KALLYOPE

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Statistical Analysis Plan

Protocol No. P006-03, 03 October 2023

A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND 13-WEEK STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND WEIGHT LOSS EFFICACY OF K-757 ALONE AND IN COMBINATION WITH K-833 IN PARTICIPANTS WHO ARE OBESE

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Table of Contents

List of Tables

Glossary and Abbreviations

Abbreviation	Term
AE(s)	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BID	twice daily
BLQ	below the lower limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
Cl	clearance
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variations
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ET	early termination
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HbA1c	hemoglobin A1C
HbsAg	hepatitis B surface antigen
ICH	International Council for Harmonisation
LLOQ	lower limit of quantification
LS	least squares
Max	maximum
MBA	multiple biochemical analysis
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MMRM	mixed model repeated measure
n	number of subjects
NE	not evaluable

Abbreviation	Term
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
PYY	peptide YY
QAM	every morning
QD	once daily
QPM	each evening
QTc	QT interval
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SE	standard error
SI	International System of Units
SOA	schedule of assessment
SOC	system organ class
T2DM	type 2 diabetes mellitus
T_{max}	time of maximum concentration
TEAE(s)	treatment-emergent adverse event(s)
TFL	table, figure, and listing
ULOQ	upper limit of quantification
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WMG	weighted mean glucose

1 Introduction

This statistical analysis plan (SAP) is a comprehensive and detailed description of strategy and statistical techniques to be used for the analyses of trial data from study protocol P006-03 dated October 03, 2023 (A Randomized, Placebo-Controlled, Double-Blind 13-Week Study to Evaluate the Safety, Tolerability, and Weight Loss Efficacy of K-757 alone and in Combination with K-833 in Participants who are Obese). This SAP will be finalized prior to database lock to ensure the credibility of the study results by pre-specifying the statistical methods for analyses.

This SAP may be revised during the course of the study to accommodate protocol amendments and to adapt to revisions in the analysis approaches. Any changes made to the SAP after database lock will be documented and detailed in the Clinical Study Report (CSR) for this study.

The statistical principles applied in the design and planned analyses of this study will be consistent with the International Council on Harmonisation (ICH) guidelines E9 (Statistical Principles for Clinical Trials) (ICH 1998).

2 Study Objectives and Endpoints

2.1 Study Objectives

2.1.1 Primary Objective

The study primary objective is:

- To assess relative (%) change from baseline in body weight after 13 weeks of treatment with K-757 alone and in combination with K-833, in comparison to placebo.

2.1.2 Secondary Objectives

The study secondary objectives are:

- To assess the proportion of participants achieving ≥5% weight loss from baseline after 13 weeks of treatment with K-757 alone and in combination with K-833, in comparison to placebo
- To assess the absolute change from baseline in body weight after 13 weeks of treatment with K-757 alone and in combination with K-833, in comparison to placebo
- To characterize the safety and tolerability of K-757 alone and in combination with K-833 over 13 weeks of treatment.

2.1.3 Exploratory Objectives

The study exploratory objectives are:

- To assess the change from baseline in hemodynamic parameters (systolic blood pressure, diastolic blood pressure and heart rate) after 13 weeks of treatment with K-757 alone and in combination with K-833, in comparison to placebo.
- To assess the change from baseline in total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides after 13 weeks of treatment with K-757 alone and in combination with K-833, in comparison to placebo.

2.2 Study Endpoints

2.2.1 Primary Endpoints

The study primary endpoint is:

Percentage change from baseline in body weight (%) after 13 weeks of treatment

2.2.2 Secondary Endpoints

The study secondary endpoints are:

- Proportion of participants achieving ≥5% weight reduction after 13 weeks of treatment

- Change from baseline in body weight (kg) after 13 weeks of treatment
- Proportion of participants who experienced 1 or more treatment-emergent AE
- Proportion of participants who discontinued study medication due to an AE

2.2.3 Exploratory Endpoints

The study exploratory endpoints are:

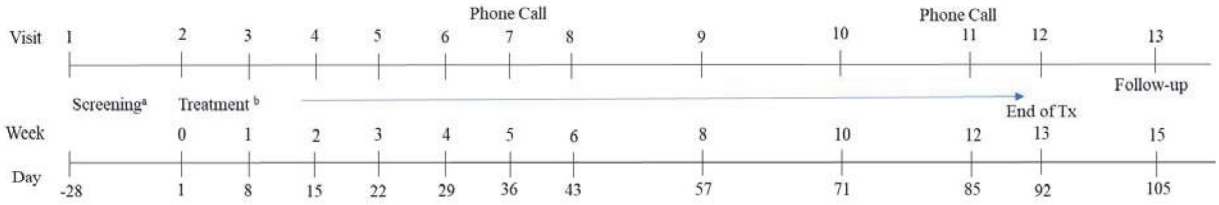
- Change from baseline in hemodynamic parameters (systolic blood pressure, diastolic blood pressure and heart rate) after 13 weeks of treatment.
- Change from baseline in total cholesterol, LDL-C, HDL-C, and triglycerides after 13 weeks of treatment.

3 Study Design

3.1 Overall Study Design

This is a randomized, double-blind, placebo-controlled 13-week study to evaluate the efficacy of K-757 alone and in combination with K-833 versus placebo in participants who are obese without type 2 diabetes mellitus (T2DM). Approximately 150 participants will be enrolled and randomized 1:1:1 to receive K-757 alone, K-757 + K-733, or matching placebos (Figure 1 and Table 1)

Figure 1: Study Schematic



[a] Screening will occur over approximately 4 weeks.

[b] Refer to the Dosing Table and Section 5.4.1 of the Clinical Study Protocol (CSP) for study drug administration details.

[c] Week indicates the duration of treatment completed prior to the visit, not the week in which the visit occurs. For example, "Week 1" visit is targeted to occur on Day8 (the first day of the 2nd week of treatment).

The study will be comprised of a Screening period (up to 28 days prior to the treatment period), a 13-week double-blind Treatment Period (dosing on Days 1 to 91; end-of-treatment visit Day 92), and a post-study Follow-Up period (approximately 14 days after their last dose). The total duration of the study for each participant will be up to approximately19 weeks. Randomization

will be stratified by gender (male/female). Enrollment into each gender strata will be capped at 70% (i.e., neither gender may exceed 70% of total enrollment).

