K-757

P006-03

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

KALLYOPE, Inc.

430 East 29th Street

New York, NY 10016

Protocol Issue Date: 03-OCT-2023

IND Number: 160779

Confidentiality Statement

1.1. Summary of Changes

Reason for Change	Section
Added optional genetic blood sample collection	Table 2, Section 14.3.2
Clarified the BMI upper range as 40.0 at screening in Inclusion Criterion #4	Synopsis, Section 8.1
Clarified contraception requirements in Inclusion Criterion #8	Synopsis, Section 8.1, Section 11.2
Clarified obesity exclusion medication use in Exclusion Criterion #5	Synopsis, Section 8.2
Clarified when a participant may be enrolled who has uncontrolled thyroid disease in Exclusion Criterion #10	Synopsis, Section 8.2
Clarified prohibited medications in Exclusion Criterion #17	Synopsis, Section 8.2
Clarified Exclusion Criterion #18 regarding various diseases and reasons for exclusion	Synopsis, Section 8.2
Updated Exclusion Criterion #33 to be consistent with Section 14.2: Blood pressure should be taken seated not semi-recumbent and after resting 5 minutes	Synopsis, Section 8.2
Added clarification to Exclusion Criterion #36 regarding the use of benzodiazepines	Synopsis, Section 8.2
Added hemoglobin and hemoglobinopathy to Exclusion Criterion #41	Synopsis, Section 8.2
Added clarification to Exclusion Criterion #44 pertaining to interpretation of efficacy and/or safety results	Synopsis, Section 8.2
Added Exclusion Criterion #47 regarding use of opiate medications	Synopsis, Section 8.2
Added Exclusion Criterion #48 regarding use of medications that affect body weight	Synopsis, Section 8.2

Administrative	
Clarified which exclusion criteria need to be confirmed prior to randomization Fixed Day 57/Week 8 column heading error on 2nd page of Table 2	Table 2
Added stimulant and opiate medications to the Prohibited Medications list	Section 10.1
Clarified diet and activity counseling will be limited to the protocol guidelines	Section 11.1
Clarified dosing interruptions procedures due to subject error	Section 13.4.3

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Kallyope, Inc.

Responsible Medical Officer:

[redacted]

10/3/2023

Date

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430 East 29th St.
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INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochures for K-757 and K-833. I have read K-757 P006-03 and agree to conduct the study as outlined in the protocol and abide by all provisions of this protocol. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice, the FDA Form 1571 and with all obligations detailed in applicable regulations and guidelines. I also agree to report all information or data in accordance with the protocol and, in particular, report any serious adverse events as defined in the protocol. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and referenced Investigator Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of this trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
24-hr Safety Mailbox		[redacted]
Drug Safety Physician/24-hr Emergency Contact	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company: Kallyope, Inc.		
Name of Investigational Product: K-757, K-833		
Name of Active Ingredients: K-757 [redacted], K-833 [redacted]		
Protocol Number: P006-03	**Phase: 2**	**Country: USA**
Title of Study: 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		
Study center(s): Multi-center study in US		
Studied period (years): 12 months Estimated date first patient enrolled: Oct 2023 Estimated date last patient completed: Jul 2024	**Phase of development: 2**	
Number of participants (planned): Approximately 150 (50 per treatment group)		

Objectives: In participants who are obese:

Primary:

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.

Hypothesis: At least one of the treatment arms is superior to the placebo arm in reducing body weight calculated as percentage change from baseline after 13 weeks of treatment.

Secondary:

1. 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.
2. 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.
3. To characterize the safety and tolerability of K-757 alone and in combination with K-833 over 13 weeks of treatment.

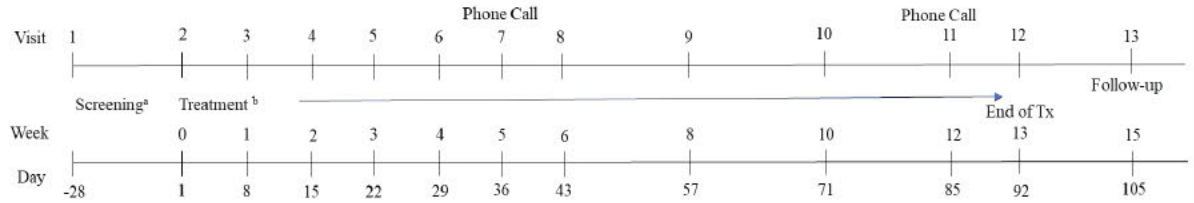
Exploratory:

1. 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.
2. 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.

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 one hundred fifty (150) participants will be enrolled and randomized (1:1:1) to receive K-757 alone, K-757+K-833, or matching placeboes.

Study Schematic



[a] Screening will occur over up to 4 weeks prior to randomization.
[b] Refer the Dosing Table and Section 5.4.1 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, the "Week 1" visit is targeted to occur on Day 8 (the first day of the 2nd week of treatment).

The study will be comprised of a Screening period (up to 28 days prior to randomization), 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). There will be 13 weeks of dosing (Days 1 through 91). 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% (ie. neither gender may exceed 70% of total enrollment).

Dosing Table

Arm	Time (AM/PM)		Week			
			Week 0 (D1-7)	Week 1 (D8-14)	Week 2 (D15-21)	Week 3 through 13 (D22-92)
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

Refer to Section 5.4.1 for additional titration information.

Participants will return to the trial site at the times described in the study schematic and schedule of assessments (SOA) 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. Nutritional counseling will focus on calorie-reduction (-500 kcal/day). This counseling will occur at randomization (Visit 2), twice during the treatment phase (Visit 6 and Visit 9), and at the post-Study follow-up visit.

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 time points are described in the SOA Table 2.

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

To mitigate mechanism-related GI intolerance, K-757 will be titrated according to the Dosing Table (see 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 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 dosing (see Section 7.1.1).

Subject/Criteria for Entry into the Trial

Inclusion criteria:

All entry criteria, including laboratory test results, need to be confirmed before administration of the first dose of study drug.

In order to be eligible for participation in this trial, the subject must:

1. Understand the trial procedures and agree to participate by providing written informed consent prior to trial related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Be willing and able to comply with the study schedule of visits, all trial procedures and restrictions, including following study diet requirements.
3. Be a male or female, age 18 to 70 years, inclusive, at the time of signing informed consent.
4. Have a body mass index (BMI) of 30.0 to 40.0. kg/m^2, inclusive at screening.
5. History of at least one self-reported unsuccessful dietary effort to lose body weight.
6. Be weight stable (<5% variation) over the last 3 months (by subject report).
7. Be a nonsmoker or has smoked ≤10 cigarettes per week for at least 3 months and agrees not to exceed this for the duration of study participation; has not used other nicotine containing products (e.g. other forms of tobacco, nicotine patch, e-cigarettes, vapes) for at least 3 months and agrees to abstain from such products throughout study participation.
8. Meet the following requirements:
    a. Is a male who agrees to **all** of the following:
        - If partner is a non-pregnant female of child-bearing potential: To use an appropriate method of contraception, which must include a condom with spermicidal cream or jelly, from the first dose of study drug until 14 days after the last dose of study drug. A male subject who has had a vasectomy procedure must use a condom but is not required to use spermicidal cream or jelly.
        - If partner is pregnant, to use a condom

          Note: Contraception/condom requirements are waived if partner is NOT of child-bearing potential (i.e. is male or is a female who is post-menopausal or surgically sterile [post-hysterectomy, post-bilateral oophorectomy, and/or post-bilateral salpingectomy]).
        - To not donate sperm from the first dose of study drug until 14 days after the last dose of study drug.

    OR

b. Is a female who is of non-childbearing potential defined by at least 1 of the following criteria:

- Postmenopausal (aged >45 years and with a minimum of 12 months of spontaneous amenorrhea with a Screening serum follicle-stimulating hormone (FSH) level in the menopausal range established for the central laboratory.
- Post hysterectomy, bilateral oophorectomy or bilateral salpingectomy, based on the subject's recall of their medical history.

OR

c. Is a female of reproductive potential and:

- agrees to not donate eggs from the first dose of study drug until 14 days after the last dose of study drug.
- agrees to remain abstinent from heterosexual activity[a] or
- agrees to use (or have their partner use) a birth control method that is highly effective and has low user dependency from the first dose of study drug until 14 days after the last dose of study drug. Acceptable methods of birth control are:
  - Progestogen-only implant (e.g. etonogestrel implant)
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
  - Vasectomized partner

[a] Abstinence can be used as the sole method of contraception if it is in line with the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ethics committees. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

This condition is waived if the subject is proven to have no child-bearing potential (eg, hysterectomy).

Exclusion criteria:

Participants are excluded from the trial if any of the following criteria apply:

Glycemia related:

1. Has a hemoglobin A1c (HbA1c) ≥6.5% (48 mmol/mol) as measured by the central laboratory at screening.
2. Has a history of clinically significant endocrine disease including T2DM.
   Note: A history of hypothyroidism does not require exclusion if the subject has been on a stable dose of thyroid hormone replacement (thyroxine) for at least 3 months prior to screening and the screening thyroid-stimulating hormone (TSH) is within the central laboratory normal range.
3. Has a history of type 1 or type 2 diabetes mellitus.
4. Had treatment with any glucose-lowering agent(s) within 90 days before screening.

Obesity related:

5. Had treatment with any medication approved for the treatment of obesity or any investigational agent being tested for obesity treatment within the past 6 months before screening. This includes agents that are approved as a component of a multi-drug combination treatment for obesity, regardless of the purpose of current use, with the exception of bupropion.

   Bupropion, which is a component of the naltrexone-bupropion combination approved for weight loss (Contrave™), is also approved as a single agent for the treatment of depression. Bupropion is not

exclusionary if it is being used for treatment of depression and eligibility criteria for anti-depressant medication stability prior to screening are met (see Exclusion Criterion #12).

6. Has been treated with/used any other medication, supplement, or device for the purpose of promoting weight loss (regardless of whether they are approved or promoted for the purpose of weight loss) in the 90 days prior to screening.
7. Treatment with any glucagon-like peptide-1 (GLP-1) receptor agonist in the prior 6 months.
8. Participation in an organized weight reduction program (e.g. Weight Watchers) within 90 days of screening.
9. Had a previous or has a planned (during the trial period) obesity treatment with surgery or a weight loss device. **Note:** Prior liposuction and/or abdominoplasty are not exclusionary if performed >2 years before screening).
10. Has uncontrolled thyroid disease, defined as thyroid stimulating hormone (TSH) outside (above or below) the reference range of the central laboratory at screening or has any history of Grave's disease unless all 3 of the following criteria are all met: 1. Grave's disease was treated with total thyroidectomy >2 years prior to screening, 2. There has been no recurrence of hyperthyroidism since thyroidectomy, ***and*** 3. TSH is the reference range of the central laboratory at screening.
11. Obesity is induced by an endocrine disorder (e.g. Cushing's disease).

Mental health:

12. Has a history of major depressive disorder within 2 years before screening unless **all** of the following criteria are met:
    a) the depressive disorder has always been unipolar (no history of mania or hypomania)
    b) in the opinion of the investigator, depressive symptoms have been stable and well controlled for ≥ 2 years prior to screening.
    c) any anti-depressant drug-treatment regimens (medications and doses) have been stable for ≥6 months prior to screening.
13. Has any history of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder) that was not clearly attributable to an intercurrent event/life circumstance, self-limited and fully resolved ≥1 year prior to screening.
14. On the screening Patient Health Questionnaire-9 (PHQ-9), has an overall score ≥15 **or** has a score >0 for Question # 9 (Thoughts that you would be better off dead or of hurting yourself)(Appendix C).
    Note: See Section 15.1.6 regarding requirements for referral to a mental health professional based on the results of the screening PHQ-9 assessment.
15. Has any lifetime history of suicide attempt or suicidal behavior. **Note:** Suicidal behavior includes any acts/preparation toward making a suicide attempt whether the attempt is never initiated or is initiated but interrupted by self or another person [31].
16. Use of any anti-psychotic agents for any purpose within 2 years before screening.
17. Use of the following prohibited agents:
    - Prohibited classes of anti-depressant agents (see Section 10.1), for any purpose, within 6 months of screening. **Note:** Use of allowable classes of anti-depressant agents (see Section 10.1) is permitted **only** if the anti-depressant regimen (agents **and** doses) has been stable for ≥6 months prior to screening and is not anticipated to change during the trial period.
    - Stimulant medications including amphetamines (e.g. dextroamphetamine, lisdexamfetamine) and methylphenidate/dexmethylphenidate within 6 months of screening.

