependency was noted as well as a decrease overall in food intake relative to placebo with tolerable nausea.

In Study GL61-001 there was no difference in pain relief response 1 hour post-dose between the dose groups 100 and 300 mcg, which were both significantly different from placebo. At 2 hours post-dose, the pain relief response was observed to diverge between the treatment groups with a difference of approximately 10 mm on the visual analogue scale (VAS) (0 to 100 mm). Both groups were significantly superior to placebo at 2 hours post-dose.

In Study RP-23-01, 14 male and female subjects were randomized to receive a sequence of placebo, 100 mcg ROSE-010, and 150 mcg ROSE-010. Eleven subjects completed all 3 treatment periods. There was a signal indicating a possible dose dependency in amount of food consumed, suggesting that ROSE-010 may have a role in weight management and obesity. No safety concerns were raised.

Nausea and vomiting were both more frequently reported with higher dose.

These data show the following:

- There is no difference in pain relief response at 1 hour post-dose between ROSE-010 100 mcg and 300 mcg; and
- The occurrence of the side effects nausea and vomiting is dose dependent with Studies RP-09-01 and GL61-001 showing approximately double the frequency of vomiting in the case of 300 mcg compared with 100 mcg.

In summary, the doses of ROSE-010 99 mcg and 150 mcg are justified as being within a pharmacologically effective range but with a lower risk for side effects as compared to 300 mcg.

5.3 Randomization and Blinding

Subjects meeting eligibility criteria at Screening and Check-In will be randomized prior to study drug administration on Day 1 in a 3:3:2 ratio to ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo, respectively. Randomization assignments will be provided by the Medpace Biostatistics Department. Following randomization, study drug will be dispensed in a double-blind manner. The Sponsor and all site personnel except the unblinded Pharmacist, unblinded pharmacy staff, and unblinded Clinical Research Associate (CRA), if assigned, will be blinded to the treatment group for each subject. Subjects will also be blinded to the treatment they receive.

Bioanalytical staff involved in analysis of PK samples will be unblinded to treatment either via receipt of the randomization code to allow for analysis of samples from subjects receiving ROSE-010 only, or by the nature of the results of sample analysis.

5.4 Breaking the Blind

Blinding is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of subject safety or by the Sponsor based on safety and tolerability and/or PK data. Unblinding at the CPU for any other reason will be considered a Protocol deviation. The Investigator should contact the Medical Monitor before breaking the blind if time permits. When the blind is broken, the reason must be fully documented. The Pharmacist at the CPU will inform the Investigator of the treatment assignment via the randomization schedule held in the pharmacy.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

ROSE-010 (300 mcg/mL) is a clear, colorless, aqueous, sterile solution for SC injection and will be provided in 2R injection vials. Each vial contains 1 mL ROSE-010 and is for single use.

Commercially available sterile normal saline (0.9% NaCl) solution for injection will be used as the placebo.

5.5.2 Study Drug Preparation and Dispensing

Individual doses of ROSE-010 or matching placebo will be prepared by the unblinded pharmacy staff and dispensed by the Pharmacist at the clinical site in a blinded manner.

5.5.3 Study Drug Administration

Study drug (ROSE-010 [99 mcg or 150 mcg] or placebo) will be administered as a single SC injection once daily (30 minutes before lunch) for 7 consecutive days (Days 1 to 7). Study drug will be administered by blinded clinical staff who are trained, qualified, and designated by the Investigator. All doses will be administered SC in the abdominal skin; the injection site location in the abdomen will be rotated at each administration.

5.5.4 Treatment Compliance

To ensure treatment compliance, all doses will be administered under the supervision of study site personnel. The route, location, date, and time of each study drug administration will be recorded in the source documentation for each subject.

5.5.5 Storage and Accountability

Study drug must be stored in a pharmacy or a locked, secure storage facility, accessible only to those individuals authorized by the Investigator to dispense the drug.

Bulk ROSE-010 vials are stable when stored at the recommended storage conditions of 2 to 8°C and protected from light. The doses will be prepared by unblinded pharmacy staff on the day of administration in close proximity to dose administration.

Normal saline used as placebo should be stored in accordance with the package insert.

Records will be maintained indicating the receipt and dispensation of all study supplies. At the conclusion of the study, any unused study drug will be destroyed on site or returned to the Sponsor or designee for final drug accountability and destruction. A certificate of destruction will be provided. If no study drug remains, this will be indicated in the Drug Accountability Log.

The site Pharmacist will perform an ongoing inventory of study drug on behalf of Rose Pharma. The responsible Pharmacist at the site must keep accurate records of all study drug received, amount used/dispensed per subject, and amount returned/disposed, as well as a temperature log to document temperature conditions during storage. A full reconciliation of drug inventory will be performed after the study has completed and the results of the inventory will be checked against the Drug Accountability Log.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Subjects with the following medications and procedures will be excluded:

- Any prescribed or OTC medication other than approved contraceptives (see Inclusion Criterion 6) within 14 days or 5 half-lives (whichever is longer) prior to dosing on Day 1 and throughout the study;

  Note: Following study drug administration, medications used for the treatment of AEs may be allowed at the discretion of the Investigator or designee.