Table 1: Dosing Table

Arm	Time (AM/PM)		Week			
			Week 0 (D1-7)	Week 1 (D8-14)	Week 2 (D15-21)	Week 3 (D22-28)
K-757+K-833	AM	757/833 (mg)	30/100	30/100	60/100	120/100
	PM	757/833 (mg)	pbo/pbo	30/100	60/100	120/100
K-757 alone	AM	757/833 (mg)	30/pbo	30/pbo	60/pbo	120/pbo
	PM	757/833 (mg)	pbo/pbo	30/pbo	60/pbo	120/pbo
Placebo to K-757 and K-833	AM	757/833 (mg)	pbo/pbo	pbo/pbo	pbo/pbo	pbo/pbo
	PM	757/833 (mg)	pbo/pbo	pbo/pbo	pbo/pbo	pbo/pbo

For additional titration information, see Section 5.4.1 of the CSP

Participants will return to the trial site at the times described in the study schematic and schedule of assessments (SOA) (Table 2) to complete study procedures. During two of the on-treatment weeks when participants do not return to the trial site, the site will contact the participants by phone in order to assess study medication compliance, new concomitant medication use, and adverse events (AEs).

Starting at the randomization visit (Visit 2), all participants will receive nutritional and physical activity counseling from a dietician, or a similarly qualified healthcare professional designated by primary investigator. This counseling will occur at select visits according to the SOA (Table 2).

Safety and tolerability will be assessed in an ongoing fashion through physical examination, vital sign assessment, 12-lead electrocardiogram (ECG), clinical laboratory assessments, and collection of serious and non-serious AEs. Specific timepoints are described in Table 2

Plasma will be obtained for pharmacokinetics (PK) pharmacodynamics (PD) at select time points during treatment (Table 2).

To mitigate mechanism-related GI intolerance, K-757 and K-833 will be titrated according to Table 1 above. In the combination arm and the K-757-only arm, K-757 will be titrated to the maintenance dose of 120 mg twice daily (BID) by Day 22. K-833 will be initiated at 100 mg every morning (QAM) and will be titrated to the maintenance dose of 100 mg BID on Day 8.

For participants experiencing gastrointestinal (GI) intolerance, all reasonable, medically appropriate efforts should be made to support them in adhering to scheduled dose/dose escalations (see Section 7.1.1 of the CSP).

3.2 Randomization

Signant Health (IWRS vendor) will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

Participants will be assigned to either placebo, K-757 alone, or K-757+K-833. Participants who meet all criteria for enrollment will be randomized at Visit 2 and assigned to their respective treatment groups via interactive web response system (IWRS) using the following stratification variables: gender (male/female). There will be equal randomization to the treatment arms (1:1:1). The randomization scheme will be performed using IWRS that will ensure balance between treatment arms.

The randomization number encodes the subject assignment to either K-757 alone, K-757 + K-833, or placebo according to the randomization schedule generated before the study. Each subject will be dispensed study drug (K-757, K-757 + K-833 or placebo) in a double-blinded manner, labeled with his/her unique randomization number, throughout the study.

3.3 Blinding and Unblinding

This is a double-blind study where the Sponsor, site staff, and participants will be blinded to the treatment assignment.

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. If possible, the Sponsor medical monitor should be contacted before the blind is broken, unless doing so poses a risk to subject safety. The need for investigator unblinding should be discussed with the Sponsor first unless the unblinding needs to occur urgently to ensure subject safety.

Any intentional or accidental unintentional unblinding will be documented and filed as per relevant study operating procedures and /or plan, filed in the relevant study TMF (folder), and summarized in the CSR.

3.3.1 Unblinded Personnel and /or Procedures.

3.3.1.1 Clinical Supplies Related Personnel

Personnel who manage and oversee (i.e., Sponsor designees) drug inventory levels within the study interactive response technology system (IRT) and who are accountable for the quality assurance review/approval processes including but not limited to the review of documentation related to the manufacture, packaging, labeling and release stages will see unblinded information. These individuals will not have access or be informed as to subject level treatment allocations during the study. Additionally, these personnel will <u>not</u> be:

- attendees to study team meetings following study initiation,
- included on study team meeting minute distribution,

- included in study team communications through the duration of the study through database lock and unblinding.

3.3.1.2 Pharmacovigilance Personnel

Designated safety management personnel (at Sponsor designated Pharmacovigilance vendor) have the capability to unblind individual subject treatment assignment in the case of determining the causality of potential suspected unexpected serious adverse reaction (SUSAR) events upon approval from the blinded Sponsor Medical Monitor who will confirm, based on blinded data review, whether the event is considered 'unexpected' for reporting purposes, and therefore a potential SUSAR. Unblinding for these circumstances is performed and recorded within the study randomization platform, i.e., the IRT system. Designated Sponsor personnel will review unblinded SUSARs that require submission to the regulatory agencies and/or central Institutional Review Boards (IRB). The Food and Drug Administration (FDA) submission vendor will receive unblinded MedWatch forms from the Pharmacovigilance vendor for submission of SUSARs to FDA.

3.3.1.3 Investigator Unblinding in Case of Medical Emergency at the Site

The site investigator may exercise the option to unblind an individual subject in case of medical emergency. The unblinding by the investigator is performed, documented, and maintained within the context of the IRT system. Subject unblinding in these circumstances by the investigator and/or sponsor medical monitor will be documented by the site within the study medical records, the eCRF and described in the CSR.

3.3.1.4 Biometrics

All biometrics personnel from sponsor and CRO (including Data management, Biostatistics and Statistical programming) will remain blinded during the study before database lock, unless otherwise specified.

a. Pharmacokinetic/Pharmacodynamic Data

Subject-level PK and exploratory PD endpoint data are unblinding. Therefore, the PK lab will not share the unblinded PK data with sponsor until after the database lock. The sample analysis for PD will not be performed until after database lock.

b. Randomization System/Process Personnel

The randomization vendor, whose function is to generate/confirm/upload the study randomization schedule and who support the day-to-day function of the IRT system (as per the

vendor established SOPs), will be unblinded. These unblinded personnel will not engage in study team meetings where any facets of the trial are being discussed.

Complete details of blinding/unblinding can be found in the Sponsor's Blinding and Unblinding Procedures Plan.

3.4 Sample Size Justification

For the primary endpoint of percentage change from baseline in body weight, a sample size of 150 participants (stratified by gender and randomized 1:1:1 into three treatment arms) provides >95% power to detect a treatment difference of 4% weight reduction after 13 weeks of treatment with a 2-sided alpha of 0.05, assuming a standard deviation of 4% and 20% drop out.