General Safety:

18. Has a recent history (within the past 3 years of the screening visit) or current diagnosis or evidence of hematological, immunological, renal, respiratory, neurologic, or genitourinary abnormalities or

diseases that, per the investigator's judgement, may jeopardize the subject's safety or compliance with the protocol, or otherwise interfere with interpretation of efficacy and/or safety results.

19. Has a recent history (within past 3 years of the screening visit) or current diagnosis of any of the following GI (gastro-intestinal) related diseases: intestinal obstruction, GI perforation, adhesions, *Clostridium difficile* colitis or have had recent unexplained GI bleeding within 3 months prior to screening.
20. Has any history of pancreatitis (acute or chronic), gastroparesis, ischemic colitis, inflammatory bowel disease (IBD), or celiac disease.
21. Has any personal or first-degree relative history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
22. Has a screening estimated Glomerular Filtration Rate (eGFR) estimated with the Modification of Diet in Renal Disease (MDRD) equation of <60 ml/min/1.73 m^2.
23. Has a history of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed if they have received treatment and follow-up consistent with local standard of care.
24. Has any history of cardiovascular disease including stable and unstable angina pectoris, myocardial infarction, transient ischemic attack, stroke, cardiac decompensation, clinically significant arrhythmias, clinically significant conduction disorders, or any history or heart failure.
25. Has any surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator.
26. Has a history of human immunodeficiency virus (HIV) infection.
27. Has any active liver disease other than non-alcoholic fatty liver disease (NAFLD), or any gallbladder disease that has been active/symptomatic within 6 months of screening.
28. Has a positive test result for hepatitis B surface antigen (Ag), hepatitis C virus antibody, or HIV antibody, at the Screening Visit. Note: Participants with positive hepatitis B virus or hepatitis C virus serology may be enrolled if quantitative polymerase chain reaction for hepatitis B virus or hepatitis C virus ribonucleic acid is negative.
29. Has alanine aminotransferase or aspartate aminotransferase (ALT or AST) of >2.0X upper limit of normal (ULN) or total bilirubin >1.5X ULN at the Screening visit. Note: An isolated bilirubin >1.5X ULN is acceptable if bilirubin is fractionated, and direct bilirubin is within the laboratory normal range.
30. Has serum amylase or lipase >1.2X the ULN at the Screening visit.
31. Has a triglycerides value of >600mg/dL at the Screening visit (if value is ≥600 mg/dL and the sample was obtained in the non-fasted state, a repeat fasting determination may be obtained to assess eligibility).
32. Has a corrected QT interval to Fridericia's formula (QTcF) >450 milliseconds (msec) for males and >470 msec for females at screening.
33. Has a mean value for triplicate seated systolic blood pressure >160 mmHg and/or diastolic blood pressure (BP) >95 mmHg measured after at least 5 minutes at rest at the Screening Visit.
    Note: If a subject's BP is exclusionary on the first triplicate assessment at the Screening visit, they may have 1 repeat triplicate BP assessment at that visit after another rest of at least 10 minutes.

    If a participant's BP is exclusionary on 2 assessments at the Screening visit, the investigator can, at their discretion, adjust and/or add anti-hypertensive medications and re-assess triplicate BP up to twice prior to dosing at the Randomization visit (Visit 2). Anti-hypertensive regimens must align with the requirements detailed in Section 10.1 (**≤2 agents** that do **not** include verapamil)

    If a participant's BP is exclusionary at the Screening visit and the Randomization visit (Visit 2), they must be excluded.

34. Has known history or suspected abuse of alcohol or recreational drugs at Screening.
35. Has excessive consumption of alcohol within 6 months prior to screening (>14 drinks/week for men and >7 drinks/week for women, where 1 drink= 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) or use of soft drugs (such as marijuana or any substances containing tetrahydrocannabinol (THC) or cannabidiol (CBD)) within 3 months prior to Screening, or hard drugs (such as cocaine) within 6 months prior to Screening.
36. Has a positive drug screen at Screening. Note: If benzodiazepines are detected on the drug screen, this is not exclusionary if they are prescribed a benzodiazepine for a therapeutic purpose (e.g. for insomnia) and confirmatory documentation is obtained from the prescribing physician.
37. Has known or suspected hypersensitivity to trial product(s) or related products.
38. Has a history of multiple significant and/or any severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
39. Has previous participation in this trial. Participation is defined as signed informed consent.
40. Has participated in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.
41. Had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the Screening Visit; has a screening hemoglobin <11.0 g/dL (males) or <10.0 g/dL (females), or has a known hemoglobinopathy (e.g. sickle cell anemia, hemolytic anemia).
42. Is a female who is pregnant, breast-feeding or intends to become pregnant during the planned course of the study. **Note:** Participants must have a negative serum pregnancy test (β-human chorionic gonadotropin (β-hCG)) performed by the central laboratory prior to enrollment in the study and prior to the randomization visit.
43. Is currently in violation of study requirements for prohibited and permissible concomitant medications or is anticipated to violate these requirements during study participation. These requirements are detailed in Section 10.1.
44. Has any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardize the subject's safety or compliance with the protocol, or otherwise interfere with interpretation of efficacy and/or safety results.
45. Is unable or unwilling to follow the study nutritional and physical activity counseling and to refrain from alternative lifestyle modification strategies throughout study participation. Refer to Section 10.
46. Is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the Sponsor or study site.
47. Has any use of opiate medications within 14 days of screening or any anticipated/potential use of opiates during study participation.
48. Use of any other medications within 6 months of screening that, in the investigator's judgement, can significantly impact (increase or decrease) body weight, regardless of the purpose for their use.

Note: Rescreening/retesting is not permitted unless specified above.

Investigational product, dosage and mode of administration:

All study medication will be orally administered.

K-757: 30 mg, and 60 mg capsules and matching placebo

K-833 100 mg and matching placebo

Duration of Treatment Period: Approximately 13 weeks

Endpoints

Efficacy

Primary:

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

Secondary

- Proportion of participants achieving ≥5% of 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 AEs
- Proportion of participants who discontinued study medication due to an AE

Exploratory

- 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, HDL, and triglycerides after 13 weeks of treatment.

Additional Safety

- Adverse events
- Vital signs
- Laboratory assessments
- 12-lead ECGs

Statistical methods:

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.

Populations:

The modified Intent-to-Treat (mITT) analysis set will 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.

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

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

Pharmacokinetics:

Plasma concentrations will be summarized for K-757 for K-757 alone and the combination of K-757+K-833. Plasma concentrations will be summarized for K-833 for the combination of K-757+K-833.

Mean plasma concentrations measured over time will be displayed graphically by treatment.

Efficacy:

For the primary endpoints, the primary estimand or the percentage change from baseline in body weight is defined as the average treatment effect of K-757 alone and the combination of K-757+K-833 relative to placebo in the mITT analysis population, had they remained on their randomized treatment for the entire planned duration of the trial. 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 or until first discontinuation of randomized treatment. An unstructured covariance will be used. If the unstructured covariance structure leads to nonconvergence, Akaike's information criteria will be used to select the best covariance structure. For the secondary continuous endpoints, the same approach will be used.

For the secondary categorical endpoint of proportion of subject achieving 5% weight reduction after 13 weeks, the same MMRM described for the primary endpoints will be used to address the primary estimand. The missing data will be imputed using MMRM assuming missing at random (MAR) and the imputed 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.

Safety:

Safety analyses will be based on the Safety Analysis Set. No formal statistical tests or inference will be performed for safety analyses.

Adverse events will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect at the time of study start. AEs will be summarized as treatment-emergent AEs (TEAEs) (defined as events that are newly reported after randomization or reported to worsen in severity from baseline). The incidence of participants with at least 1 TEAE and the incidence of TEAEs by preferred term and system organ class will be presented by treatment group. The frequency and percentage of TEAEs will be presented. The incidence of participants with at least 1 TEAE assessed as related to the study drug will be summarized by treatment group. All serious AEs (SAEs) will be summarized and listed by patient. Discontinuations to study and study drug due to TEAEs will be summarized by treatment group. All adverse events will be listed by patient.

Other safety endpoints (safety laboratory endpoint, vital signs, and ECGs) will be summarized by treatment group and nominal timepoint.

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 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.

Table 2: Study Schedule of Assessments

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: Study Schedule of Assessments (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	
General Safety Labs: Hematology	X	X						X				X	X
Liver Function Test			X	X	X			X		X			
Urine Drug Screen	X												

Table 2: Study Schedule of Assessments (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: Study Schedule of Assessments (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 except at Screening.
[d] Serum hCG at screening and Post-study; urine hCG at randomization and Weeks 4, and 8 for females of childbearing potential. FSH test at screening only for females of non-childbearing 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

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse events of special interest
Ag	Antigen
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}24h}$	Area under the concentration time curve from time 0 to 24 hours
BCRP	Breast cancer resistance protein
BID	Twice daily dosing
BMI	Body mass index
BP	Blood pressure
BSEP	Bile salt exporting protein
CCK	Cholecystokinin
CFR	Code of Federal Regulations Code of Federal Regulations
CI	Coordinating Investigator, Confidence Interval
Cl	Clearance
C_{max}	Maximum concentration
COVID-19	Corona Virus Disease 19
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum vitae, Cardiovascular
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trials
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DPP-4i	Dipeptidyl peptidase-IV inhibitors

Abbreviation or Specialist Term	Explanation
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EEC	Enteroendocrine cell
EFD	Embryofetal development
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ERCP	Endoscopic retrograde cholangiopancreatography
ET	Early Termination
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FIH	First in human
FOCBP	Females of childbearing potential
FSH	Follicle stimulating hormone
F/U	Follow-up
g	Gram
GCP	Good Clinical Practice
GD	Gestational day
GDIS	Glucose-dependent insulin secretion
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLP	Good Laboratory Practices
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
GPR40	G-protein coupled receptor 40
GPR119	G-protein coupled receptor 119
HbA1c	Hemoglobin A1C
HBE	Harris Benedict Equation
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HDPE	High density polyethylene

Abbreviation or Specialist Term	Explanation
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HPMC	Hydroxypropyl cellulose
HR	Heart rate
hr or h	Hour
HRT	Hormone replacement therapy
IB	Investigational Brochure
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational medicinal product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive web response system
kcal	Kilocalorie
kg	Kilogram
L	Liter
LCFA	Long chain fatty acids
LDL	Low-density lipoprotein
LFT	Liver function test
m	Meter
M	Male
MAR	Missing at random
MATE	Multidrug and toxin extrusion protein
MBA	Multiple biochemical analysis
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration

Abbreviation or Specialist Term	Explanation
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
µM	Micromolar
µM•h	Micromolar-hour
mg	Milligram
MHP	Mental health professional
min	Minute
mITT	Modified Intent-to-Treat
mIU	Mili-international unit
mL	Milliliter
mmHg	Millimeters of mercury
MMRM	Mixed model for repeated measurements
mpk	Milligram per kilogram
msec	Millisecond
N	Number
NAFLD	Non-alcoholic fatty liver disease
NCI	National Cancer Institute
NOAEL	No adverse effect level
NSAID	Nonsteroidal anti-inflammatory drug
OAT	Organic anion transporter
OXM	Oxyntomodulin
PBO	Placebo
PD	Pharmacodynamic
PE	Physical examination
P-gp	P-glycoprotein
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PK	Pharmacokinetic
PR	Period, in milliseconds, that extends from the beginning of the P wave until the beginning of the QRS in an ECG tracing
PVC	Polyvinyl chloride

Abbreviation or Specialist Term	Explanation
PvDC	Polyvinylidene chloride
PYY	Peptide YY
QD	Once daily
QTc	QT corrected
QTcF	QT corrected with Fridericia's formula
RBC	Red blood cells
RDW	Red cell distribution width
RR	Respiratory rate
RUQ	Right upper quadrant
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOA	Schedule of assessments
SOC	System Organ Class
SOP	Standard operating procedure
SSRI	Selective serotonin reuptake inhibitors
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
T2DM	Type 2 diabetes mellitus
TEE	Total energy expenditure
THC	Tetrahydrocannabinol
TEAE	Treatment emergent adverse event
TK	Toxicokinetics
T_{max}	Time of maximum concentration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
V_{dss}	Volume of distribution at steady-state
WBC	White blood cells

5. INTRODUCTION

5.1. Program and Study Rationale

Currently approved orally administered pharmacologic therapies for weight loss generally provide modest weight loss (~5%) and are associated with tolerability or safety concerns [18]. Bariatric surgery provides long term and robust weight loss in the majority of participants [19]. While there are many mechanisms that have been postulated to contribute to the weight loss following this procedure, one leading hypothesis is that increased activation of gut enteroendocrine cells (EECs) results in enhanced secretion of satiety hormones. After surgery, nutrients are not absorbed in the proximal, bypassed intestinal segment and reach more distal segments of the gastrointestinal (GI) tract. This results in enhanced activation of various nutrient receptors on distal EECs, which in turn results in higher post-prandial levels of various gut hormones including known satiety hormones.