- Any GLP-1 receptor agonist, GLP-1/glucose-dependent insulinotropic polypeptide dual agonist (eg, tirzepatide), or any prescription or OTC medications intended for weight loss or with a potential impact on weight and appetite regulation (eg, stimulant medications) within 6 months of Screening;
- Previous bariatric surgery, procedure for obesity, or GI surgery altering GI passage, motility, and/or nutrient absorption;
- Surgical procedures within 4 weeks of Check-In or planned elective surgery during the study period;
- Blood donation ≥500 mL within 8 weeks prior to Screening, blood transfusion/severe blood loss within 3 months prior to Screening; and
- Actively participating in an experimental therapy study; or received experimental therapy with a small molecule within 30 days of the first dose of study drug or 5 half-lives, whichever is longer; or received experimental therapy with a large molecule within 90 days of the first dose of study drug or 5 half-lives, whichever is longer.

5.6.2 Restricted Medications and/or Procedures

Following study drug administration, medications used for the treatment of AEs may be allowed at the discretion of the Investigator or designee.

5.6.3 Allowed Medications and/or Procedures

Medically accepted contraceptive methods are permitted as outlined in Inclusion Criterion 6.

5.6.4 Lifestyle Restrictions

Subjects must not have a history of alcoholism or drug/chemical abuse within 12 months prior to Screening or be unwilling to abstain from alcohol and drugs throughout the study. Subjects must not have a typical consumption of ≥14 alcoholic drinks weekly. Subjects must not use tobacco- or nicotine-containing products (including vaping devices) within 6 months prior to Screening and throughout the study. Subjects must refrain from strenuous exercise from 4 days prior to Day 1 until discharge from the CPU on Day 8.

5.6.5 Documentation of Prior and Concomitant Medication Use

Any treatment or medication (including nutritional supplements) or procedure administered from the time of informed consent and throughout the study is considered a concomitant medication/procedure. This includes medications that were started before the study and are ongoing during the study. Any concomitant procedures/medications will be documented in the appropriate eCRF. Any medications administered within 6 months prior to the first dose of study drug and during the study must be recorded in the eCRF.

6 STUDY PROCEDURES

Study procedures will follow the Schedule of Events (Appendix A).

7 EFFICACY AND PK ASSESSMENTS

7.1 Endpoints

7.1.1 Primary Endpoint

The primary endpoint is the amount of food (weight and energy content) consumed during lunch on each day of treatment (Day 1 to Day 7) after administration of ROSE-010 at 2 dose levels (99 mcg and 150 mcg) compared to placebo.

7.1.2 Secondary Endpoints

The secondary endpoints are the following:

- Hunger score on a VAS (0 to 100 mm) measured pre-dose; 20 minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours after study drug administration;
- Satiety score on a VAS (0 to 100 mm) measured pre-dose; 20 minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours after study drug administration;
- Prospective consumption score on a VAS (0 to 100 mm) measured pre-dose; 20 minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours after study drug administration;
- Desire to eat score on a VAS (0 to 100 mm) measured pre-dose; 20 minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours after study drug administration;
- Palatability (tastiness) score on a VAS (0 to 100 mm) measured at the start of lunch;
- Incidence and severity of nausea on a VAS (0 to 100 mm) measured pre-dose; 20 minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours after study drug administration; and
- Plasma PK analysis of ROSE-010: maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration-time curve (AUC), terminal phase elimination half-life ($t_{½}$), and other plasma PK parameters.

7.1.3 Exploratory Endpoint

The exploratory endpoint is the effect of 7 days of treatment with ROSE-010 on body weight, measured as the relative change (ie, percent change) in body weight from baseline to Day 8.

7.2 Clinical Efficacy Assessments

7.2.1 Amount of Food Consumed (Weight and Energy Content)

The start time of the standardized lunch will be 30 minutes post-dose; start time will be recorded. Subjects will consume as much of the standardized lunch as desired, and food will be weighed prior to and after eating to assess food intake.

7.2.2 Efficacy Visual Analogue Scales

On Days 1 through 7, the VAS questionnaire to evaluate hunger, satiety, prospective consumption, and desire to eat will be administered pre-dose; 20 (±5) minutes after study drug administration;

and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours (±5 minutes) after study drug administration. On Day -1, the VAS questionnaire to evaluate hunger, satiety, prospective consumption, and desire to eat will be administered 10 (±5) minutes prior to the start of lunch and 1, 2, 3, 4, 5, and 6 hours (±5 minutes) after the start of lunch. On Day -1 and on Days 1 through 7, the VAS questionnaire to evaluate palatability will be administered at the start of lunch (see Appendix A). For details regarding the VAS questionnaire to evaluate nausea, which is a safety assessment, see Section 8.14. VAS questionnaires are provided in Appendix C.

7.2.2.1 Hunger

Hunger will be assessed by the subject using a VAS graded from 0 to 100 mm with 0 mm corresponding to "not hungry at all" and 100 mm corresponding to "extremely hungry".