4 Analysis Sets

The following analysis set are defined and used for this study.

4.1 Screened Set

The Screened Set includes all subjects who sign the informed consent form.

4.2 Modified Intent-to-Treat (mITT) Analysis Set

The mITT analysis set consist of all randomized participants who receive at least one dose of the study drug during the double-blind treatment period. The participants will be analyzed as randomized. The mITT analysis set will be used for demographic, baseline characteristics and efficacy analyses.

4.3 Safety Analysis Set

The Safety Analysis Set consist of all randomized participants who receive at least one dose of study drug during the double-blind treatment period. The safety analysis set will be used for safety analysis and analyzed as treated.

4.4 Pharmacokinetic (PK) Analysis Set

The PK analysis set consist of all participants who receive study drug and have at least 1 measurable plasma concentration.

4.5 Per Protocol Analysis Set

The per protocol analysis set consist of all participants who completed 13-week treatment and have weight assessment at week 13 and treatment compliance >=80%. Participants who completed treatment but have week 13 assessment done more than 3 days after last dose date and participants whose weights at week 13 are collect at non-fasted state are excluded.

5 Statistical Methods

5.1 General Considerations

Unless otherwise specified, all statistical analyses of the study will be performed using the statistical software Statistical Analysis System (SAS) for Windows Version 9.4 or later (SAS Institute, Inc., Cary, NC). All by-subject data used in the analyses will be displayed in listings.

5.1.1 Data Summary

All summary tables will be presented by treatment group (K-757, K-757 + K-833, and placebo) and/or overall, as needed.

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, the number of participants (n), mean, standard deviation (SD), minimum (min), first quartile (Q1), median, third quartile (Q3) and maximum (max). The min and max values will be presented to the same number of decimal places as the raw data. If the raw data has 3 decimal places or more, 3 decimal places will be presented for the mean and SD; 2 decimal places will be presented for medium, Q1, Q3, min and max. Otherwise the mean and median will be presented to one more decimal place than the raw data. The SD will be presented to two more decimal places than the raw data. .

Summaries for categorical (discrete or dichotomous) variables will include the number and/or percentage of subjects in a particular category. Percentages will be presented to one decimal place, unless otherwise specified. Population counts (either number of subjects or number of time points at the assessment) for each treatment group will be used as the denominator in the calculation of percentages unless otherwise specified.

All tests of treatment effects will be conducted at a two-sided alpha level of 0.05 and/or two-sided 95% CI, unless otherwise stated.

5.1.2 Baseline

Unless otherwise specified, baseline is defined as the last available observation prior to dosing during the double-blind treatment period.

Change from baseline is defined as the difference between the post-baseline assessment value and the baseline value, i.e.,

Post-baseline Assessment Value – Baseline Value.

Percent change from baseline is defined as

(Change from baseline value/Baseline value) × 100%

5.1.3 Study Day

Study day is relative to the day of first dose of study drug. Day 1 is defined as the day of the first dose of study drug. Study day after Day 1 is calculated as:

Assessment date – date of Day 1 + 1.

Study day prior to Day 1 is calculated as:

Assessment date – date of Day 1.

The day prior to Day 1 is Day -1.

5.1.4 Unscheduled Visits

An unscheduled visit value may be used to provide a measurement for a scheduled visit, a baseline, a last or a worst value, if appropriate according to their definitions. Unscheduled visits measurements may also be included in analyses for body weight, hemodynamic data (systolic blood pressure, diastolic blood pressure and heart rate) and lab measures (total cholesterol, LDL, HDL, and triglycerides). For lab data (safety lab and lipid panels), if an unscheduled visit occurs on the same date of a scheduled visit, it will be mapped to the scheduled visit. The duplicated lab values will be averaged for summary analysis. Other unscheduled visit values will not be summarized, but will be presented chronologically in the listings.

5.1.5 Handling of Missing or Incomplete Data

For Efficacy endpoints, PK and PD, handling of missing data is described in Sections 5.7.2 and 5.10.

Unless otherwise specified, missing or incomplete dates for prior/concomitant medications, AEs and laboratory data will be imputed as follows:

Adverse Events

The following imputation rules for missing or partial AE start dates are used:

- If only Day is missing, the start day will be the first day of the month or the date of study drug first dose if the AE end date is on/after the date of study drug first dose or is missing/partial AND the start year and month of the AE are the same as year and month of the study drug first dose date;
- If Day and Month are both missing, the start date will be the date of study drug first dose if the AE end date is on/after the date of study drug first dose or is missing/partial AND the start year of the AE is the same as year of the study drug first dose date; the start date will be imputed to January 1 of the year otherwise.

- If Day, Month, and Year are all missing, the date will not be imputed. However, if the AE end date is on/after the date of study drug first dose, then the AE will be considered a treatment emergent adverse event (TEAE).

Missing or partial AE stop dates will not be imputed.

If the severity of an AE is missing, it will be classified as "severe" in the summary tables. If the assessment of relationship of study medication is missing, it will be classified as "related" to the study drug.

Prior or Concomitant Medications

The same imputation rule as applied to missing or partial AE start date will be used for missing or partial medication start dates.

Missing or partial medication stop dates will not be imputed.

Safety Laboratory Data

For the analysis/summary of laboratory data, lab values preceded by a "<" or a ">" sign (i.e., those below the lower limit of quantification [LLOQ] or above the upper limit of quantification [ULOQ]) will be considered equal to the LLOQ or ULOQ, respectively. The original values preceded by a "<" or a ">" sign will be presented in the listings.

5.1.6 Analysis Visit Windows

For body weight, hemodynamic data (systolic blood pressure, diastolic blood pressure and heart rate) and lab measures (total cholesterol, LDL, HDL, and triglycerides), unscheduled visits and end of treatment visits and follow-up visits for participants who discontinued study drug earlier will be mapped based on analysis visit window below. The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, end of treatment visits and follow-up visits for participants who discontinued study drug earlier have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits.

For other safety measures, analysis visit windowing will not be applied. The visits and time points reported on the electronic case report form (eCRF) will be used.

The following analysis visit windows will be used to map the unscheduled visits, end of treatment visits and follow-up visits for participants who discontinued study drug earlier of body weight.