Bariatric surgery in humans results in post-prandial elevations of multiple EEC-derived gut hormones that can be sustained for many years. In a published small Phase 1 study, subcutaneous infusion of three hormones (glucagon-like peptide-1 (GLP-1), oxyntomodulin (OXM), peptide YY (PYY)) at levels characteristic of those following bariatric surgery resulted in significant reductions in food intake after a single infusion and modest weight loss compared to placebo after 4 weeks of infusions indicating that elevation of multiple hormones at physiologic levels could result in weight loss [20]. This study was too small and of too short a duration to fully characterize the weight loss potential of this regimen. When measuring endogenous gut hormones in plasma, it is probable that measured levels are lower than the local concentrations in the gut where the hormone-producing EECs are located and where some of them may signal both to neighboring EECs and to the afferent vagal nerves [21,22]. To date, no pharmaceutical therapy has been capable of recapitulating the complex pattern of hormone release characteristic of bariatric surgery.

Parenteral administration of analogs of some gut hormones including GLP-1 results in weight loss in humans and rodents [23]. Additionally, cholecystokinin (CCK), PYY, and OXM have been identified as satiety hormones in humans capable of favorably modulating food intake.

In addition to inducing satiety, some gut hormones produced by EECs such as GLP-1 and GIP also stimulate glucose-dependent insulin secretion (GDIS) [18,23]. Analogs of these hormones improve glucose control with a low risk of hypoglycemia in people with type 2 diabetes mellitus (T2DM).

An alternative to administering analogs of gut hormones would be to directly target the enteroendocrine cells in the gut that produce these incretin and satiety hormones. Such an approach might result in elevation of a broad spectrum of hormones beyond GLP-1. Additionally, this approach is predicted to result in high local levels of hormones near the vagal afferents that signal satiety and lower circulating levels that could trigger nausea by activation of the area postrema in the brainstem [21,22]. As such, the therapeutic index between efficacy and GI tolerability could be improved with this approach.

Approach to Maximizing Gut Hormone Secretion from EECs

[redacted]

[redacted] Because GPR40 and GPR119 use distinct second messengers for signaling, co-agonism on cells expressing both receptors would be predicted to result in enhanced hormone secretion vs single agent therapy [24,25]. [redacted]

GPR40 is activated by medium to long-chain fatty acids (LCFA) [25]. Stimulation by LCFAs or synthetic *partial* GPR40 agonists results in enhanced glucose-dependent insulin secretion (GDIS) presumably due to GPR40 activation directly on pancreatic ß-cells, though such partial agonists do not enhance the secretion of gut satiety peptides. Synthetic full agonists of GPR40 do stimulate robust secretion of gut peptides in addition to GDIS [25]. GPR119 is activated by medium chain fatty acids. In participants with T2DM, administration of agonists of GPR40 or GPR119, results in improved glucose control in humans, although the glucose lowering effects observed with GPR119 agonists are very modest [5,6,26]. To date there are no reports of co-administration of a GPR40 and GPR119 agonist in humans and single agent therapy to date has not resulted in weight loss.

K-757 is a novel, highly selective, gut restricted full activator of GPR40. [redacted]. K-833 is a novel oral gut restricted small molecule agonist of GPR119 [redacted]

[redacted]

[redacted]

Accordingly, the eventual goal will be to investigate the combination of K-757 and K-833 in early clinical studies to determine whether the hormone secretion profile supports full co-development of K-757 and K-833 for the treatment of obesity and other metabolic disorders such as T2DM. It is anticipated that the two agents may need to be used in combination to achieve hormone levels similar to those seen following bariatric surgery and to induce meaningful weight loss and glucose control. It is further anticipated that K-757 and K-833 may be co-developed and eventually co-marketed and that neither individual agent may be developed as a stand-alone product for any indication. This study will test the weight loss potential of the combination of K-757 and K-833 and K-757 alone. Because prior human studies with other GPR119 agonists have not demonstrated weight loss [(26)] coupled with the very modest hormone secretion and lack of weight loss observed with K-833 alone in phase 1 studies, a K-833 only arm is not included in this study. However, a K-833 only control arm may be included in future studies as needed to justify co-development of these two novel chemical entities.

Prior experience with other GPR40 agonists

There has been prior clinical experience with systemically bioavailable agonists of GPR40 that were designed to activate GPR40 on pancreatic beta cells for the treatment of T2DM through promotion of glucose-dependent insulin secretion.

One partial GPR40 agonist, TAK-875 (fasiglifam), underwent an extensive clinical development program as an anti-hyperglycemic agent and did reduce hemoglobin A1C (HbA1c) to a clinically meaningful degree[(1,2)]. However, TAK-875 was terminated for drug-induced liver injury (DILI), which is presumed to be molecule (not mechanism)-specific[(3)], with potential contributing factors including extensive metabolism with the formation of reactive metabolites, bile salt export pump (BSEP) inhibition, and impairment of hepatocyte mitochondrial function[(4)]. In preclinical studies, fasiglifam caused increases in alanine aminotransferase (ALT), bilirubin, and bile acids[(4)]. [redacted]

[redacted]

[redacted] mportantly, and consistent with preclinical data, fasiglifam, a partial agonist, does not result in stimulation of gut peptide secretion and did not induce weight loss in human studies[1,2,5].

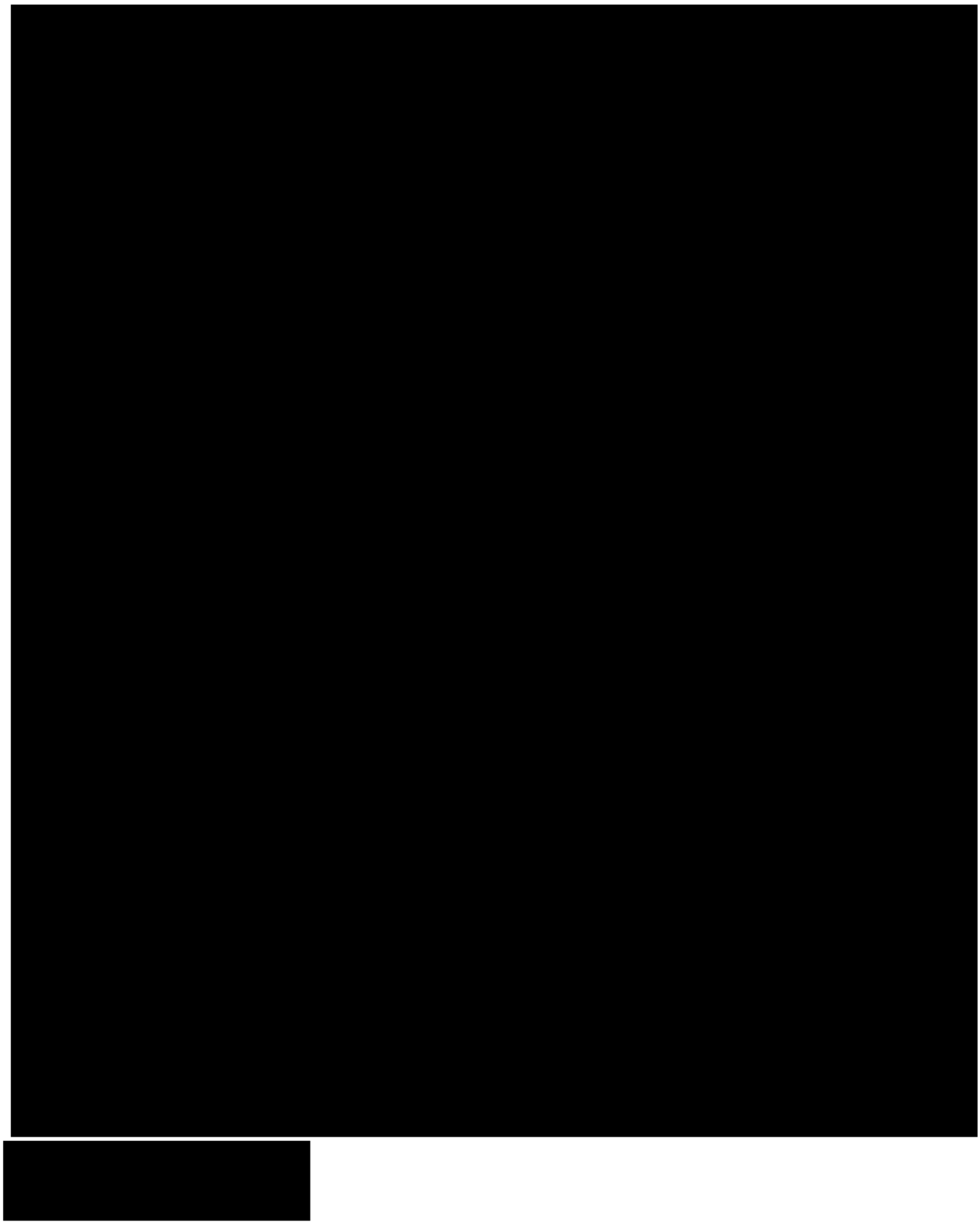
SCO-267, a GPR40 full agonist, is currently in Phase 1 development and activates both pancreatic and gut GPR40, stimulates gut hormones secretion, and improves oral glucose tolerance[6]. Some generally mild dose-dependent GI AEs of nausea were reported which are likely related to secretion of gut hormones. A few AEs of increased AST/ALT were reported with this molecule in Phase 1 studies and were rated as "mild" in intensity. No signs or symptoms of liver toxicity were reported.

Potential liabilities of certain GPR40 full agonists observed in preclinical species include depletion of pancreatic β cell insulin content, which was reported in one strain of rats and resulted in hyperglycemia[7]. [redacted] GPR40 agonism can regulate glucose levels via direct activity on pancreatic β cells or via release of incretin hormones from the gut. In either case, the glucose lowering is glucose dependent, which suggests a low risk for hypoglycemia.

Prior experience with other GPR119 agonists

At least three GPR119 agonists have been evaluated in human studies.[26,27,28,29,30] All were designed as systemic compounds, had greater oral bioavailability than K-833, and were intended as treatments for T2DM via effects on GDIS resulting from agonism of GPR119 on pancreatic β cells. In general, in participants with T2DM, only modest non-clinically significant effects were noted on hemoglobin A1C (HbA1C) after 12 weeks of dosing (approximately 0.3% reduction from baseline). As expected for a GDIS mechanism, hypoglycemia was not reported in studies in healthy volunteers and was infrequently reported in participants with T2DM. Known GI-related AEs associated with parenteral administration of GLP-1 and GIP (nausea and vomiting) were not frequently reported in GPR119 agonist trials. Additionally, the modest heart rate increases characteristically seen after acute administration of GLP-1 or GIP analogs were not reported with GPR119 agonists. In general, GPR119 agonists were well tolerated in clinical studies with no MTD identified and no clear-cut on-target related safety or tolerability issues reported.