7.2.2.2 Satiety

Satiety will be assessed by the subject using a VAS graded from 0 to 100 mm with 0 mm corresponding to "not full at all" and 100 mm corresponding to "extremely full".

7.2.2.3 Prospective consumption

Prospective consumption will be assessed by the subject using a VAS graded from 0 to 100 mm with 0 mm corresponding to "nothing at all" and 100 mm corresponding to "a large amount".

7.2.2.4 Desire to eat

Desire to eat will be assessed by the subject using a VAS graded from 0 to 100 mm with 0 mm corresponding to "no wish to eat at all" and 100 mm corresponding to "extreme wish to eat".

7.2.2.5 Palatability

Palatability will be assessed by the subject using VASs for odor, taste, and texture graded from 0 to 100 mm with 0 mm corresponding to "not pleasant at all" and 100 mm corresponding to "extremely pleasant".

7.2.3 Change in Body Weight

Body weight should be measured while the subjects are wearing a gown or light indoor clothing without shoes, while fasting for at least 10 hours, and after voiding. Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms to 1 decimal place. Body weight will be assessed at Screening, Check-In, and Day 8/ET, as indicated in the Schedule of Events (Appendix A).

7.3 PK Assessments

Blood samples will be collected to evaluate PK at the times indicated in the Schedule of Events (Appendix A). The actual date and time of collection of each PK sample will be recorded.

The following plasma PK parameters will be determined for ROSE-010 following SC administration on Day 1, as the data permit:

- C_{max};
- T_{max};

- AUC from Day 1 to infinity; and
- AUC from time 0 to the time of the last measurable concentration (AUC_{0-t}).

The following plasma PK parameters will be determined for ROSE-010 following the final dose on Day 7, as the data permit:

- C_{max};
- Plasma trough concentration;
- T_{max};
- AUC over a dosing interval;
- AUC_{0-t};
- $t_{½}$;
- Apparent first-order terminal elimination rate constant;
- Apparent plasma clearance;
- Observed accumulation index for C_{max} and AUC;
- Average concentration over the dosing interval τ;
- Swing; and
- Percent fluctuation (fluctuation %).

8 SAFETY ASSESSMENTS

Safety assessments will include injection site reactions, incidence and severity of nausea on a VAS (see list of endpoints in Section 7.1.2), clinical laboratory parameters, blood glucose monitoring, vital signs, ECGs, physical examinations, incidence and severity of treatment-emergent AEs, and C-SSRS.

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded in the appropriate eCRF. The Investigator should update the appropriate eCRF if additional follow-up information becomes available (eg, the AE has subsided, stabilizes, or the condition becomes chronic in nature).

AEs, which include clinical laboratory test results, will be monitored and documented from the time of informed consent until study participation is complete. Subjects should be instructed to report any event that they experience to the Investigator, whether or not they think the event is due to study drug. From the time of informed consent, Investigators should make an assessment for AEs at each visit and record the event in the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded in the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE in the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at the time of informed consent should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline change in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at the time of informed consent and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Thus, abnormal test results that are determined to be an error should not be reported as an AE, while laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should usually be reported as an AE if any of the following are applicable:

- An intervention is required as a result of the abnormality;
- Action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

8.1.1 Adverse Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse reaction. "Responses" to a medicinal product mean that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Reaction

An unexpected adverse reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.1.3 Assessment of AEs by the Investigator

The Investigator will assess the severity (intensity) of each AE and will also categorize each AE as to its potential relationship to study drug.

8.1.3.1 Assessment of severity

Any local injection-site related AE (eg, pain, tenderness, erythema, and/or induration) should be documented and characterized as described in Section 8.18. The severity of all other AEs should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; or
- CTCAE Grade 5: Death related to the AE.

8.1.3.2 Causality assessment

The relationship of an AE to the administration of study drug is to be assessed according to the following definitions:

- **No (not related or unlikely related):** The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and/or another cause (concomitant drugs, therapies, complications, etc) is suspected; or
- **Yes (possibly, probably, or definitely related):** The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

Note: The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- **The temporal sequence from study drug administration:** The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event;
- **Underlying, concomitant, intercurrent diseases:** Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have;
- **Concomitant drug:** The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question;
- **Known response pattern for this class of study drug:** Clinical and/or pre-clinical data may indicate whether a particular response is likely to be a class effect;
- **Exposure to physical and/or mental stresses:** The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event; and
- **The pharmacology and PK of the study drug:** The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.2 Serious AEs

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalization;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;

- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 SAE Reporting − Procedures for Investigators

8.3.1 Initial Reports

All SAEs occurring from the time of informed consent until the follow-up phone call must be reported to Medpace Safety and Pharmacovigilance within 24 hours of the knowledge of the occurrence. After the follow-up phone call, any SAE that the Investigator considers related to study drug must be reported to Medpace Safety and Pharmacovigilance or the Sponsor/designee. Of note, reporting of SAEs after participation is complete is dependent on spontaneous reporting by the subject. The Investigator is not required to have further contact to elicit this information after completion of the final visit but should instruct the subject to contact the site to report any such events.