Visit	Target Day	Analysis Visit Window Based on Study day
Baseline	1	1
Week 4	29	[2, 43]
Week 8	57	[44, 74]

Week 13 for Participants Discontinued Treatment	92	[75, 95]
Week 13 for Participants Completed Treatment	92	[75, Last Dose Date +3]
Week 15 for Participants Discontinued Treatment	105	>95

The following analysis visit windows will be used to map the unscheduled visits, end of treatment visits and follow-up visits for participants who discontinued study drug earlier hemodynamic data (systolic blood pressure, diastolic blood pressure and heart rate).

Visit	Target Day	Analysis Visit Window Based on Study day
Baseline	1	1
Week 1	8	[2,11]
Week 2	15	[12,18]
Week 3	22	[19,25]
Week 4	29	[26, 36]
Week 6	43	[37, 50]
Week 8	57	[51, 64]
Week 10	71	[65, 81]
Week 13 for Participants Discontinued Treatment	92	[82, 95]
Week 13 for Participants Completed Treatment	92	[82, Last Dose Date +3]
Week 15 for Participants Discontinued Treatment	105	>95

In the event of multiple measurements of the same test in the same window, if the measurements are from different visit categories, the priority order is scheduled visit, end of study visits and follow-up visits, then unscheduled visit. For the measurements in the same visit category, the value measured nearest to the target day will be used; if they are at the same distance to the target day, the latest one will be used.

5.2 Subject Disposition

The number and percentage of participants who were randomized, who were randomized but did not receive the study drug as randomized, who were treated with the study drug, who completed the double-blind treatment and/or the study, who prematurely discontinued the study drug and/or study and the primary reason discontinuation (study drug and/or study) will be summarized by treatment group and overall.

A separate summary will be provided for the number and/or percentage of subjects that were screened, enrolled and screened failed (including initial screen and re-screen) and reason for screen failure.

Subject disposition will be listed for all randomized participants. Also, the eligibility status for the study will be listed for all screened participants, using the Screened Set.

5.3 Protocol Deviations

Protocol deviations identified during the course of the study will be classified as major or minor.

A major protocol deviation (sometimes referred to as a protocol violation or a significant protocol deviation) is a deviation to the protocol that might significantly impact the completeness, accuracy or reliability of the study data or that may significantly affect a participant's rights, safety or well-being.

Before the database lock, all protocol deviations will be reviewed by the Sponsor. Final determination of major deviations is the responsibility of the Sponsor. Major protocol deviations will be identified and listed in the CSR.

Major protocol deviations will be summarized by treatment group and overall, and by category and sub-category if there is a sufficient number of major protocol deviations.

All protocol deviations will be presented in a listing. A by-subject listing will be provided for major protocol deviations.

5.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and overall using the mITT set. Demographics and baseline characteristic include age, age group (< 65 years or ≥ 65 years), sex, childbearing potential if female, race, ethnicity, baseline height (cm), weight (kg) and body mass index (BMI; kg/m^2).

BMI, if not available, will be calculated as the ratio of subject's weight (kg) to the square of the subject's height (m):

$$BMI = \text{Weight (kg)}/(\text{Height [m]})^2.$$

Continuous variables (age, height, weight and BMI) will be summarized by n, mean, SD, median, min, and max. Number of subjects and percentages will be used to describe categorical variables (sex, race, ethnicity and age group.).

Demographic and baseline characteristics data will be listed

5.5 Medical History

Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Medical history will be summarized by system organ class (SOC) and preferred term (PT) using the mITT set. A by-subject listing will be provided for medical history.

5.6 Prior and Concomitant Therapies

5.6.1 Prior and Concomitant Medications

Any medication or vaccine that the subject is receiving at the time of enrollment or receives during the study will be recorded in the subject's source documentation and the eCRF.

Medications will be classified into prior medications and concomitant medications.

- Prior medications are defined as medications that started and stopped prior to the first dose of study drug.
- Concomitant medications are defined as any medications that were ongoing or started on or after the first dose of study drug.

A given medication can be classified as a prior medication or a concomitant medication.

Medications will be recorded and coded using the latest version of World Health Organization (WHO) Drug Enhanced Dictionary. Prior and concomitant medications will be summarized separately by Anatomical Therapeutic Chemical (ATC) classification pharmacological or therapeutic subgroup (Level 2) and preferred drug name for the Safety Analysis Set. At each level of summarization, a subject is counted once if he/she reported 1 or more medications at that level. Medications will be listed by subject, including ATC classification, preferred drug name and reported drug name, the start and end dates (or ongoing status), dose, unit, frequency, route, and indication.

5.6.2 Medications for Managing Gastrointestinal (GI) Adverse Events (AEs)

Medications for managing GI AEs is defined as any initiation and modification of medication taken on or after first dose to treat GI AEs. Number and proportion of participants with medication for GI AEs will be summarized by Anatomical Therapeutic Chemical (ATC) classification pharmacological or therapeutic subgroup (Level 2) and preferred drug name for the safety analysis set.

5.7 Study Treatment Exposure and Compliance

5.7.1 Exposure to Study Drug

Duration of exposure will be descriptively summarized by treatment group in the Safety Analysis Set.

Duration of exposure (days) will be calculated as:

Date of last dose – Date of first dose + 1.

5.7.2 Treatment Compliance

Number and percent of participants with missing dose(s) and the total number of days with missing doses will be descriptively summarized by treatment group in the Safety Analysis Set.

Compliance will be calculated as follows:

Treatment compliance = Total number of days with complete dosing / Total number of actual dosing days * 100

Participants are considered as taking complete dosing if full AM and full PM doses are taken. Treatment compliance will be summarized as a continuous variable with descriptive statistics by treatment group in the Safety Analysis Set. Treatment compliance will also be presented by the following specific ranges by treatment group: <50%, ≥50% to ≤ 80%, >80% to <100% and 100%.

A by-subject listing will be presented for drug administration and compliance in the Safety Analysis set.

5.8 Efficacy Analyses

All efficacy analyses will be performed using the mITT Set unless otherwise specified.

5.8.1 Primary Efficacy Endpoint

The primary efficacy outcome is the % weight change from baseline (Week 0) to Week 13.

Per the protocol, weight will be taken in duplicate throughout the study, therefore, all analyses and summaries of weight will be based on the average of the duplicate weight measurements.

5.8.1.1 Primary Estimand

Primary trial objective: To assess relative (%) change from baseline in body weight after 13 weeks of treatment with K-757 alone and in combination with K-833, in comparison to placebo

Estimand Scientific Question of Interest: What is the effect on body weight of assigning participants to K-757 alone and in combination with K-833, in comparison to placebo on treatment?