[redacted]



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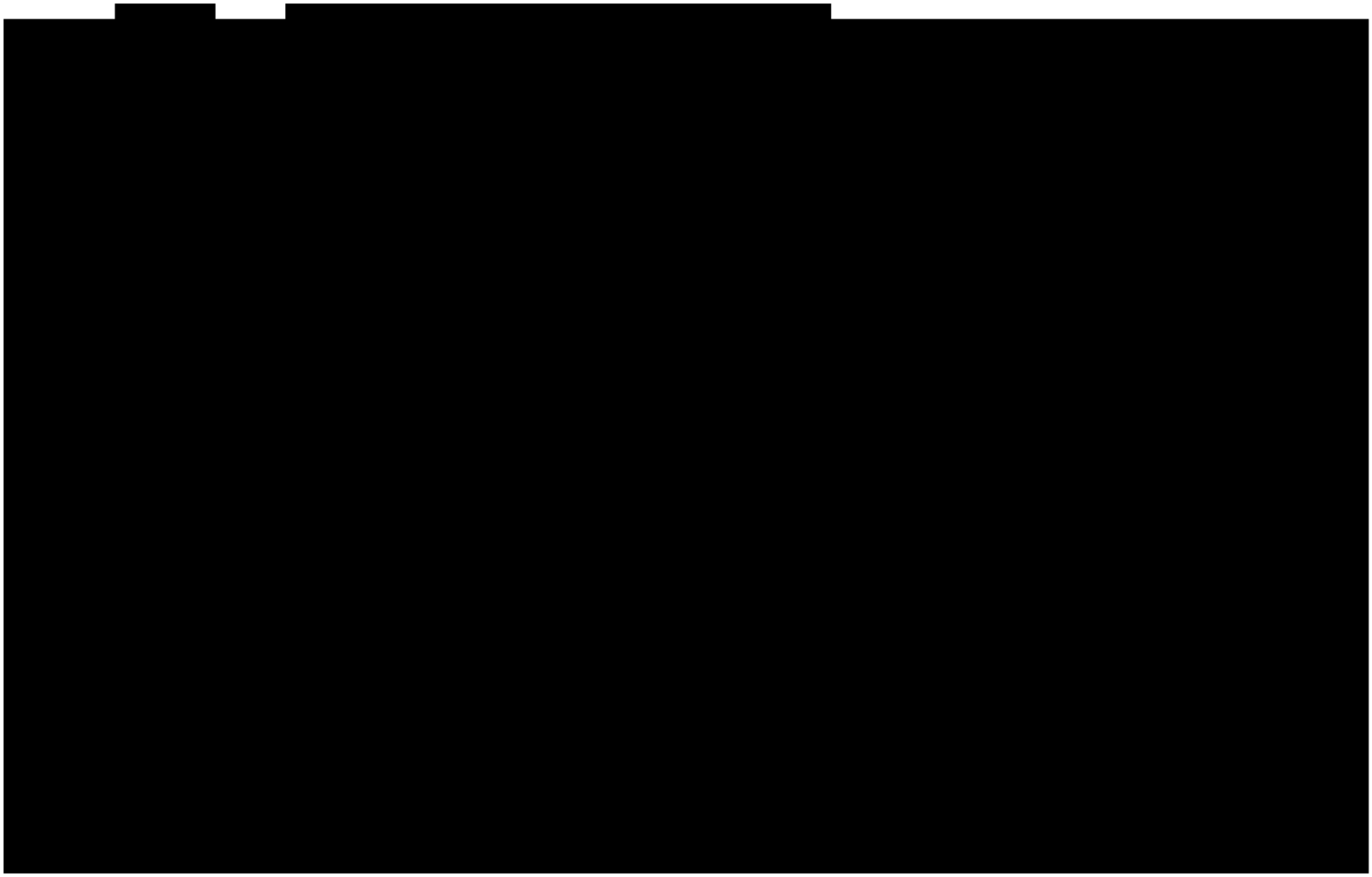
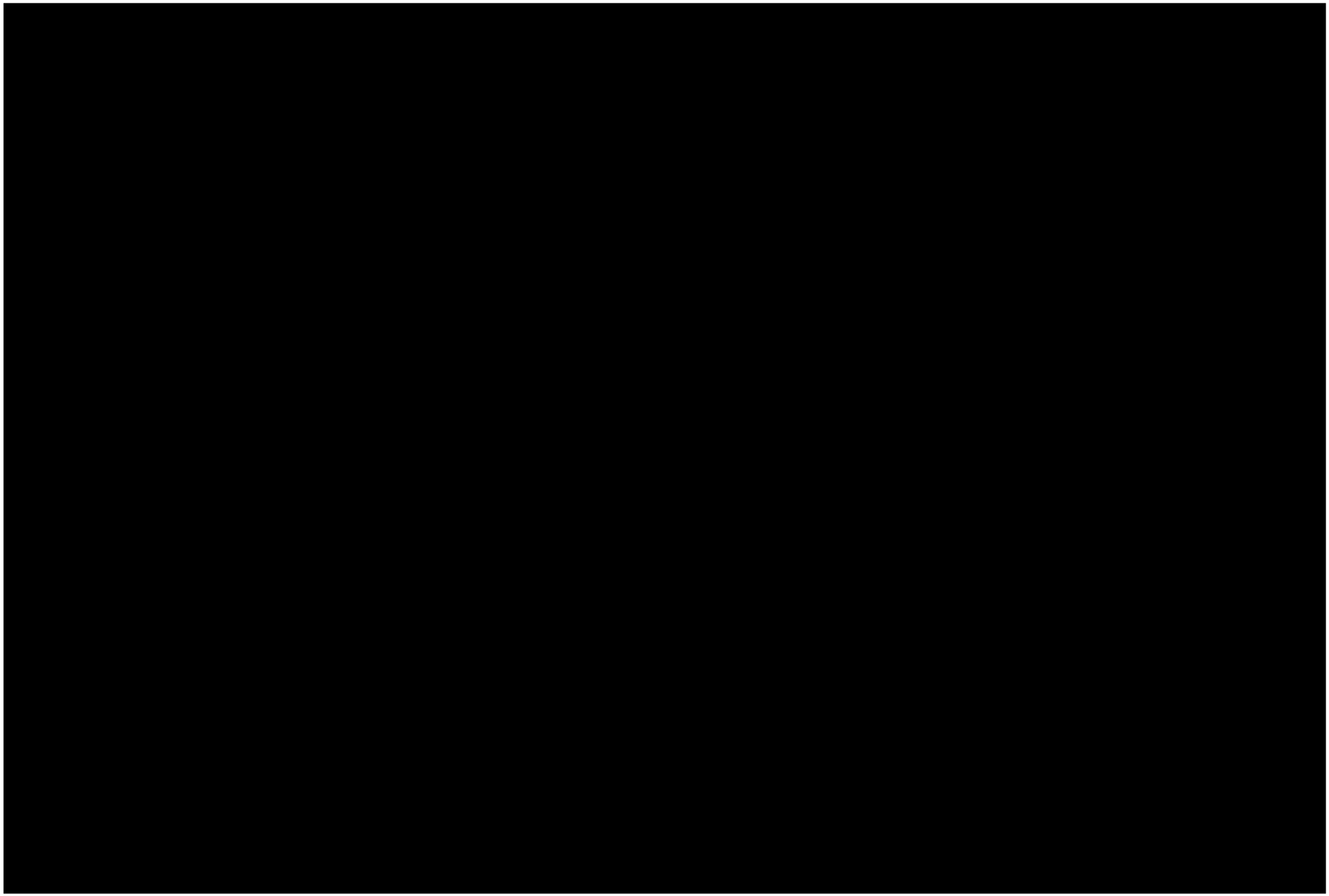
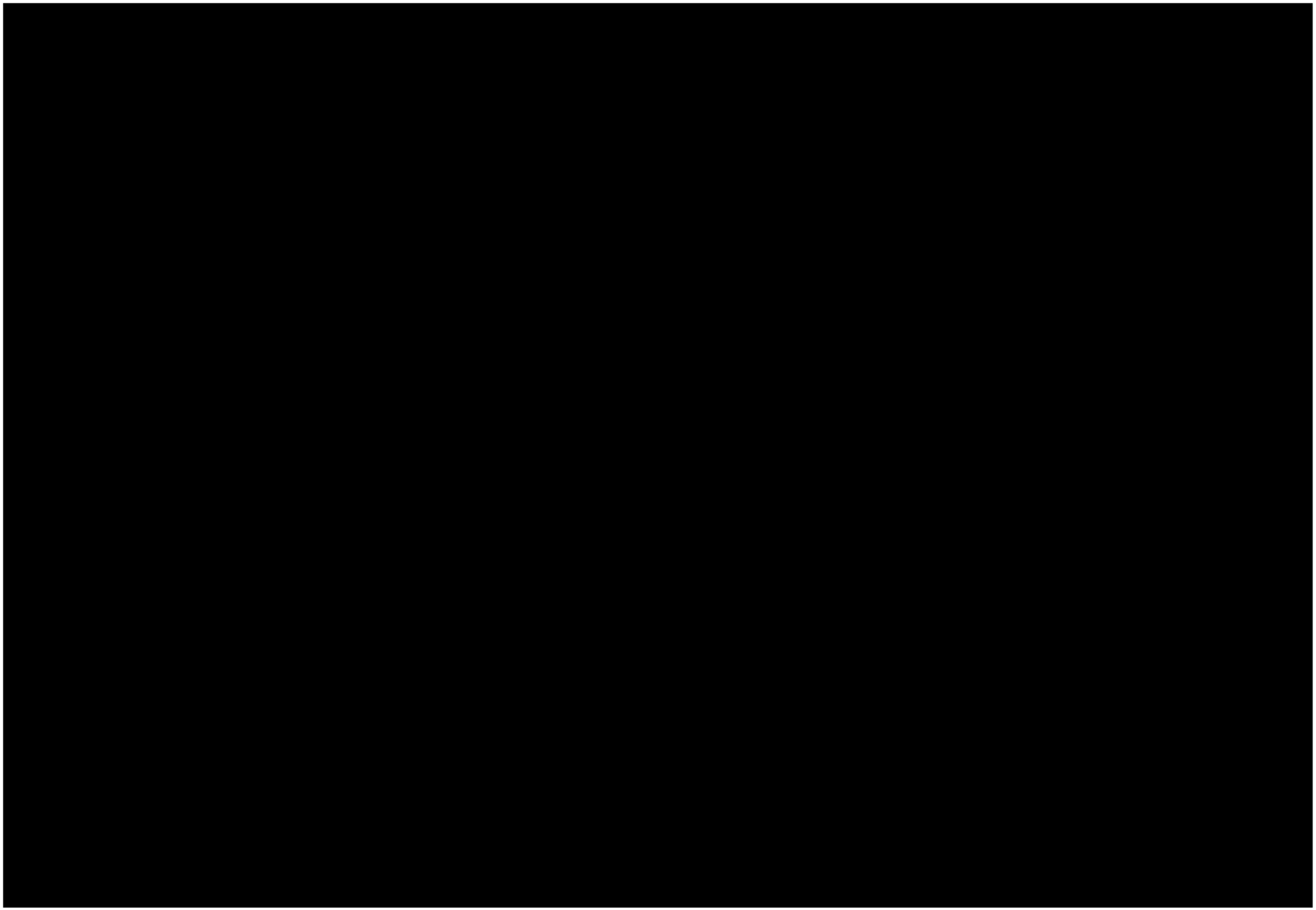
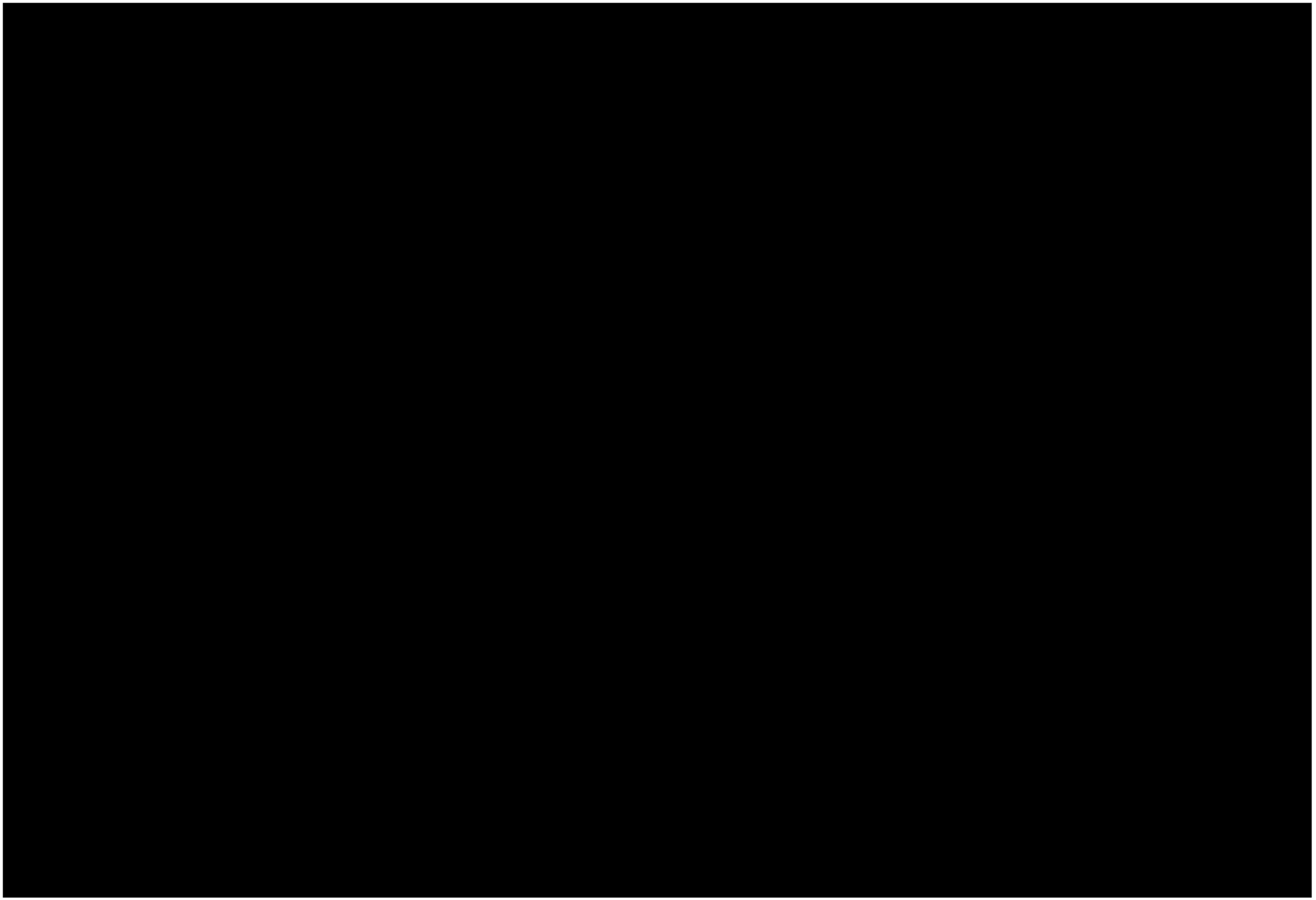
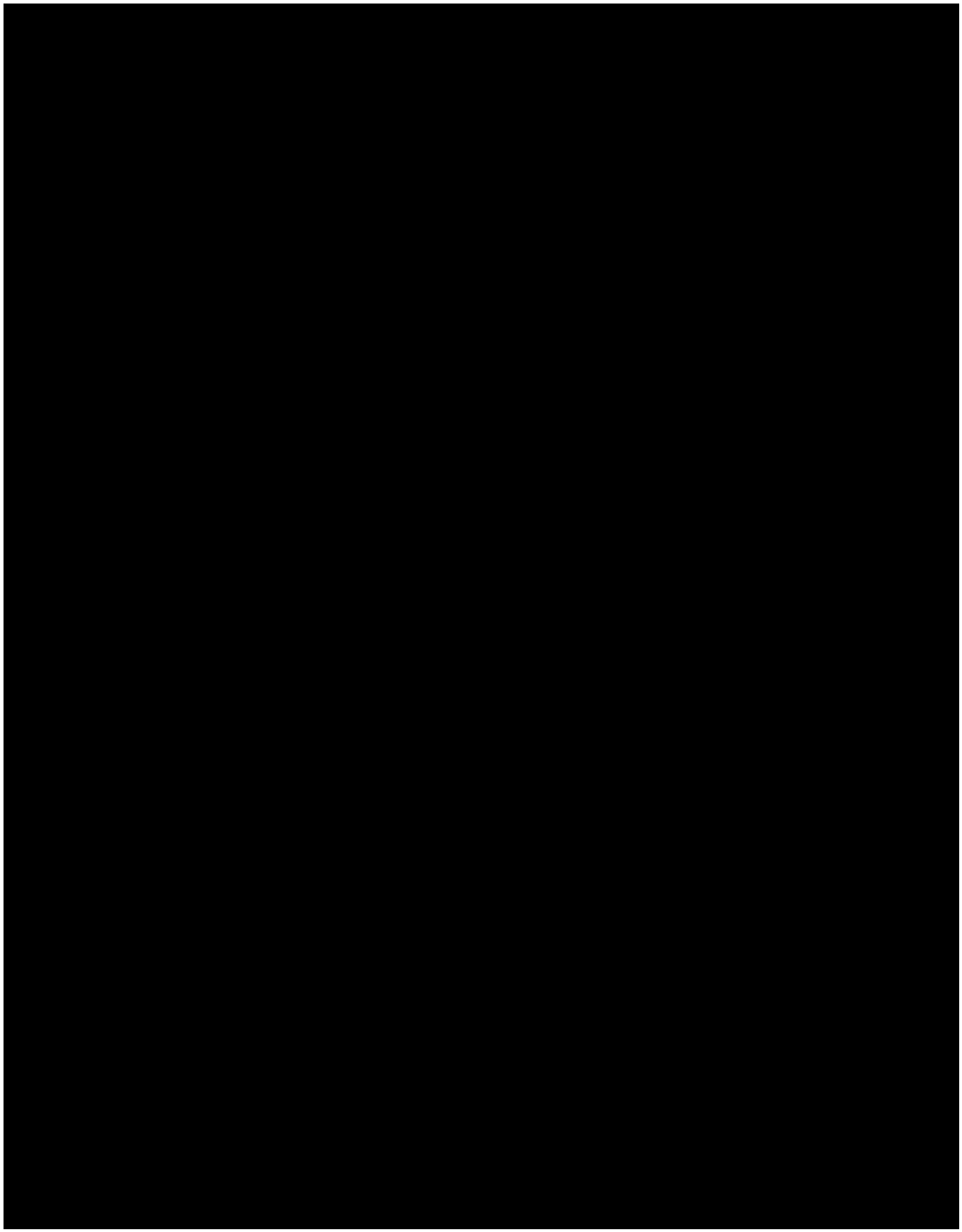