To report the SAE, complete the AE form with the SAE information electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety and Pharmacovigilance personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety and Pharmacovigilance at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line, and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered as soon as possible.

8.3.2 Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, subject discharge summary or autopsy reports) to Medpace Safety and Pharmacovigilance via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a subject becomes pregnant during the study, the Investigator is to stop dosing with study drug(s) immediately and the subject should be withdrawn from the study.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring during the study and up to 60 days after the last dose of study drug must be reported to Medpace Safety and Pharmacovigilance within 24 hours of knowledge of the event. Medpace Safety and Pharmacovigilance will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Safety and Pharmacovigilance. Of note, reporting of pregnancy after the follow-up phone call is dependent on spontaneous reporting by the participant. The Investigator is not required to have further contact to elicit this information after completion of the follow-up phone call but should instruct the participant to contact the site to report any pregnancy which may occur after the follow-up phone call.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Safety and Pharmacovigilance. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA) and Institutional Review Boards (IRBs), and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported, as applicable, to the FDA, other regulatory authorities, as applicable, and to the applicable IRB(s) as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also submit any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to the study drug.

8.6 Special Situation Reports

Special Situation Reports include reports of investigational medicinal product overdose, misuse, abuse, and medication error.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the Protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s) or the Investigator has reason to suspect that the subject has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the Protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.

- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, subject, or consumer. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of subjects missing doses of investigational product are not considered reportable as medication errors.

All special situation events as described above must be reported on the Special Situation Report form and faxed/emailed to Medpace Safety and Pharmacovigilance (contact information listed below) within 72 hours of knowledge of the event. All AEs associated with these Special Situation Reports should be reported as AEs or SAEs as well as recorded in the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Medpace Safety and Pharmacovigilance Contact Information:
Medpace SAE reporting line (office location: Cincinnati, Ohio, United States):
Telephone: +1-513-579-9911, dial 3
Fax: +1-513-570-5196
Email: medpace-safetynotification@medpace.com

8.7 Clinical Laboratory Evaluations

Clinical laboratory evaluations will include chemistry (including total cholesterol and triglycerides), hematology, coagulation, TSH, calcitonin, HbA1c, and urinalysis collected as indicated in the Schedule of Events (Appendix A). See Appendix B for a list of clinical laboratory analytes.

8.8 Blood Glucose Monitoring

Finger stick blood glucose monitoring for hypoglycemia (defined as blood glucose value <54 mg/dL [<3.0 mmol/L]) will be conducted at 1 and 2 hours after each dose on Days 1 through 7 (see Appendix A) and as needed for symptoms of hypoglycemia (ie, dizziness or light-headedness, blurred vision, anxiety, irritability or mood changes, fast heartbeat, sweating, slurred speech, hunger, confusion or drowsiness, feeling jittery, shakiness, weakness, headache).

8.9 Serology

Subjects will be tested for HIV antibody, HCV antibody, and hepatitis B virus surface antigen at Screening to determine eligibility.

8.10 Pregnancy and FSH Testing

A serum pregnancy test will be performed for all subjects during the Screening Period and at Check-In. A serum FSH test will be performed at Screening for subjects who are postmenopausal (ie, have experienced spontaneous amenorrhea for at least 2 years).

8.11 Vital Signs

Vital signs include temperature, respiratory rate, heart rate, and blood pressure. Vital signs will be performed with the subject in a seated position after at least a 5-minute seated rest. Vital signs will

be assessed at Screening; Check-In; pre-dose, 1 hour post-dose, and 6.5 hours post-dose on Days 1 through 7; and on Day 8/ET (see Appendix A).

8.12 Electrocardiograms

All 12-lead ECGs will be performed in triplicate approximately 1 minute apart after the subject has been resting in the supine position for at least 10 minutes. ECGs will be performed at Screening, Check-In, approximately 1 hour post-dose on Day 1, and on Day 8/ET (see Appendix A).

8.13 Physical Examinations

A full physical examination (including head, eyes, ears, nose, and throat; cardiovascular; respiratory; GI; neurological; dermatological; and musculoskeletal systems) will be performed at Screening. Symptom-based physical examinations will be performed at Check-In, Day 1 pre-dose, and Day 8/ET (see Appendix A).

8.14 Nausea

Nausea will be assessed by the subject using a VAS graded from 0 to 100 mm with 0 mm corresponding to "not at all nauseated" and 100 mm corresponding to "extremely nauseated". The VAS questionnaire to evaluate nausea will be administered pre-dose; 20 (±5) minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours (±5 minutes) after study drug administration (see Appendix A). The VAS questionnaire to evaluate nausea is provided in Appendix C.

8.15 Weight, Height, and BMI

Weight will be assessed at Screening, Check-In, and Day 8/ET. Weight is considered to be an efficacy assessment and is described in Section 7.2.3.

Height will be collected at the Screening Visit only and will be used to calculate BMI at Screening only.

8.16 Coronavirus Disease 2019 Testing

A test for severe acute respiratory syndrome-coronavirus-2 will be administered to subjects at the study site on Day -1 prior to admission (see Appendix A). Subjects testing positive for COVID-19 are not eligible for the study.

