STATISTICAL ANALYSIS PLAN

Protocol 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
Protocol Version/Date:	V1.0 / 01 August 2024 V2.0 / 15 October 2024
Investigational Product:	ROSE-010
Sponsor:	Rose Pharma Inc. 3500 Pacific Ave Virginia Beach, Virginia 23451 United States
SAP Version/Date:	V2.0 / 19 February 2025

SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature		**Date**
Wyatt Seed	*Electronically signed by: Wyatt Seed* *Reason: Approved* *Date: Feb 24, 2025 09:18 EST*	24-Feb-2025

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VERSION HISTORY

Version	Version Date	Description
1.0	04 November 2024	Original signed version
2.0	19 February 2025	Updating mixed model language for the primary efficacy endpoint to reflect possible analyses. Updates to nomenclature.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUE	Area under effect
AUC	Area under the plasma concentration-time curve
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
C_{max}	Maximum Plasma Concentration
CPU	Clinical Pharmacology Unit
CRF	Case report form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
ET	Early Termination
GLP-1	Glucagon-like Peptide-1
LOCF	Last Observation Carried Forward
mcg	Micrograms
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
PK	Pharmacokinetics
QTcF	Heart-rate corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SDTM	Study Data Tabulation Model
SI	International System of Units
$t_{1/2}$	Terminal phase elimination half-life
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFLs	Tables, Figures, and Listings
T_{max}	Time to maximum plasma concentration
VAS	Visual Analogue Scale
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number RP-24-02. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 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 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.

2.1.3 Exploratory Objectives

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

2.2 Study Design

2.2.1 Overview

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.
- 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 or placebo, followed by discharge on Day 8.
- Follow-up phone call, which will be completed 7 (±2) days after the final dose of study drug.

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 CPU on Day -1 and will remain confined to the CPU until discharge on Day 8/Early Termination (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.

2.2.2 Randomization and Blinding

This is a randomized, double-blind Phase 2 study. It 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.

2.2.3 Study Drug

Study drug (ROSE-010 [99 mcg or 150 mcg] or placebo) will be administered as a single subcutaneous 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.

2.2.4 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.

2.3 Study Endpoints

2.3.1 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.

2.3.2 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.
- 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.

2.3.3 Exploratory Endpoints

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

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the CRF. All scheduled visits will be included within analysis, all unscheduled visits will be listed unless specified otherwise.

3.1.3 Definition of Baseline

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

3.1.4 Summary Statistics

Data will be presented by treatment (ROSE-010 99 mcg, ROSE-010 150 mcg, or placebo). Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum. Change from baseline, defined as the post-baseline assessments subtracted by the respective baseline value, will also be calculated for continuous data and summarized using descriptive statistics.

In the event that a subject takes the wrong study drug (i.e., did not take the randomized study drug), the actual treatment received will be used for analysis.

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

3.1.5 Handling of Dropouts and Missing Data

Date imputations for partial dates and other imputations are described in the respective analysis sections.

3.2 Analysis Populations

3.2.1 Per Protocol Analysis Set

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.

3.2.2 Safety Analysis Set

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.

3.2.3 Pharmacokinetic (PK) Analysis Set

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.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Subject disposition will be presented for all randomized/enrolled subjects. The number and percentage of subjects in each of the following categories will be summarized by actual dose group and overall, as appropriate:

- Randomized / enrolled;

- Dosed;
- Completed the study; and
- Prematurely withdrew from the study and the primary reasons for early withdrawal;

3.3.2 Protocol Deviations

Counts and percentages of subjects with CSR-reportable protocol deviations by deviation will be summarized by dose group and in total for the Safety Analysis Set.

All protocol deviations will be listed.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized by dose group and in total based on all randomized subjects. Reasons for exclusion from each analysis population will also be summarized.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by dose group and in total for the Safety Analysis Set.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by dose group and in total based on the Safety Analysis Set.

3.3.6 Prior and Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary B3 Global, March 2024G B3.

For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for

missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by dose group and in total based on the Safety Analysis Set.

3.3.7 Study Drug Exposure and Compliance

Study drug administration data will be listed by dose group for all subjects in the Safety Analysis Set.

3.4 Pharmacokinetic Assessment

All Pharmacokinetic Assessments will be described in a separate document.

3.5 Clinical Efficacy Assessment

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

3.5.1 Analysis of Efficacy

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

3.5.1.1 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.

Observed values will 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 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.

3.5.1.2 Secondary Efficacy Analysis

Observed values 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.

The area under effect (AUE) will also be calculated from time 0 to 6.5 hours (390 minutes) for each VAS scale, except palatability, on Day 1 and Day 7. $AUE_{0\text{-}6.5}$ will be calculated using the trapezoid method. If any observations are missing for the scheduled timepoints for the AUE calculation, the missing values will be imputed using the last observation carried forward (LOCF) method.