5.3. Rationale for Study Design

This study is designed to assess the weight loss efficacy and safety/tolerability of K-757 alone and in combination with K-833 in comparison to placebo. The overall study goal is to inform whether K-757+K-833 combination and/or K-757 alone merit further clinical evaluation as pharmacologic therapy for weight loss. Up-titration of K-757 or the combination is being used to mitigate mechanism-related GI intolerance as was observed in Phase 1 and has been consistently reported for GLP-1 analogs. No K-833-only arm is included in this first proof of concept study as neither the reported human experience with other GPR119 agonists, nor the Phase 1 experience with K-833 support the potential for K-833 monotherapy to achieve meaningful weight loss. Should weight loss with the combination of K-757+K-833 be superior to K-757 alone in the present study, future characterization of the efficacy and safety/tolerability of K-833 monotherapy may be needed to provide the necessary regulatory justification for co-development of K-757 and K-833.

The randomized, double-blind, double-dummy approach is being used to minimize the potential impact of bias on study assessments. The 13-week duration of dosing is the longest treatment duration supported by completed toxicology studies. Though 13 weeks may not be long enough

to ascertain maximal achievable weight loss, it expected to be sufficient to determine whether placebo-adjusted weight loss in one or more of the active treatment arms is sufficient to support continued development. As detailed in Section 16.2, the sample size of 50/arm was selected to enable demonstration of the primary hypothesis of weight loss superiority of ≥1 of the active treatment arms vs. placebo. The study is not expected to be of adequate size or duration to confirm differential efficacy between the combination and K-757-alone but may provide evidence of separation.

The rationale for the study population is discussed below in Section 5.5.

Post-randomization site visits will occur weekly for the first 4 weeks, and every 2 to 3 weeks thereafter. This will allow sites to assess safety/tolerability and compliance at each step during the titration phase and frequently thereafter. This relatively intense visit schedule is justified by the limited experience with K-757 and K-833 and the substantially longer treatment duration in this compared to prior studies (maximum 28 days). See Table 2 (SOA) and Section 7.1 for more specifics on safety monitoring.

As weight loss agents are prescribed as adjuncts to healthy lifestyle modification, all participants will be advised on calorie restriction and appropriate physical activity (see Section 7.1 and Section 11.1).

The weight related endpoints are standard for weight loss trials. Heart rate (HR), blood pressure (BP), lipids are other endpoints sometimes impacted by incretin-based therapies.

5.4. Rationale for Doses

The proposed mechanism of weight loss for K-757 and the K-757+K-833 combination involves enhanced secretion of satiety hormones from the gut. The satiety-promoting effects of these hormones are understood to be dose-responsive and track closely with ambient concentrations ('rapid on, rapid off'). Therefore, the target/maintenance dose-regimens in this study were selected to resulting in maximal and sustained satiety hormone secretion to maximize potential weight loss.

BID dosing results in sustained hormone levels throughout the dosing interval and a dose of K-757 120 mg BID + K-833 100 mg BID resulted in maximal hormone secretion and maximal rate of weight loss (Section 5.2.1). Collectively, these data support the expectation that BID co-dosing of 120 mg K-757 and 100 mg K-833 will provide the maximal weight loss attainable with this strategy.

[redacted]

GI intolerance (e.g. nausea, vomiting, constipation, diarrhea) is the expected result of GI hormone secretion and has been observed in Phase 1 studies. [redacted] As discussed below, titration approaches will be used in the current study to mitigate GI intolerance. [redacted]

[redacted] It is noted that the Phase 1 studies conducted to date have been, at most, 1/3 the duration of the current study. Because this is the first phase 2 study, and the first study with extended outpatient dosing, study visits are frequent to allow for careful monitoring of AEs, laboratory safety tests, and vital signs.