8.17 Urine Drug, Cotinine, and Breath Alcohol Screen

A urine screen for drugs of abuse, a urine cotinine test, and a breath alcohol screen will be performed for all subjects at Screening and Check-In (see Appendix A). Subjects with any positive findings are not eligible for the study.

See Appendix B for a complete list of urine drug screen analytes.

8.18 Injection Site Reactions

Injection site reactions will be considered AEs and will be assessed on Day 1 at 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose and once daily on Days 2 through 7 at 1.5 hours (±30 minutes) post-dose (see Appendix A).

An injection site reaction evaluation will include visual examination of the skin surrounding the SC injection site. Any local injection-site related AE (eg, pain, tenderness, erythema, and/or induration) should be documented and characterized as described in "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" based on the following 4 parameters: 1) degree of pain; 2) tenderness; 3) erythema/redness; and 4) induration/swelling.[7] See details in Table 1.

Table 1. Toxicity Grading Scale for Local Reactions After SC Injection

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ED visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ED visit or hospitalization
Erythema/redness	2.5 to 5 cm	5.1 to 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling	2.5 to 5 cm and does not interfere with activity	5.1 to 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

Note 1: In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
Note 2: Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.
ED = emergency department; SC = subcutaneous; US = United States.
Source: Center for Biologics Evaluation and Research (CBER). Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Guidance for Industry. US Dept of Health and Human Services, Food and Drug Administration, September 2007

8.19 Columbia-Suicide Severity Rating Scale

The C-SSRS will be performed at the times indicated in Appendix A. The "Baseline" C-SSRS questionnaire will be administered during the Screening Period. At all other visits, subjects will be given the "Since Last Visit" questionnaire. See Appendix D for the C-SSRS questionnaires.

8.20 Patient Health Questionnaire 9

The PHQ-9[8] will be performed at Screening and Check-In (see Appendix A). Subjects with a baseline score >15 will be excluded from the study. See Appendix E for the PHQ-9.

9 STATISTICS

9.1 Analysis Populations

The Per Protocol Analysis Set will include all randomized subjects who have received all doses and have evaluable efficacy data, and no major Protocol deviation that significantly affects the evaluability of the subjects in the study.

The Safety Analysis Set will include all randomized subjects who have received at least 1 dose of study drug (ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo). Subjects will be analyzed according to the treatment they actually received if this differs from that to which the subject was randomized.

The PK Analysis Set will include subjects who have received at least 1 dose of ROSE-010 99 mcg or ROSE-010 150 mcg and have at least 1 measurable post-dose plasma PK concentration.

9.2 Statistical Methods

Study data will be summarized by treatment group using descriptive statistics, figures, and/or raw data listings where appropriate.

Continuous data and change from baseline will be presented in terms of evaluable observations (n), arithmetic mean, standard deviation, median, minimum, and maximum value.

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment (ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo) and by assessment time. Individual subject data will be listed by treatment, subject number, and, where applicable, by assessment time.

All descriptive summaries and statistical analyses will be performed using SAS version 9.4 or later (SAS Institute, Inc., Cary, North Carolina).

Baseline will be defined as the last data collection point (assessment) prior to the first dose of ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo.

Details of the statistical analyses will be provided in a separate Statistical Analysis Plan.

9.2.1 Analysis of Efficacy

Efficacy analyses will be performed using the Per Protocol Analysis Set.

9.2.1.1 Primary efficacy analysis

For each treatment group, descriptive statistics will be calculated at each visit for amount of food (weight and energy content) consumed during lunch.

Absolute and change from baseline will each be analyzed using a mixed model of repeated measures approach using a significance level of alpha = 0.1. Fixed effects for the model will be baseline, treatment, visit, and treatment-by-visit interaction with a random effect for subject. Least squares mean values, differences in least squared means values, standard errors, p-values, and 90% confidence intervals will be presented.

9.2.1.2 Secondary efficacy analysis

Absolute and change from baseline values of hunger, satiety, prospective consumption, desire to eat, and palatability (tastiness) scores on a VAS (0 to 100 mm) will be summarized using descriptive statistics for all measured visits and timepoints.

9.2.1.3 Other efficacy analysis

Absolute and change from baseline values of body weight and will be summarized using descriptive statistics at all measured visits and timepoints.

9.2.2 Analysis of Safety

Safety analysis will be performed using the Safety Analysis Set.

Safety assessments will include injection site reactions, incidence and severity of nausea on a VAS (0 to 100 mm), clinical laboratory parameters, vital signs, ECGs, physical examinations, incidence and severity of treatment-emergent AEs, and C-SSRS.

AEs will be coded using the Medical Dictionary for Regulatory Activities. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

Triplicate 12-lead ECG values will be averaged on each timepoint and visit of measurement for analysis purposes.

Absolute and change from baseline values of incidence and severity of nausea scores on a VAS (0 to 100 mm) will be summarized using descriptive statistics for all measured visits and timepoints.

All safety assessments will be summarized using descriptive statistics or counts and percentages as appropriate at all measured visits and timepoints.