- Variable: % change in body weight
- Analysis Set: Modified intent-to-treat set
- Analysis time point: 13 weeks post-baseline
- Treatment: Average treatment effect of K-757 alone and in combination with K-833 relative to placebo
- Analysis methodology: Mixed model for repeated measures (MMRM)

- Intercurrent events: Treatment discontinuation - All available data at Week 13 had participants remained on their randomized treatment for the entire planned duration of the trial are used in the analysis ("hypothetical" estimand).
- Missing data: Missing data is imputed using MMRM based on missing at random (MAR) assumption at Week 13.

5.8.1.2 Primary Analysis

A mixed model for repeated measurements (MMRM) analysis will be applied with gender, treatment, visit and treatment-by-visit interaction as fixed effect, and baseline body weight as a covariate. The MMRM model will use assessments only from participants who are taking the randomized treatment until end of treatment if they complete treatment or until 3 days after discontinuation of randomized treatment; scheduled follow up assessment will also be included in analysis. An unstructured covariance will be used. If the unstructured covariance structure leads to nonconvergence, other covariance structures, such as, compound symmetry (CS) and autoregressive (AR(1)) will be used. Akaike's information criteria will be used to select the best covariance structure.

The least squares (LS) means, difference in LS mean (K757 vs placebo, K-757+K-833 vs placebo), the corresponding 95% CI and the p-value will be provided. In addition, descriptive statistics including number of participants, mean and standard error will be provided.

5.8.1.3 Secondary Estimand

The only attributes that changes from the definition of the primary estimand is how the handling strategy is adopted for treatment discontinuation.

- Intercurrent events: Treatment discontinuation - All available data up to Week 15 including the participants who have discontinued treatment but completed visit after discontinuation ("retrieved dropouts") are used for the analysis ("treatment policy" estimand)
- Missing data: Same missing data imputation will be performed as the primary estimand.

5.8.1.4 Completer Analysis

Completer analysis will also be performed. The only attributes that changes from the definition of the primary estimand is that analysis is done for per protocol analysis set, ie only participants who complete 13-week treatment and with a week 13 assessment and treatment compliance >=80% will be included for analysis. Participants who completed treatment but have week 13 assessment done more than 3 days after last dose date and participants whose weights at week 13 are collect at nonfasted state will be excluded from analysis.

Additional sensitivity analysis may be performed using multiple imputation (MI) approach.

5.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are described in Section 2.2.2.

5.8.2.1 Proportion of Participants Achieving ≥ 5% Weight Reduction after 13 Week of Treatment

The same MMRM described for the primary endpoint will be used to address the primary estimand. Missing data will be imputed using MMRM assuming missing at random (MAR) and the imputed value based on the predicted value will be used to classify each subject as a responder or not. A logistical regression using gender and treatment as factors and baseline body weight as covariate will be applied to analyze the imputed data. In addition, cumulative distribution plot and waterfall plot of % weight by treatment change from baseline (Week 0) to Week 13 based on imputed data will be provided.

In addition, the number and percent of participants with weight decreases of ≥5% will be summarize at each timepoint by treatment group. Percentages will be based on the number of participants available at the given timepoint without imputation.

5.8.2.2 Change from Baseline in Body Weight (kg) after 13 Weeks of Treatment

The change from baseline will be analyzed to address the primary estimand using the same MMRM described for the primary endpoint.

5.8.3 Subgroup Analyses

To assess the consistency in the treatment effect across different subgroups, subgroup analyses will be performed for the primary efficacy endpoint and secondary efficacy endpoints using same method as primary estimand, with respect to the following:

- Gender (male, female)
- Baseline Body Weight (< 100KG , >= 100 KG)
- BMI (< 35, >=35)

Forest plot will be presented for subgroup analyses.

5.8.4 Exploratory Endpoints

The exploratory endpoints are described in Section 2.2.3.

5.8.4.1 Change from Baseline in Hemodynamic parameters after 13 Weeks of Treatment

The hemodynamic parameters include systolic blood pressure, diastolic blood pressure and heart rate.

The change from baseline in hemodynamic parameters will be analyzed using the same MMRM approach described for the continuous secondary endpoints. For triplicate measurements, the average value will be analyzed.

5.8.4.2 Change from Baseline in Total Cholesterol, LDL, HDL, and Triglycerides after 13 Weeks of treatment

Post-baseline Last observation carried forward (LOCF) approach will be used to impute missing value at Week 13. Only assessments for subjects who are on treatment for more than 28 days, collected on or before treatment discontinuation + 3 days will be used for LOCF. The change from baseline in total cholesterol, LDL and HDL will be analyzed using ANCOVA model with change from baseline at Week 13 as the response variable, treatment, gender, baseline value as covariates.

Triglycerides is not expected to be normally distributed. The Hodge-Lehmann method will be used to estimate the median difference with 90% CI between treatment groups. A Wilcoxon rank sum test will be performed.

5.8.4.3 Proportion of Participants with Hemoglobin A1c ≥ 5.7% after 13 Week of Treatment

Post-baseline Last observation carried forward (LOCF) approach will be used to impute missing value at Week 13. Only assessments, for subjects who are on treatment for more than 28 days, collected on or before treatment discontinuation + 3 days will be used for LOCF. Number and percent of participants with hemoglobin A1c ≥ 5.7 % will be summarize at baseline and week 13 by treatment group.

5.9 Pharmacokinetic Analysis

PK analyses for K-757 and K-833 will be performed based on the PK Analysis Set.

Plasma concentration of K-757 or K-833 at the timepoints specified in the SOA (Table 2) will be descriptively summarize by treatment arm with n, mean, SD, median, minimum, maximum, geometric mean and geometric CV%, as appropriate.

For the purpose of descriptive summaries, plasma concentrations of K-757 or K-833 below the lower limit of quantification (BLQ) will be set to zero except for calculating geometric means and geometric CV%. For the geometric means and geometric CV%, the BLQ value is set to LLOQ/2.

The PK concentrations will be displayed with the same precision as concentration data received, but no more than 3 decimal places. In descriptive statistics, calculations derived from PK concentrations will follow the same precision. The CV% will be displayed with one decimal place.

Raw PK concentrations in ng/mL will be converted to nM for each study drug. The molecular weight for K-757 is 541.71 and the molecular weight for K-833 is 640.15. Specifically, the following formula will be used to convert from ng/mL to nM: (concentration in ng/mL /molecular weight) × 1000 = concentration in nM.