[redacted]

[redacted]

Subjects will be closely monitored with site visits occurring weekly during the titration phase and every 2-3 weeks thereafter. Laboratory safety evaluations will also be conducted frequently throughout dosing. The protocol specifies clear criteria for discontinuation of study medication, including for abnormal liver transaminase values (Section 8.3.1.1). [redacted]

5.4.1. Rationale for Dosing Regimen

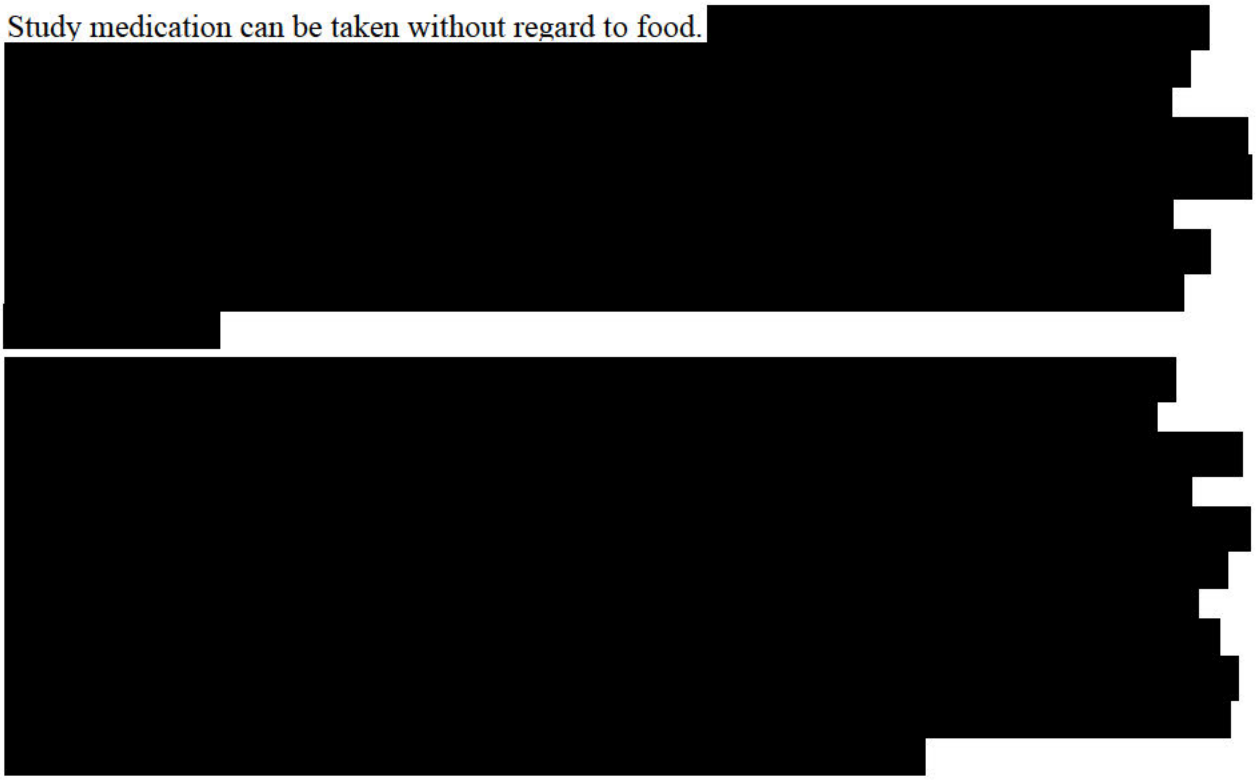
Titration to maintenance doses will be employed to mitigate mechanism-related GI intolerance. As discussed above, the titration regimens employed here (detailed in Section 7.1) are supported by approaches already evaluated in Phase 1 studies. Further, the weekly titration interval and the 2x K-757 dose increments are generally consistent with titration regimens that have been successfully employed for some GLP-1 receptor analogs, such as liraglutide [8]. The doses and titration scheme of K-757 in the K-757-only arm matches that used in the combination arm to facilitate comparisons between the active-treatment arms. Because the mechanism-amplifying effect of K-833 is lacking, tolerability in the K-757-only arm is expected to be similar to or better than in the combination arm.

This study will use forced titration on a fixed schedule. Though tactics such as delayed dose escalation and temporary dose reductions have been used to manage GI intolerance in some trials of GLP-1-mechanism agents, neither are permitted in this study for two reasons. First, the ability of participants to adhere to the prescribed treatment schedules will be highly informative regarding GI tolerability and the need for further regimen optimization in future studies. Second,

rigid dosing schedules facilitate the use of pre-packaged blister packs (see Section 13.2) which are considered critical to support participant compliance given the complexity of the double-blind, double-dummy dosing approach. As similar dosing regimens were tolerable in Phase 1, the risk that this approach will lead to a high rate of non-compliance or discontinuation is considered low. Instructions for managing GI intolerance are in Section 7.1.1.

As discussed above, BID dosing is being employed to provide maximal levels of several satiety hormones around-the-clock.

Study medication can be taken without regard to food. [redacted]



Instructions on study drug administration are in Section 13.4.

5.5. Rationale for Study Population

The trial population will consist of individuals who are obese (BMI 30.0 to 40.0 kg/m^2, inclusive) These participants represent a clinically relevant population for pharmacotherapeutic weight management as they are at significant risk for weight related morbidities (such as hypertension, dyslipidemia, obstructive sleep apnea) and mortality and are likely to benefit from weight reduction. People with known cardiovascular disease (CVD) are excluded given the early stage of development and limited characterization of the safety profiles of the study regimens. A BMI > 40.0kg/m^2 is exclusionary to limit potential for occult CVD or other health issues that might increase the risk of participating in an early-stage clinical trial. People with T2DM are excluded due to the well-described confounding effect that improved glycemic control has on response to weight-loss interventions.

As first line treatment in weight management is lifestyle modification through a reduced-calorie diet and increased physical activity, only people who have tried but failed to attain weight loss goals with lifestyle modification will be eligible for participation.

Sex is an important response covariate with females typically achieving greater weight loss that males in obesity trials. Randomization will be stratified by sex to minimize potential bias. Weight loss trials have historically enrolled substantially more female than male participants. To ensure meaningful representation of both sexes, neither strata will be permitted to exceed 70% of total enrollment. Females of childbearing potential (FOCBP) are eligible for participation. Given the early stage of development and current lack of definitive embryo-fetal toxicology data for either K-757 or K-833, FOCBP must be using highly effective contraception with low user-dependence and undergo pregnancy testing at screening and specified timepoints during study participation.

Given the priority of avoiding spurious liver toxicity signals, excessive alcohol consumption, known history of liver disease (other than non-alcoholic fatty liver disease [NAFLD]), and excessive elevations in ALT, AST, and/or bilirubin at screening are exclusionary as specified in Section 8.2.

Observational data have suggested the possibility that agents enhancing Glucagon-like peptide-1 receptor (GLP-1R) mediated pharmacology, including GLP-1R agonists and DPP-4is, may increase the risk of acute pancreatitis, though statistically significant effects have not been identified in large cardiovascular outcomes trials (CVOTs) conducted with these agents. A recent metanalysis of CVOT data did identify a 75% risk increase of acute pancreatitis with DPP-4is, though found no effect of GLP-1R agonists [9]. No preclinical or clinical data generated to date have suggested that K-757 may increase the risk of pancreatitis. However, given the early stage of K-757 development, individuals with any history of acute or chronic pancreatitis are excluded from this study, as are those with excessively elevated amylase and/or lipase at screening. Markedly elevated fasting triglycerides are also exclusionary given the potential for hypertriglyceridemia to precipitate pancreatitis. Though GLP-1R agonists and DPP-4 is are commonly associated with increases in serum amylase and lipase activity, such isolated biochemical changes in the absence of suggestive signs/symptoms have not been predictive of pancreatitis [10, 11]. Serum lipase will be assessed at specified junctures during treatment (see Table 2). Note that protocol criteria for interrupting and discontinuing study medication for suspicion of acute pancreatitis require symptoms and/or imaging consistent with pancreatitis (see Section 8.3).

Review to Section 10.1 for discussion of prohibited and allowed concomitant medications.

Full inclusion and exclusion criteria are provided in Section 8.1 and Section 8.2, respectively.

6. TRIAL OBJECTIVES, HYPOTHESES AND PURPOSE

6.1. Primary Objective/Hypothesis

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.

Hypothesis: At least one of the treatment arms is superior to the placebo arm in reducing body weight calculated as percentage change from baseline after 13 weeks of treatment.

6.2. Secondary Objectives

1. 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.
2. 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.
3. To characterize the safety and tolerability of K-757 alone and in combination with K-833 over 13 weeks of treatment.

6.3. Exploratory Objectives

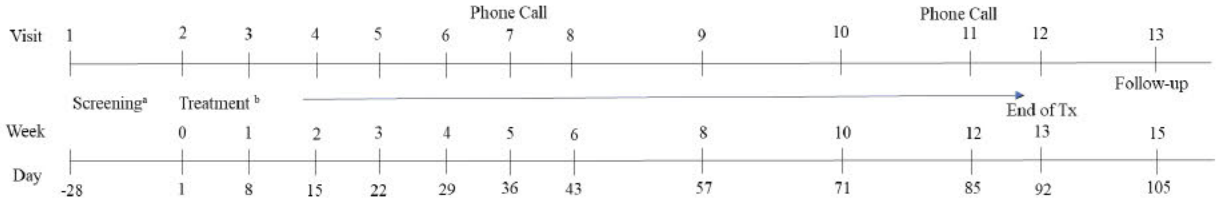
1. To assess the change from baseline in hemodynamic parameters (systolic blood pressure, diastolic blood pressure and heart rate) after 13 weeks of treatment with K-757 alone and in combination with K-833, in comparison to placebo.
2. To assess the change from baseline in total cholesterol, low-density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

7. INVESTIGATIONAL PLAN

7.1. 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 T2DM. Approximately 150 participants will be enrolled and randomized (1:1:1) to receive K-757 alone, K-757+K-833, or matching placeboes (Figure 4, Table 9).

Figure 4: Study Schematic



[a] Screening will occur over approximately 4 weeks.
[b] Refer the Dosing Table and Section 5.4.1 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). There will be 13 weeks of dosing (Days 1 through 91). 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% (ie. neither gender may exceed 70% of total enrollment).

Table 9: Dosing Table

Arm	Time (AM/PM)		Week			
			Week 0 (D1-7)	Week 1 (D8-14)	Week 2 (D15-21)	Week 3 through 13 (D22-92)
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

Refer to Section 5.4.1 for additional titration information.

Participants will return to the trial site at the times described in the 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 AEs.

Starting at the randomization visit (Visit 2), all participants will receive nutritional and physical activity counseling from a dietician or similarly qualified healthcare professional designated by primary investigator see Section 11.1. 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 adverse events (AEs). Specific time points are described in Table 2.

Plasma will be obtained for PK and 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 9. In the combination arm and the K-757-only arm, K-757 will be titrated to the maintenance dose of 120 mg BID by Day 22. K-833 will be initiated at 100 mg QAM and will be titrated to the maintenance dose of 100 mg BID on Day 8.

7.1.1. GI Intolerance Management

For participants experiencing GI intolerance, all reasonable, medically appropriate efforts should be made to support them in adhering to scheduled dose/dose escalations. Depending on the specific GI AEs and per the investigator's judgement, this may include the use of stool softeners, laxatives, enemas, and/or the anti-emetic ondansetron. [redacted]

7.2. Number of Participants

One hundred fifty (150) participants will be enrolled; 50 participants per treatment arm.

7.3. Treatment Assignment

7.3.1. Assignment of Screening and Randomization Numbers

All consented participants will be given a unique screening number that will be used to identify the subject for all procedures that occur before randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be reused for different participants.

Participants will be assigned to either placebo, K-757 alone, 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 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.

7.3.2. Study Drug Assignment

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 in a double-blinded manner, labeled with his/her unique randomization number, throughout the study.

7.3.3. Subject Replacement

No participants will be replaced.

7.4. Dose Adjustment Criteria

No dose adjustment will be allowed, as this is a forced titration study.

7.5. Criteria for Study Termination

The overall study begins when the first subject signs the study informed consent form.

The overall study ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit (this can be a phone contact), discontinues from the study, or is lost to follow-up (e.g., the Investigator is unable to contact the subject).

Study discontinuation because of non-safety reasons, such as the following:

- A finding (e.g., PK, PD, efficacy) from another nonclinical or clinical study using the study treatment(s) results in the study being stopped for a non-safety related reason.
- The study is stopped because of nonscientific and non-safety reasons, such as slow enrollment.

Study discontinuation because of safety reasons:

Early study termination because of unanticipated concerns of safety to the study participants arising from clinical or nonclinical studies with the study treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

7.5.1. Criteria for Premature Termination or Suspension of Trial or Site

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, or is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

7.5.2. Procedures for Premature Termination or Suspension of the Trial or Site

In the event that the Sponsor, an Investigational Review Board (IRB)/Independent Ethics Committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Subject Inclusion Criteria

All entry criteria, including laboratory test results, need to be confirmed before administration of the first dose of study drug.