9.2.3 Interim Analysis

No interim analysis is planned for the study.

9.2.4 Sample Size Determination

Approximately 40 subjects will be enrolled.

No formal sample size calculation was performed. Given the exploratory nature of this study, the proposed sample size is considered sufficient to provide adequate information for the study objectives.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be entered into eCRFs in the EDC system by personnel allocated to this task, as documented on the site delegation log, and will be reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data will be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data will be recorded using the EDC system as the study is in progress. All delegated site personnel will log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR) Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

The following dictionaries will be used for coding medical information:

- Medical Dictionary for Regulatory Activities for AEs and medical history; and
- WHO Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the data, will be applied to ensure accurate, consistent, and reliable data. Data identified as erroneous or missing will be referred to the investigative site for resolution through data queries.

The eCRFs will be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or

destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study (study completion) is defined as the date of the last Protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible. This study will be conducted in compliance with the Protocol and with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) guidelines for GCP, and applicable regional regulations.

11.2 Institutional Review Board

It is the responsibility of the Sponsor or their designee (ie, Medpace) to ensure the IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where written IRB approval has been obtained. The Protocol, Investigator's Brochure, Informed Consent Form (ICF), advertisements (if applicable), written information given to the subject, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and ICH guidelines require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to study onset, the Protocol, any Protocol Amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent Procedures

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor/designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

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, and that subjects have sufficient opportunity to have all questions answered in a suitable facility. The Investigator must ensure that the subject has been informed of his/her rights to privacy and his/her rights and guarantees regarding his/her protection, in particular the right to refuse to participate and the right to withdraw from the clinical study at any time without any resulting detriment and without having to provide any justification. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed, unless the activity is part of standard-of-care for the subject and/or indication, and should document in the source that consent was obtained prior to enrollment in the study.

The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies.

A copy of the signed ICF will be given to the subject.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the Protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor, in the maintenance of complete, legible, well-organized, and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor/designee will review with the Investigator and site personnel the following documents: Protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor/designee to monitor the study as frequently as deemed necessary to determine that data recording and Protocol adherence are satisfactory. Study monitoring may include onsite, remote, or a combination of both onsite and remote monitoring. During the monitoring visits, information recorded in the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site designee, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the Sponsor/designee, regulatory authorities, and the IRB, as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, such as eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator or institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any Amendments to the study Protocol will be communicated to the Investigators by Medpace or the Sponsor. All Protocol Amendments will undergo the same review and approval process as the original Protocol. A Protocol Amendment may be implemented after it has been approved by the IRB and applicable competent authorities unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB and applicable competent authorities without undue delay and at the latest within 7 calendar days of the Sponsor becoming aware.

13 REFERENCES

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APPENDIX A: SCHEDULE OF EVENTS

Table 2. Schedule of Events

	Screening	Check-In	Treatment Period								Follow-Up Phone Call
Day (±Visit Window)	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET[a]**	**14 (±2)**
Informed consent[b]	X										
Inclusion/exclusion criteria[c]	X	X[d]									
Demographic information	X										
Medical/surgical/psychiatric history	X	X[d]									
Prior/concomitant medications[e]	X	X	X	X	X	X	X	X	X	X	X
Weight, height, BMI[f]	X	X								X	
Physical examination[g]	X	X	X							X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	
Drug/cotinine/alcohol screening[i]	X	X									
C-SSRS[j]	X	X	X			X				X	
PHQ-9	X	X									
Serology (HIV antibody, HCV antibody, HBsAg)	X										
Pregnancy test[k]	X	X									
Serum FSH[l]	X										
SARS-CoV-2 testing[m]		X									
12-lead ECG[n]	X	X	X							X	
Chemistry (including total cholesterol and triglycerides), hematology, coagulation[o]	X	X	X		X		X		X		
TSH, calcitonin, HbA1c[o]	X								X		
Urinalysis	X	X	X		X		X		X		
PK[p]			X		X		X		X		
Admission/discharge		Admission								Discharge	
Randomization[q]			X								
Study drug administration[r]			X	X	X	X	X	X	X		
Injection site reaction[s]			X	X	X	X	X	X	X		
Food intake (weight, energy content)[t]			X	X	X	X	X	X	X		

Table 2. Schedule of Events (Continued)

	Screening	Check-In	Treatment Period								Follow-Up Phone Call
Day (±Visit Window)	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET[a]**	**14 (±2)**
VAS (hunger, satiety, prospective consumption, desire to eat, palatability, nausea)[u]		X[u]	X	X	X	X	X	X	X		
Finger stick blood glucose monitoring[v]			X	X	X	X	X	X	X		
AE monitoring[w]	X	X	X	X	X	X	X	X	X	X	X

When several assessments are required at the same time point, evaluations should be completed so that the PK sample is collected at the required time. It is understood that other assessments such as ECGs, vital signs, etc will be performed as close to the actual time as possible but may be collected earlier or later than the actual time point.