A by-subject listing will be provided.

5.10 Pharmacodynamic Analysis and DNA Sample

PD parameters including gut hormone levels (eg. GLP-1, PYY) assessed in samples collected at the timepoints specified in the SOA (Table 2) may be summarized.

Results of any analyses performed on the optional genetic blood sample (Table 2) may be summarized.

5.11 Safety Analyses

The safety measurements include AEs, clinical laboratory assessments, vital signs, 12-lead ECG and physical examination. All summaries will be performed and reported by treatment group using the Safety Analysis Set.

No formal statistical tests or inference will be performed for safety analyses.

5.11.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All AEs will be recorded starting from the signing of informed consent form throughout the end of the follow-up or early study termination.

A TEAE is defined as an AE that starts or worsens after the time of randomization up to 2 weeks after the last dose of the study medication.

A SAE is defined as any untoward medical occurrence that:

- Results in death
- Is immediately life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

All AEs will be coded and classified using the version of the Medical Dictionary of Regulatory Activities (MedDRA) in affect at the start of the study. The severity/intensity of AE is assessed by the Investigator as mild, moderate or severe. The relationship to study drug is judged by the Investigator as related or unrelated.

5.11.1.1 Incidence of Adverse Events

Overall summary tables of TEAEs will be presented showing the number and percentages of subjects with any TEAEs, any TEAEs by maximum severity, any study drug-related TEAEs, treatment-emergent SAEs, any treatment-emergent GI AE, TEAEs leading to study drug withdrawal, and TEAEs with fatal outcome.

The following TEAEs will be summarized by frequency and percentage of subjects by SOC (in alphabetical order) and PT (by decreasing frequency in the K-757 + K-833 arm):

- TEAEs
- TEAEs by maximum severity
- Study drug-related TEAEs
- Treatment-emergent SAEs
- TEAEs leading to study drug withdrawal

If the same AE (preferred term) is reported more than once for the same subject, it will be only counted once in the summary table. For the summary table by severity, if the same AE (preferred term) is reported more than once for the same subject, the maximum severity grade (severe > moderate > mild) will be counted in the summary table.

The following by-subject listings will be provided:

- AEs
- SAEs
- TEAEs leading to study drug withdrawal

5.11.1.2 Gastrointestinal (GI) Adverse Event

GI relationship of each AE will be assessed during study. Number and proportion of participants experiencing any treatment-emergent GI AE, nausea, vomiting, diarrhea, constipation, during each week will be summarized by week for each treatment group, respectively. Proportion will be

calculated based on number of participants reached specified week during on-treatment period. On-treatment period for safety analyses are defined as from randomization to earlier of end of study date or last dose date +2 weeks. Days from randomization for each week will follow table below. By-week incidence of any GI AE, nausea, vomiting will also be presented by maximum severity using line graph.

Week	Days from Randomization of when experiencing AE
Week 0	1
Week 1	2 - 8
Week 2	9 - 15
Week 3	16 - 22
Week 4	23 - 29
Week 5	30 - 36
Week 6	37 - 43
Week 7	44 - 50
Week 8	51 - 57
Week 9	58 - 64
Week 10	65 - 71
Week 11	72 - 78
Week 12	79 - 85
Week 13	86 - 92
Week 14	93 - 99
Week 15	100 - 106

Time from randomization to treatment-emergent gastrointestinal adverse events (weeks) will also be analyzed. For participants who experienced any GI AE, time from randomization to any gastrointestinal adverse events is defined as duration of time from randomization to start date of first GI AEs. Participants who did not have a GI TEAEs will be censored at earlier date of end of study date or the date of last dose date + 2 weeks. The Kaplan-Meier curves will be displayed by treatment group. Same analyses will be repeated for time from randomization to treatment-emergent nausea, time from randomization to treatment-emergent vomiting, time from randomization to treatment-emergent diarrhea and time from randomization to treatment-emergent constipation.

Time from randomization to treatment discontinuation (weeks) will also be analyzed. For participants who discontinued treatment, time to treatment discontinuation is defined as duration of time from date of randomization to the date of treatment discontinuation. Participants who complete treatment will be censored at last treatment date. The Kaplan-Meier curves will be

displayed by treatment group.

Time from randomization to treatment discontinuation due to any adverse events (weeks) will also be analyzed. For participants who discontinued treatment due to AE, time to treatment discontinuation due to AE is defined as duration of time from date of randomization to the date of treatment discontinuation. Participants who discontinue treatment due to any other reasons will be censored at the date of treatment discontinuation. Participants who complete treatment will be censored at last treatment date. The Kaplan-Meier curves will be displayed by treatment group.

Time from randomization to treatment discontinuation due to any gastrointestinal adverse events (weeks) will also be analyzed. For participants who discontinued treatment due to GI AE, time to treatment discontinuation due to GI AE is defined as duration of time from date of randomization to the date of treatment discontinuation. Participants who discontinue treatment due to any other reasons will be censored at the date of treatment discontinuation. Participants who complete treatment will be censored at last treatment date. The Kaplan-Meier curves will be displayed by treatment group.

A swimmer plot for subjects with GI AEs by preferred term and severity may be provided.

5.11.2 Clinical laboratory Assessments

The clinical laboratory parameters presented in Table 3 will be assessed at the specific times as outlined in the SOA (**Error! Reference source not found.**).

Observed values and change from baseline to each visit and time point during on-treatment period (from first dose date up to 2 weeks after the last dose of the study medication) and follow up visit in the clinical laboratory parameters for hematology and clinical chemistry will be summarized by treatment group, using descriptive statistics.

In addition, hematology and clinical chemistry parameters during on-treatment period that meet the Sponsor's pre-defined limits of change as presented in Table 4 will be summarized by treatment group, using frequency and percentage.

Clinical laboratory test parameters for hematology, clinical chemistry and urinalysis along with the associated reference ranges will be listed for individual subjects; abnormal values will be flagged as high or low in the listings. Individual measurements of laboratory tests from hematology, chemistry, and urinalysis that meet the abnormal criteria will be categorized to and listed by not clinical significant and clinical significant. Other clinical laboratory tests, such as,

virus serology, COVID-19 testing, drug screen, pregnancy, and follicle stimulating hormone (FSH) will be presented listings only.

Laboratory data will be summarized or listed in International System of Units (SI).