In order to be eligible for participation in this trial, the subject must:

1. Understand the trial procedures and agree to participate by providing written informed consent prior to trial related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Be willing and able to comply with all trial procedures and restrictions, including following study diet requirements.
3. Be a male or female, age 18 to 70 years of age, inclusive, at the time of signing informed consent.
4. Have a body mass index (BMI) of 30.0 to 40.0. kg/m^2, inclusive at screening.
5. History of at least one self-reported unsuccessful dietary effort to lose body weight.
6. Be weight stable (<5% variation) over the last 3 months (by subject report).
7. Be a nonsmoker or has smoked ≤10 cigarettes per week for at least 3 months and agrees not to exceed this for the duration of study participation; has not used other nicotine containing products (e.g. other forms of tobacco, nicotine patch, e-cigarettes, vapes) for at least 3 months and agrees to abstain from such products throughout study participation.
8. Meet the following birth control requirements:
    a. Is a male subject who agrees to **all** of the following:
        - If partner is a non-pregnant female of child-bearing potential: To use an appropriate method of contraception, which must include a condom with spermicidal cream or jelly, from the first dose of study drug until 14 days after the last dose of study drug. A male subject who has had a vasectomy procedure must use a condom, but is not required to use spermicidal cream or jelly.
        - If partner is pregnant, to use a condom
        - Note: Contraception/condom requirements are waived if partner is NOT of child-bearing potential (i.e. is male or is a female who is post-menopausal or surgically sterile [post-hysterectomy, post-bilateral oophorectomy, and/or post-bilateral salpingectomy]).
        - To not donate sperm from the first dose of study drug until 14 days after the last dose of study drug.

    OR

    b. Is a female who is of non-childbearing potential defined by at least 1 of the following criteria:

- Postmenopausal (aged >45 years and with a minimum of 12 months of spontaneous amenorrhea with a Screening serum follicle-stimulating hormone (FSH) level in the menopausal range established for the central laboratory.
- Post hysterectomy, bilateral oophorectomy or bilateral salpingectomy, based on the subject's recall of their medical history.

OR

c. Is a female of reproductive potential and:

- agrees to not donate eggs from the first dose of study drug until 14 days after the last dose of study drug.
- agrees to remain abstinent from heterosexual activity[a] or
- agrees to use (or have their partner use) a birth control method that is highly effective and has low user dependency from the first dose of study drug until 14 days after the last dose of study drug. Acceptable methods of birth control are:
  - Progestogen-only implant (e.g. etonogestrel implant)
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
  - Vasectomized partner

[a] Abstinence can be used as the sole method of contraception if it is in line with the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ethics committees. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

This condition is waived if the subject is proven to have no child-bearing potential (eg, hysterectomy).

8.2. Subject Exclusion Criteria

Participants are excluded from the trial if any of the following criteria apply:

Glycemia related:

1. Has a HbA1c ≥6.5% (48 mmol/mol) as measured by the central laboratory at screening.
2. Has a history of clinically significant endocrine disease including T2DM.

   Note: A history of hypothyroidism does not require exclusion if the subject has been on a stable dose of thyroid hormone replacement (thyroxine) for at least 3 months prior to screening and the screening TSH is within the central laboratory normal range.
3. Has a history of type 1 or type 2 diabetes mellitus.
4. Had treatment with any glucose-lowering agent(s) within 90 days before screening.

Obesity related:

5. Had treatment with any medication approved for the treatment of obesity or any investigational agent being tested for obesity treatment within the past 6 months before screening. This includes agents that are approved as a component of a multi-drug combination treatment for obesity, regardless of the purpose of current use, with the exception of bupropion.

   Bupropion, which is a component of the naltrexone-bupropion combination approved for weight loss (Contrave™), is also approved as a single agent for the treatment of depression. Bupropion is not exclusionary if it is being used for treatment of depression and eligibility criteria for anti-depressant medication stability prior to screening are met (see Exclusion Criterion #12).

6. Has been treated with/used any other medication, supplement, or device for the purpose of promoting weight loss (regardless of whether they are approved or promoted for the purpose of weight loss) in the 90 days prior to screening.
7. Treatment with any GLP-1 receptor agonist in the prior 6 months.
8. Participation in an organized weight reduction program (e.g. Weight Watchers) within 90 days of screening.
9. Had a previous or has a planned (during the trial period) obesity treatment with surgery or a weight loss device. **Note:** Prior liposuction and/or abdominoplasty are not exclusionary if performed >2 years before screening).
10. Has uncontrolled thyroid disease, defined as thyroid stimulating hormone (TSH) outside (above or below) the reference range of the central laboratory at screening or has any history of Grave's disease unless all 3 of the following criteria are all met: 1. Grave's disease was treated with total thyroidectomy >2 years prior to screening, 2. There has been no recurrence of hyperthyroidism since thyroidectomy, ***and*** 3. TSH is the reference range of the central laboratory at screening.
11. Obesity is induced by an endocrine disorder (e.g. Cushing's disease).

Mental health:

12. Has a history of major depressive disorder within 2 years before screening, unless **all** of the following criteria are met:
    a. the depressive disorder has always been unipolar (no history of mania or hypomania)
    b. in the opinion of the investigator, depressive symptoms have been stable and well controlled for ≥2 years prior to screening
    c. any anti-depressant drug-treatment regimens (medications and doses) have been stable for ≥6 months prior to screening
13. Has any history of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder) that was not clearly attributable to an intercurrent event/life circumstance, self-limited and fully resolved ≥1 year prior to screening.
14. On the screening Patient Health Questionnaire-9 (PHQ-9), has an overall score ≥15 **or** has a score >0 for Question # 9 (Thoughts that you would be better off dead or of hurting yourself). **Note:** See Section 15.1.6 regarding requirements for referral to a mental health professional based on the results of the screening PHQ-9 assessment (Appendix C).

15. Has any lifetime history of suicide attempt or suicidal behavior. **Note:** Suicidal behavior includes any acts/preparation toward making a suicide attempt whether the attempt is never initiated or is initiated but interrupted by self or another person[31].
16. Use of any anti-psychotic agents for any purpose within 2 years before screening.
17. Use of the following prohibited agents:
    - Prohibited classes of anti-depressant agents (see Section 10.1) for any purpose, within 6 months of screening. **Note:** Use of allowable classes of anti-depressant agents (see Section 10.1) is permitted **only** if the anti-depressant regimen (agents **and** doses) has been stable for ≥6 months prior to screening and is not anticipated to change during the trial period.
    - Stimulant medications including amphetamines (e.g. dextroamphetamine, lisdexamfetamine) and methylphenidate/dexmethylphenidate within 6 months of screening.

General Safety:

18. Has a recent history (within the past 3 years of screening visit) or current diagnosis or evidence of hematological, immunological, renal, respiratory, neurologic, or genitourinary abnormalities or diseases that, per the investigator's judgement, may jeopardize the subject's safety or compliance with the protocol, or otherwise interfere with interpretation of efficacy and/or safety results.
19. Has a recent history (within past 3 years of screening visit) or current diagnosis of any of the following GI (gastrointestinal) related diseases: intestinal obstruction, GI perforation, adhesions, *Clostridium difficile* colitis or have had recent unexplained GI bleeding within 3 months prior to screening.
20. Has any history of pancreatitis (acute or chronic), gastroparesis, ischemic colitis, inflammatory bowel disease (IBD), or celiac disease.
21. Has a personal or first-degree relative history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
22. Has a screening estimated Glomerular Filtration Rate (eGFR) estimated with the Modification of Diet in Renal Disease (MDRD) equation of <60 ml/min/1.73 m^2.
23. Has a history of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed if they have received treatment and follow-up consistent with local standard of care.
24. Has any history of cardiovascular disease including stable and unstable angina pectoris, myocardial infarction, transient ischemic attack, stroke, cardiac decompensation, clinically significant arrhythmias, clinically significant conduction disorders, or any history or heart failure.
25. Has surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator.
26. Has a history of human immunodeficiency virus (HIV) infection.

27. Has any active liver disease other than non-alcoholic fatty liver disease (NAFLD), or any gallbladder disease that has been active/symptomatic within 6 months of screening.
28. Has a positive test result for hepatitis B surface antigen (Ag), hepatitis C virus antibody, HIV antibody, at the Screening Visit. Note: Participants with positive hepatitis B virus or hepatitis C virus serology may be enrolled if quantitative polymerase chain reaction for hepatitis B virus or hepatitis C virus ribonucleic acid is negative.
29. Has alanine aminotransferase or aspartate aminotransferase (ALT or AST) of >2.0X upper limit of normal (ULN) or total bilirubin >1.5X ULN at the Screening visit. Note: An isolated bilirubin >1.5X ULN is acceptable if bilirubin is fractionated, and direct bilirubin is within the laboratory normal range).
30. Has serum amylase or lipase >1.2X the ULN at the Screening Visit.
31. Has a triglyceride value >600mg/dL at the Screening visit (if value is ≥600 mg/dL and the sample was obtained in the non-fasted state, a repeat fasting determination may be obtained to assess eligibility).
32. Has a corrected QT interval to Fridericia's formula (QTcF) >450 milliseconds (msec) for males and >470 msec for females at screening.
33. Has a mean value for triplicate seated systolic blood pressure >160 mmHg and/or diastolic blood pressure (BP) >95 mmHg measured after at least 5 minutes at rest at the Screening Visit. **Note:** If a subject's BP is exclusionary on the first triplicate assessment at the Screening visit, they may have 1 repeat triplicate BP assessment at that visit after another rest of at least 10 minutes. If a participant's BP is exclusionary on 2 assessments at the Screening visit, the investigator can, at their discretion, adjust and/or add anti-hypertensive medications and re-assess triplicate BP up to twice at the Randomization visit (Visit 2). Anti-hypertensive regimens must align with the requirements detailed in Section 10.1 **(≤2 agents** that do **not** include verapamil). If a participants BP is exclusionary at the Screening visit and the randomization visit (Visit 2), they must be excluded.
34. Has known history or suspected abuse of alcohol or recreational drugs.
35. Has excessive consumption of alcohol within 6 months prior to screening (>14 drinks/week for men and >7 drinks/week for women, where 1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) or use of soft drugs (such as marijuana or any substances containing tetrahydrocannabinol (THC) or cannabidiol (CBD)) within 3 months prior to Screening, or hard drugs (such as cocaine) within 6 months prior to Screening.
36. Has a positive drug screen at Screening. Note: If benzodiazepines are detected on the drug screen, this is not exclusionary if they are prescribed a benzodiazepine for a therapeutic purpose (e.g. for insomnia) and confirmatory documentation is obtained from the prescribing physician.
37. Has known or suspected hypersensitivity to trial product(s) or related products.

38. Has a history of multiple significant and/or any severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
39. Has previous participation in this trial. Participation is defined as signed informed consent.
40. Has participated in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.
41. Had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the Screening Visit; has a screening hemoglobin <11.0 g/dL (males) or <10.0 g/dL (females), or has a known hemoglobinopathy (e.g. sickle cell anemia, hemolytic anemia).
42. Is a female who is pregnant, breast-feeding or intends to become pregnant during the planned course of the study. **Note:** Participants must have a negative serum pregnancy test (β-human chorionic gonadotropin (β-hCG)) performed by the central laboratory prior to enrollment in the study and prior to the randomization visit.
43. Is currently in violation of study requirements for prohibited and permissible concomitant medications or is anticipated to violate these requirements during study participation. These requirements are detailed in Section 10.1.
44. Has any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardize the subject's safety or compliance with the protocol, or otherwise interfere with interpretation of efficacy and/or safety results.
45. Is unable or unwilling to follow to follow the study nutritional and physical activity counseling and to refrain from alternative lifestyle modification strategies throughout study participation. Refer to Section 11.1.
46. Is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the Sponsor or study site.
47. Has any use of opiate medications within 14 days of screening or any anticipated/potential use of opiates during study participation.
48. Use of any other medications within 6 months of screening that, in the investigator's judgement, can significantly impact (increase or decrease) body weight, regardless of the purpose for their use.