a. If a subject withdraws prematurely from the study for any reason, study staff should make every effort to complete the full panel of assessments scheduled for Day 8/ET. The reason for subject withdrawal must be documented in the eCRF.
b. Signed informed consent must be obtained before any study-related procedures are performed.
c. Subjects meeting eligibility criteria at Screening and Check-In will be randomized into the study pre-dose on Day 1.
d. Any updates since Screening will be assessed.
e. Any medications administered within 6 months prior to the first dose of study drug and during the study must be recorded in the eCRF.
f. Height will be collected at the Screening Visit only and will be used to calculate BMI at Screening only. Body weight should be measured while the subjects are wearing a gown or light indoor clothing without shoes, while fasting for at least 10 hours, and after voiding. Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms to 1 decimal place.
g. A full physical examination (including head, eyes, ears, nose, and throat; cardiovascular; respiratory; gastrointestinal; neurological; dermatological; and musculoskeletal systems) will be performed at Screening. Symptom-based physical examinations will be performed at Check-In, Day 1 pre-dose, and Day 8/ET.
h. Vital signs include temperature, respiratory rate, heart rate, and blood pressure. Vital signs will be performed with the subject in a seated position after at least a 5-minute seated rest. Vital signs will be assessed at Screening; Check-In; pre-dose, 1 hour post-dose, and 6.5 hours post-dose on Days 1 through 7; and on Day 8/ET. Abnormal vital signs may be repeated no more than 1 time for eligibility purposes.
i. A urine screen for drugs of abuse, a urine cotinine test, and a breath alcohol screen will be performed for all subjects.
j. The "Baseline" C-SSRS questionnaire will be administered during the Screening Period. At all other visits, subjects will be given the "Since Last Visit" questionnaire.
k. A serum pregnancy test will be performed for all subjects during the Screening Period and at Check-In.
l. A serum FSH test will be performed at Screening for subjects who are postmenopausal (ie, have experienced spontaneous amenorrhea for at least 2 years).
m. A test for SARS-CoV-2 will be administered to subjects at the study site on Day -1 prior to admission. Subjects testing positive for COVID-19 are not eligible for the study.
n. All 12-lead ECGs will be performed in triplicate approximately 1 minute apart after the subject has been resting in the supine position for at least 10 minutes. On Day 1, ECG should be performed approximately 1 hour post-dose.
o. Subjects are required to fast overnight (ie, no food or beverage [except water]) for at least 10 hours. All evaluations should be obtained prior to study drug administration. Abnormal laboratory tests may be repeated no more than 1 time for eligibility purposes.
p. Blood samples will be collected to evaluate PK on Days 1 and 7 at pre-dose (within 30 minutes prior to study drug administration) and 10, 20, 30, 45, 60, 120 and 180 minutes post-dose. The following windows will be permitted for the collection of post-dose PK samples: within ±5 minutes of the nominal time up to and including the 45 minutes sample and within ±10 minutes for samples collected 60, 120, and 180 minutes post-dose. In addition, pre-dose samples will be collected on Days 3 and 5 (within 30 minutes prior to study drug administration).
q. Randomization will occur after all Check-In assessments are performed and results are reviewed at pre-dose on Day 1 to confirm and verify that the subject meets all inclusion and no exclusion criteria. All subjects will be randomized to 1 of the 3 parallel treatment groups in a 3:3:2 ratio to receive ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo, respectively.

r. Study drug will be administered 30 minutes before lunch as a single SC injection in the abdominal skin; the injection site location in the abdomen will be rotated at each administration.
s. Injection site reactions will be considered AEs and will be assessed on Day 1 at 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose and once daily on Days 2 through 7 at 1.5 hours (±30 minutes) post-dose.
t. The start time of the standardized lunch will be 30 minutes post-dose; start time will be recorded. Subjects will consume as much of the standardized lunch as desired, and food will be weighed prior to and after eating to assess food intake.
u. On Days 1 through 7, the VAS questionnaire to evaluate hunger, satiety, prospective consumption, desire to eat, and nausea will be administered pre-dose; 20 (±5) minutes after study drug administration; and 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours (±5 minutes) after study drug administration. On Day -1, the VAS questionnaire to evaluate hunger, satiety, prospective consumption, desire to eat, and nausea will be administered 10 (±5) minutes prior to the start of lunch and 1, 2, 3, 4, 5, and 6 hours (±5 minutes) after the start of lunch. On Day -1 and on Days 1 through 7, the VAS questionnaire to evaluate palatability will be administered at the start of lunch.
v. Finger stick blood glucose monitoring for hypoglycemia (defined as blood glucose value <54 mg/dL [<3.0 mmol/L]) will be conducted at 1 and 2 hours after each dose on Days 1 through 7 and as needed for symptoms of hypoglycemia (ie, dizziness or light-headedness, blurred vision, anxiety, irritability or mood changes, fast heartbeat, sweating, slurred speech, hunger, confusion or drowsiness, feeling jittery, shakiness, weakness, headache).
w. AEs will be monitored and documented from the time of informed consent until study participation is complete. Any medical condition already present at the time of informed consent should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline change in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