5.11.3 Vital Signs

Vital signs parameters include systolic and diastolic blood pressure, heart rate, respiratory rate and temperature and are collected at the specified timepoints as outlined in the SOA (Table 2). Blood pressure and heart rate are measured in triplicate.

Descriptive statistics for observed values and the change from baseline in the vital sign parameters will be summarized and presented for each visit and time point by treatment group. For triplicate measurements, the average value will be summarized.

A by-subject listing for the vital signs results will be provided.

5.11.4 Twelve-Lead Electrocardiogram

A triplicate 12-lead ECG will be collected at all specified timepoints as outlined in the SOA (Table 2).

The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, QRS interval, PR interval, QT interval, and QT (corrected) (Fredericia's).

Trial sites will calculate the triplicate average QTcF at the screening visit to assess the QTcF exclusion criterion. No other calculation of ECG parameter averages is required for trial sites.

QTcF values and changes from baseline that reach the threshold of pre-defined limits of change as presented in Table 4 will be summarized using the number and percentage of subjects. Average of triplicates will be used to determine if subject meet pre-defined criteria.

ECGs as interpreted by the Investigator to be within normal limits, abnormal but not clinically significant, or abnormal and clinically significant, will be listed.

A by-subject listing for the ECG results will be provided.

5.11.5 Physical Examination

Physical examination (PE) will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities, and will be performed at visits as indicated in the SOA (Table 2). Interim PEs will be performed at the discretion of the Investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

The shift from baseline to post-baseline visit in the PE result (including normal; abnormal, not clinically significant; abnormal, clinically significant) by body system will be provided.

A by-subject listing for the results of physical examinations will be provided.

5.12 Timing of Analyses

A final analysis will be performed after all subjects complete the study and the database has been locked.

6. Multiplicity

The study tests the primary hypothesis that at least one of the treatment arms is superior to the placebo arm in reducing the body weight calculated as percentage change from baseline after 13 weeks of treatment. Each of the two comparisons between K-757 alone and the combination of K-757+K-833 vs placebo is tested at two-sided alpha of 0.05 with a familywise error rate of 0.10. No other multiplicity adjustment will be performed for secondary and exploratory objectives, which will be tested at two-sided alpha of 0.05.

7. Interim Analysis

No interim analysis is planned for this study.

8 Changes from Pre-specified Analyses in the Protocol

There were no changes in the analyses or definitions planned in the CSP.

9 Revision History

Version	Date	Description of Change and/or Rationale	Sections Affected

10 Programming Specifications and Considerations

The corresponding programming specifications for variables and programming validation will be provided in a separate document.

11 Table, Figure, and Listing (TFL) Shells

The corresponding TFL shells for this SAP will be provided in a separate document.

12 References

ICH. 1998 Statistical principles for clinical trials, E9. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. https://database.ich.org/sites/default/files/E9_Guideline.pdf. Published 1998

APPENDIX 1 Schedule of Events

Table 2 Schedule of Events

SOA													
	Screening Period	**Treatment Phase by Week**											**ET or Post Study F/U**
Visit Number	**1**	**2** Rand.	**3**	**4**	**5**	**6**	**7[g]**	**8**	**9**	**10**	**11[g]**	**12**	**13**
Week[e]	**~4 Weeks**	**Week 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**EoT 13**	**Week 15**
Study Day	**-28**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**57**	**71**	**85**	**92**	**105**
Visit Window (days)	**0**	**0**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Administrative													
Informed Consent	X												
Inclusion/ Exclusion[a]	X	X											
Med History/ Demographics	X												
Prior/Concomitant Med	X	X											X
Diet and activity counseling		X				X			X				X
Clinical Assessment													
Physical Examination	X												X
Height	X												

Table 2: Schedule of Events (continued)

SOA													
	Screening Period	Treatment Phase by Week											ET or Post Study F/U
Visit Number	1	2 Rand.	3	4	5	6	7[g]	8	9	10	11[g]	12	13
Week[e]	~4 Weeks	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 12	EoT 13	Week 15
Study Day	-28	1	8	15	22	29	36	43	57	71	85	92	105
Visit Window (days)	0	0	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3
Administrative													
Informed Consent	X												
Inclusion/ Exclusion[a]	X	X											
Med History/ Demographics	X												
Prior/Concomitant Med	X	X											X
Diet and activity counseling		X				X			X				X
Clinical Assessment													

SOA													
	Screening Period	Treatment Phase by Week											ET or Post Study F/U
Visit Number	1	2 Rand.	3	4	5	6	7[g]	8	9	10	11[g]	12	13
Week[e]	~4 Weeks	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 12	EoT 13	Week 15
Study Day	-28	1	8	15	22	29	36	43	57	71	85	92	105
Visit Window (days)	0	0	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3
Physical Examination	X												X
Height	X												

Table 2: Schedule of Events (continued)

SOA													
	Screening Period	Treatment Phase by Week											ET or Post Study F/U
Visit Number	1	2 Rand.	3	4	5	6	7[g]	8	9	10	11[g]	12	13
Week[e]	~4 Weeks	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 12	EoT 13	Week 15
Study Day	-28	1	8	15	22	29	36	43	57	71	85	92	105
Visit Window (days)	0	0	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3
Heart Rate/Blood Pressure	X	X	X	X	X	X		X	X	X		X	X
Respiratory Rate/Temperature	X	X											X
Triplicate 12-lead ECG	X	X						X				X	
PHQ-9	X												
Laboratory and Safety Assessments													
General Safety Labs: Chemistry[b, c]	X	X				X			X			X	X
Fasting lipid Panel		X										X	

SOA													
	Screening Period	Treatment Phase by Week											ET or Post Study F/U
Visit Number	1	2 Rand.	3	4	5	6	7[g]	8	9	10	11[g]	12	13
Week[e]	~4 Weeks	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 12	EoT 13	Week 15
Study Day	-28	1	8	15	22	29	36	43	57	71	85	92	105
Visit Window (days)	0	0	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3
General Safety Labs: Hematology	X	X						X				X	X
Liver Function Test			X	X	X			X		X			
Urine Drug Screen	X												

Table 2: Schedule of Events (continued)