3.5.1.3 Other Efficacy Analysis

Observed values, change from baseline, and relative change (i.e. percent change) values of body weight and will be summarized using descriptive statistics at all measured visits and timepoints.

3.6 Safety Assessment

Safety analysis will be performed using the Safety Analysis Set.

3.6.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using MedDRA version 27.0. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug.

An overview of AEs will be provided including counts and percentages of subjects (and event counts) with the following:

- Any Adverse Events
- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs (overall and by maximum severity)
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to discontinuation of study
- Any AEs leading to death

Counts and percentages of subjects (and event counts) will also be presented by system organ class and preferred term for each of the categories in the overview.

Listings will be presented specifically for SAEs, TEAEs leading to discontinuation of study drug, and TEAEs leading to discontinuation of study.

3.6.2 Clinical Laboratory Tests

Clinical laboratory assessments are listed in Appendix B of the Clinical Study Protocol and will be summarized using descriptive statistics at the scheduled visits and/or timepoints that are specified within the Schedule of Events within the Protocol. A list of laboratory tests to be performed is included within the protocol.

Observed values and change from baseline will be presented at each scheduled visit and/or timepoint and baseline by laboratory test. The incidence of abnormalities (as defined by normal ranges) prior to the first dose of study drug and after the first dose of study drug will be summarized with counts and percentages of subjects.

All laboratory data will be summarized using the International System of Units (SI).

All laboratory data will be listed.

3.6.3 Vital Signs

Vital signs will be summarized using descriptive statistics at the scheduled visits and/or timepoints that are specified within the Schedule of Events within the Protocol. The vital signs parameters to be summarized are the following:

- Systolic Blood Pressure
- Diastolic Blood Pressure
- Heart Rate
- Respiratory Rate
- Temperature

Observed values and change from baseline will be presented at each scheduled visit and/or timepoint and baseline by vital sign.

All vital sign data will be listed.

3.6.4 Electrocardiograms

Electrocardiogram (ECG) data will be summarized using descriptive statistics at the scheduled visits and/or timepoints that are specified within the Schedule of Events within the Protocol. The electrocardiogram parameters to be summarized are the following:

- Heart Rate
- PR Interval
- RR Interval
- QRS Duration
- QT Interval
- QTcF Interval

The average value of the collected triplicates will be calculated for each parameter at each timepoint and will be used for all summary statistics for numeric parameters. The "worst" triplicate value for overall interpretation at each timepoint will be used for all categorical summaries.

Observed values and change from baseline will be presented at each scheduled visit and/or timepoint and baseline by electrocardiogram parameter.

The overall interpretation and clinical significance of the interpretation will be summarized with counts and percentages at each scheduled visit and/or timepoint.

All ECG data will be listed.

3.6.5 Physical Examinations

All physical examination data will be listed.

3.6.6 Injection Site Reactions

The toxicity of injection site reactions will be summarized with counts and percentages at the scheduled visits and/or timepoints that are specified within the Schedule of Events within the Protocol.

The injection site reaction parameters to be summarized are the following:

- Pain
- Tenderness
- Erythema/Redness
- Induration/Swelling

All injection site reaction data will be listed.

3.6.7 Columbia-Suicide Severity Rating Scale

All data from the C-SSRS will be listed.

3.6.8 Other Safety Assessments

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

The area under effect (AUE) will also be calculated from time 0 to 6.5 hours (390 minutes) for the nausea scale on Day 1 and Day 7. $AUE_{0\text{-}6.5}$ will be calculated using the trapezoid method. If any observations are missing for the scheduled timepoints for the AUE calculation, the missing values will be imputed using the LOCF method.

4 ANALYSIS TIMING

4.1 Interim Analysis

No interim analysis is planned for this study.

4.2 Pre-Final Analysis

After the database is locked and exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated. Pre-final Tables, Figures, and Listings (TFLs) will be provided approximately 3 weeks after database lock.

4.3 Final Analysis

Final TFLs will be provided approximately 1 week after Sponsor comments are returned on the Pre-Final TFLs. Any comments or edits from pre-final analysis will be implemented for final analysis. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The mixed model of repeated measures within section 9.2.1.1 of the protocol was updated in version 2.0 of the SAP. Change from baseline of food (weight and energy content) consumed during lunch was removed from the planned study analyses. Baseline food consumption was also removed as a covariate. These analyses cannot be completed, as food (weight and energy content) consumed during lunch is not collected prior to first dose of study drug.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. Detailed Programming Specifications will be provided in a separate document.