AE = adverse event; BMI = body mass index; COVID-19 = Coronavirus Disease 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; ET = Early Termination; FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PHQ-9 = Patient Health Questionnaire 9; PK = pharmacokinetic(s); SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; SC = subcutaneous; TSH = thyroid-stimulating hormone; VAS = visual analogue scale.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total cholesterol	Total protein
Triglycerides	Uric acid

Additional Chemistry Parameters

Calcitonin	Glycated hemoglobin (HbA1c)

Coagulation Parameters

Activated partial thromboplastin time	International normalized ratio
Prothrombin time	

Serology

Hepatitis B surface antigen	Hepatitis C virus antibody
Human immunodeficiency virus antibody	Severe acute respiratory syndrome coronavirus 2

Finger Stick Blood Glucose [1]

1. Finger stick blood glucose monitoring for hypoglycemia (defined as blood glucose value <54 mg/dL [<3.0 mmol/L]) will be conducted at 1 and 2 hours after each dose on Days 1 through 7 and as needed for symptoms of hypoglycemia (ie, dizziness or light-headedness, blurred vision, anxiety, irritability or mood changes, fast heartbeat, sweating, slurred speech, hunger, confusion or drowsiness, feeling jittery, shakiness, weakness, headache).

Endocrinology

Follicle-stimulating hormone [1]	Human chorionic gonadotropin (hCG)
Thyroid-stimulating hormone	

1. Follicle-stimulating hormone will be performed at Screening for subjects who are postmenopausal (ie, have experienced spontaneous amenorrhea for at least 2 years).

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [1]	

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Microscopy is performed only as needed based on positive dipstick test results.

Urine Drug Screen

3,4-methylenedioxymethamphetamine	Amphetamines
Barbiturates	Benzodiazepines
Cannabinoids	Cocaine
Methadone	Methamphetamines
Opiates	Oxycodone
Phencyclidine	Tricyclic antidepressants

Urine Cotinine Test, Breath Alcohol Test

APPENDIX C: APPETITE AND PALATABILITY VISUAL ANALOGUE SCALE QUESTIONNAIRES

Appetite Visual Analogue Scale Questionnaire

Protocol:			
|__|__|__|	|__|__|__|	|__|__|__|	Day ___ VAS for Appetite Ratings
Site	Subject	Initials	

Visit Date |__|__|__|__|__|__|__|__|__|__|
dd mmm yyyy

Initials of Administrator_____

Timepoint: X Hour

Actual Time: |__|__|:|__|__|

Mark a vertical line through the horizontal line below that corresponds to each question about how you are feeling.

How hungry do you feel right now?

Not hungry at all — 0 mm

_____

Distance from 0: _____ mm Initials:_____ Date: _____

Extremely hungry — 100 mm

How full do you feel right now?

Not at all full — 0 mm

_____

Distance from 0: _____ mm Initials:_____ Date: _____

Extremely full — 100 mm

How much do you think you can eat right now?

Nothing at all — 0 mm

_____

Distance from 0: _____ mm Initials:_____ Date: _____

A large amount — 100 mm

How strong is your desire to eat right now?

No wish to eat at all — 0 mm

_____

Distance from 0: _____ mm Initials:_____ Date: _____

Extreme wish to eat — 100 mm

How nauseated do you feel right now?

Not at all nauseated — 0 mm

_____

Distance from 0: _____ mm Initials:_____ Date: _____

Extremely nauseated — 100 mm

Palatability Visual Analogue Scale Questionnaire

Protocol:			
|__|__|__|	|__|__|__|	|__|__|__|	**Day ___ VAS for Food Palatability**
Site	Subject	Initials	

Visit Date |__|__|__|__|__|__|__|__|__|__|
dd mmm yyyy

Initials of Administrator_____

Timepoint: **X Hour**

Actual Time: |__|__|:|__|__|

Mark a vertical line through the horizontal line below that corresponds to each question about how you are feeling.

How pleasant is the odor of this food right now?

Not at all pleasant _____ **Extremely pleasant**

Distance from 0: _____ mm Initials:_____ Date: _____

0 mm **100 mm**

How pleasant is the taste of this food right now?

Not at all pleasant _____ **Extremely pleasant**

Distance from 0: _____ mm Initials:_____ Date: _____

0 mm **100 mm**

How pleasant is the texture of this food right now?

Not at all pleasant _____ **Extremely pleasant**

Distance from 0: _____ mm Initials:_____ Date: _____

0 mm **100 mm**

APPENDIX D: COLUMBIA-SUICIDE SEVERITY RATING SCALES

Columbia-Suicide Severity Rating Scale – Baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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Columbia-Suicide Severity Rating Scale – Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

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C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USori.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it"*.
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them"*.
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
—

Duration
When you have the thoughts how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
—

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
—

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
—

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
—

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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APPENDIX E: PATIENT HEALTH QUESTIONNAIRE 9

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

ID #: _____ DATE: _____

Over the last *2 weeks*, how often have you been bothered by any of the following problems? *(use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
	add columns		+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

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PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder
- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder
- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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Source: The F.A.S.T. Lab. Printable versions of imAPP measures. Stanford Medicine. https://med.stanford.edu/fastlab/research/imapp/msrs.html. Accessed 09 October 2024.