SOA

	Screening Period	Treatment Phase by Week											ET or Post Study F/U
Visit Number	1	2 Rand.	3	4	5	6	7[g]	8	9	10	11[g]	12	13
Week[e]	~4 Weeks	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 12	EoT 13	Week 15
Study Day	-28	1	8	15	22	29	36	43	57	71	85	92	105
Visit Window (days)	0	0	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3
Hepatitis Screen	X												
HIV Screen	X												
hCG Pregnancy Test/FSH Test[d]	X	X				X			X				X
Thyroid Stimulating Hormone Test	X												
HbA1c Test	X	X										X	
Lipase/Amylase	X	X						X				X	
AE Monitoring	X	X											X
Study Drug Administration and Compliance													
Study Drug Dispensing[f]		X	X	X	X	X		X	X	X			
Drug Compliance Check		X	X	X	X	X	X	X	X	X	X	X	

Table 2: Schedule of Events (continued)

SOA													
	Screening Period	**Treatment Phase by Week**											**ET or Post Study F/U**
Visit Number	**1**	**2** Rand.	**3**	**4**	**5**	**6**	**7[g]**	**8**	**9**	**10**	**11[g]**	**12**	**13**
Week[e]	**~4 Weeks**	**Week 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**EoT 13**	**Week 15**
Study Day	**-28**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**57**	**71**	**85**	**92**	**105**
Visit Window (days)	**0**	**0**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Efficacy and Other Endpoint Related Assessments													
Blood for K-757/K-833 PK (trough)						X			X			X	
Blood Samples for PD (trough)		X							X			X	
Body Weight	X	X				X			X			X	X
Other													
Telephone Check[g]							X				X		
Optional Genetic Blood Sample[h]												X	

[a] Just prior to Randomization. it will be confirmed that no excluded/prohibited medications are being taken and, in females of child-bearing potential, that the V2/Randomization urine pregnancy test is negative.

[b] Urinalysis at Screening only.

[c] Safety labs will be collected in the fasted state.

[d] Serum hCG at screening and Post-study; urine hCG at randomization and Weeks 5, and 9 for females of childbearing potential. FSH test at screening only for females of non-child bearing potential due to menopause. If screening FSH test is not consistent with menopausal status, subjects may return for a serum pregnancy test and participate under requirements for females of child-bearing potential (contraception and pregnancy testing).

[e] Week indicates the duration of treatment completed prior to the visit, not the week in which the visit occurs. For example, the "Week 1" visit is targeted to occur on Day 8 (the first day of the 2nd week of treatment).

[f] Titration will occur according to Table 9. On trial site visit days when laboratory safety tests are collected, participants will fast overnight and prior to study drug administration. Dosing will end with the PM dose on Day 91.

[g] Telephone calls at Visits 7 and 11 (Day 85) to confirm drug compliance, assess AEs, and concomitant medications.

[h] The optional genetic sample may be collected at any time during the study.

Abbreviations: EoT = end of treatment; ET = end of trial; FU = follow up; hCG = human chorionic gonadotropin

APPENDIX 2 Clinical Laboratory Assessments

Table 3: Protocol-Required Laboratory Assessments

Hematology	
White blood cell (WBC) count[a]	Hemoglobin
Red blood cell (RBC) count[b]	Hematocrit
Platelet count	HbA1c
Clinical Chemistry	
Alanine aminotransferase (ALT)	Phosphorus
Albumin	Potassium
Alkaline phosphatase (ALP)	Sodium
Aspartate aminotransferase (AST)	Total bilirubin
Bicarbonate	Direct bilirubin
Chloride	Total Protein
Cholesterol (full lipid panel on Day 1 and EoT only)	Triglycerides
Creatinine	Urea
Calcium	Gamma-glutamyl transferase (GGT)[c]
Glucose	Magnesium
TSH (Screening)	Multiple biochemical analysis (MBA)[c]
	Amylase
	Lipase
Urinalysis	
Dipstick:	Microscopic:
Nitrite	WBC
Protein	RBC
Glucose	Epithelial cells
pH	Casts (specify)
Specific gravity	
Ketones	
Bilirubin	
Urobilinogen	
Leucocyte Esterase	

Blood	

[a] Differential white blood cell count will include percentages for neutrophils, lymphocytes, monocytes, eosinophils, and basophils and absolute counts for neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

[b] Differential red blood cell count will include mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW).

[c] MBA testing will include, in addition to above tests: estimated glomerular filtration rate (eGFR) measured by MDRD at screening

Table 4: Pre-Defined Limits of Change for Laboratory Parameters and Electrocardiogram

Hematology	
Hemoglobin (g/dL)	1. Decrease ≥ 1.5 g/dL 2. Increase > 2.0 g/dL 3. Increase > 2.0 g/dL and value > ULN Both criteria 2 and 3 will be flagged.
WBC count (10^3/microL)	1. Decrease ≥50% and value < LLN 2. Increase ≥20% and value > ULN
Neutrophil count(10^3/microL)	1. Decrease ≥20% and value < LLN 2. Increase ≥20% and value > ULN
Lymphocyte count (10^3/microL)	1. Decrease ≥20% and value < LLN 2. Increase ≥20% and value > ULN
Platelet count (10^3/microL)	1. Decrease ≥25% and value < LLN 2. Increase ≥100% and value > ULN
Clinical Chemistry	
BUN mg/dL	Increase ≥ 50% and value > ULN
Total bilirubin mg/dL	Value > 2x ULN
AST (IU/L)	Value ≥ 3x ULN Value > 5x ULN Value > 10 x ULN Value > 20x ULN
ALT (IU/L)	Value ≥ 3x ULN Value > 5x ULN Value > 10 x ULN Value > 20x ULN
AST or ALT (IU/L)	Value ≥ 3x ULN Value > 5x ULN Value > 10 x ULN Value > 20x ULN
AST or ALT (IU/L) + Total bilirubin (mg/dL)	AST or ALT ≥3x ULN with concurrent bilirubin > 2x ULN
Alkaline phosphatase (IU/L)	Value > 1.5x ULN
Sodium (mmol/L)	1. Decrease ≥ 10 and value <LLN 2. Increase ≥ 10 and value >ULN 3. Value > 155
Potassium (mmol/L)	1. Decrease ≥ 1 and value <LLN 2. Increase ≥ 1 and value >ULN 3. Value > 5.4 and increased 15% above baseline 4. Value ≥ 6.0

Calcium (mg/dL)	1. Increase≥ 1 and value > ULN 2. Decrease≥ 1 and value < LLN
Magnesium (mg/dL)	1. Increase≥ 1 and value > ULN 2. Decrease≥ 1 and value < LLN
QTc (ms)	
Males	Value ≥ 450 msec
Females	Value ≥ 470 msec
QTc Change from Baseline (ms)	
All Subjects	Increase ≥ 60 msec