Note: Rescreening/retesting is not permitted unless specified above.

8.3. Subject Withdrawal Criteria

8.3.1. Procedures for Discontinuation or Withdrawal of a Subject

8.3.1.1. Discontinuation of Trial Treatment

Discontinuation of trial product can be decided by either the investigator or the subject. A participant may discontinue his or her participation without giving a reason at any time during the trial.

Participants who discontinue trial product should continue with the scheduled visits and assessments to ensure continued counselling and data collection.

If the subject does not wish to attend the scheduled clinic visits, efforts should be made to have the visits converted to phone contacts. However, all efforts should be made to have the subject attend at least the 'end of treatment' clinic visit containing the final data collection of primary and confirmatory secondary efficacy endpoints, and the 'end of trial' visit.

The 'end of trial' visit is scheduled approximately 2 weeks after the final data collection, to ensure the safety of the subject. If the subject has discontinued trial product >2 weeks prior to the 'end of treatment' visit, and the requirements for the follow-up period prior to the 'end of trial' visit is fulfilled, then the 'end of trial' visit can be performed in combination with 'end of treatment' visit.

If the subject refuses to attend the 'end of treatment' and/or 'end of trial' visit, information about the attempts to follow up with the subject must be documented in the subject's medical record.

The subject must be discontinued from trial product if any of the following applies:

1. Safety concern as judged by the investigator
2. Pregnancy
3. Intention of becoming pregnant
4. Liver function test (LFT) abnormalities meeting specified discontinuation criteria (refer to Appendix A for discontinuation criteria and instruction on management of LFT abnormalities
5. Confirmed pancreatitis (see below)

If acute pancreatitis is suspected based on clinical signs and symptoms, blinded study medication should be interrupted immediately, and appropriate diagnostic assessments should be performed.

- A diagnosis of acute pancreatitis requires at least 2 of the following 3 findings [14]:
  - abdominal pain consistent with acute pancreatitis (persistent, severe epigastric pain, frequently radiating to the back); abdominal pain is often associated with nausea and vomiting.
  - serum lipase and/or amylase activity ≥3X the laboratory ULN
  - characteristic findings of acute pancreatitis on imaging

- If a diagnosis of pancreatitis is confirmed, the subject will be discontinued from blinded K-757/placebo and appropriate treatment and monitoring must be initiated.
- If the investigator and Sponsor agree that acute pancreatitis has been ruled out, all investigational medicinal products (IMP) should be resumed.

The primary reason for discontinuation of trial product must be specified in the source data at the time of discontinuation, and the subject should continue to follow the visit and assessment schedule. The reasons for treatment discontinuations are:

- Adverse event
- Withdrawal of consent
- Lost to follow up
- Pregnancy/Intention to become pregnant
- Death
- Investigator decision
- Significant protocol deviation

8.3.1.2. Early Withdrawal from the Trial

Early withdrawal from the trial may occur due to voluntary withdrawal of consent, lost to follow up (see below), or death.

In all other cases of trial product discontinuation, participants should be followed as described above in Section 8.3.1.1.

If a subject ends his/her participation, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to the ‘end of treatment’ visit.

Final drug accountability must be performed even if the subject is not able to come to the trial site.

Although a subject is not obliged to give his/her reason(s) for withdrawing early, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end of trial form in the case report forms (CRF).

8.3.1.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a subject fails to return to the trial site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the trial.

- Before a subject is deemed lost to follow-up, the investigator must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document. Should the subject continue to be unreachable at the ‘end of treatment’ visit, he/she will be considered to have withdrawn from the trial with a primary reason of lost to 'follow-up'.

9. STUDY SCHEDULE AND STUDY PROCEDURES

The order of priority can be changed during the study with joint agreement of the Investigator and KALLYOPE, Inc.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments. The suggested order of the assessments:
  - Electrocardiogram (ECGs) and vital signs (including body weight when assessed)
  - Blood samples
  - Mental health assessment instrument
  - Other assessments
- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be the subject's medical records. Additional recording to be considered source data includes, but is not limited to laboratory reports, ECG and Mental Health assessments.
- Subject's weight history must be recorded in the subject's medical record.
- Review of mental health assessment instruments, ECG and laboratory reports must be documented either on the documents or in the subject's source documents.
  - Repeat laboratory samples may be taken for technical issues.
  - Efficacy assessments and procedures are described in Section 14
  - Safety assessments and procedures are described in Section 15
  - Procedures related to AE evaluation and reporting are in Section 15.2
  - Procedures around study drug admin are in Section 13

9.1. Prestudy (Screening) Procedures

Informed consent must be obtained before any trial related activity.

At screening the investigator should ascertain whether there may be important barriers to participant motivation for lifestyle change and compliance with the protocol (e.g. density and timing of study visits). The interview must be conducted at screening to assist in identifying subjects who are unable or unwilling to comply with protocol procedures as per the exclusion criteria. In addition, the interview will ensure that any minor barriers are addressed during lifestyle counselling.

Within 4 weeks of Randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in the Inclusion and Exclusion Criteria. The Investigator will discuss with each subject the nature of the study, its requirements, and its restrictions.

The pre-study screening assessments (V1) are detailed in the SOA. Subjects need not be fasted for this visit.

- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- For details on the procedures, please refer to Table 2 and Section 15.

9.2. Procedures Weeks 1 through 13 (Treatment Period)

Participants will return to the clinical research unit at various Weeks/Visits until completion of the Visit 12 post-dose procedures (Day 92). The specific procedures that will be performed during this timeframe and at each visit are detailed in Table 2. Details related to timing of specific procedures relative to meals and dosing are in Section 15.

Visits 2 through 12 will be performed during the Treatment Period. Two of these visits (V7 (Day 36) and V11 (Day 85)) are phone call only visits with the others requiring a clinic visit. At these visits, the clinical research unit will conduct a telephone call to all participants to determine if any new AEs have arisen or concomitant medications have been taken. Study drug compliance will also be checked.

Mandatory fasted visits:

Amongst the in-person clinic visits during the Treatment Period, V2 (randomization), V6 (Day 29), V9 (Day 57) and V12 (Day 92), subjects should come to the clinic in the fasted state because body weight and fasting lipids need to be assessed in the fasted state. These fasted visits should be scheduled in the morning and the AM dose of study medication should be taken after collection of blood. Dosing should be witnessed at these visits. Other in-person visits during the Treatment Period can be in the fasted or fed state and may be scheduled without regard to timing of study medication.

9.3. Poststudy Procedures

Participants will return to the clinical research unit for the Poststudy procedures at V13. Participants should fast prior to this visit and arrive at the clinic in the fasted state. The specific assessments to be performed are list in the SOA (Table 2).

10. STUDY RESTRICTIONS

10.1. Prior and Concomitant Medications

Participants should be instructed not to start any new medications (prescription or non-prescription) or supplements without first consulting with the investigator. If this is not possible due to medical urgency, the participant should inform the investigator as soon as possible.

Any medication (including over-the-counter and prescription medicines) other than the trial product, that the participant is taking at the time of screening or receives during the trial must be recorded on the appropriate electronic case report form (eCRF). Information collected will include:

1. Medication name
2. Indication
3. Dates of administration including start and stop dates
4. Dose

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation of study medication may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy requires the agreement of the Sponsor.

Prohibited Medications

Medications listed below are prohibited from screening through the post-study follow-up visit.

[redacted]

2. Corticosteroids: Treatment for ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids. **Note:** Inhaled, nasal, and topical corticosteroids and physiological replacement doses of adrenal steroids are permitted.
3. Any anti-hyperglycemic medications
4. Any weight-loss medications: Treatment with or initiation of any weight-loss medication (e.g., semaglutide, liraglutide, orlistat, phentermine, phentermine-topiramate, bupropion-naltrexone) is prohibited. This includes agents that are approved as a

component of a multi-drug combination treatment for obesity, regardless of the purpose of current use, with the exception of bupropion.

Bupropion, which is a component of the naltrexone-bupropion combination approved for weight loss (Contrave™), is also approved as a single agent for the treatment of depression. Bupropion is allowed if it is being used for treatment of depression and eligibility criteria for anti-depressant medication stability prior to screening are met (see Exclusion Criterion #12).

5. Marijuana: Legal (including medicinal marijuana and any marijuana-derived product including THC or CBD) or illegal use is prohibited.
6. Supplements and/or Traditional Medicines: The introduction of new agents during the course of the study is not allowed. The use of prior agents is described below.
7. Lipid-lowering agents other than HMG-CoA reductase inhibitors (statins) and ezetimibe are prohibited. Prohibited agents include:
    - Bile acid binding resins (e.g. cholestyramine, colesevelam)
    - Fibric acid derivatives (e.g. fenofibrate, clofibrate)
8. Anti-psychotic agents are prohibited, regardless of the purpose for their use.
9. Use of the following anti-depressants is prohibited, regardless of the purpose for their use:
    - Tricyclic (e.g. amitriptyline, clomipramine) and tetracyclic (maprotiline) anti-depressants
    - Mirtazapine
10. Stimulant medications including amphetamines (e.g. dextroamphetamine, lisdexamfetamine) and methylphenidate/dexmethylphenidate.
11. Opiates: Brief (≤2 total days) use of opiates for unanticipated pain management needs during study participation is permitted. All other use of opiates is prohibited.
12. Use of any other medications that, in the investigator's judgement, can significantly impact (increase or decrease) body weight, regardless of the purpose for their use.

Guidance for Other Medications

The investigator or participant's physician/health care provider are permitted to make adjustments in other therapies throughout the trial if clinically warranted. Guidance for specific medications which are permitted during the study is provided below.

1. Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may be used for minor ailments (e.g. minor injuries, osteoarthritis, upper respiratory tract infections) without prior consultation with the Sponsor Clinical Director. **Note:** Acetaminophen is a known hepatotoxin and is therefore prohibited.
2. HMG-CoA reductase inhibitors (statins) and ezetimibe: Concomitant use of a statin (e.g. atorvastatin, simvastatin) and/or ezetimibe is permitted if the regimen (agents and doses) has been stable for ≥3months prior to screening. It is preferable that the lipid-lowering

regimen (agents and doses) remain stable throughout study participation (from screening through the post-study follow-up visit).

3. Antihypertensive medications: ≤2 anti-hypertensive agents are permitted. These may not include verapamil given potential for verapamil to perpetrate a DDI with K-757. It is preferable that doses of anti-hypertensive medications remain stable from randomization through the post-study follow-up visit.
4. Post-menopausal hormonal replacement therapy (HRT): Post-menopausal HRT is permissible, but participants should be on a stable HRT regimen at screening and are expected to remain on this stable regimen throughout study participation.
5. Thyroid Hormone Replacement Therapy: Thyroid hormone replacement medication (e.g., thyroxine) is permitted, but subjects should be on a stable dose for at least 3 months prior to screening. It is preferable that doses of thyroid hormone replacement remain stable throughout study participation (from screening through the post-study follow-up visit).
6. Nicotine/Nicotine products: Smoking is permitted during the study; however, participants should refrain from smoking >10 cigarettes per week. No other forms of nicotine (other forms of tobacco, nicotine patch, e-cigarettes, vapes) are permitted during study participation. **Note:** Participants should avoid cigarette use at least 30 minutes prior to measuring blood pressure.
7. Ondansetron may be used as necessary to manage GI intolerance (see Section 7.1.1).
8. Anti-depressants: Anti-depressant agents that are not prohibited (see above) are permissible if the treatment regimen (agents and doses) has been stable for ≥6 months prior to screening. Permissible classes/agents include selective serotonin reuptake inhibitors (SSRIs; e.g. fluoxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (e.g. desvenlafaxine, duloxetine), serotonin modulators (e.g. nefazadone, trazadone), and bupropion. It is preferable that anti-depressant regimens (agents and doses) remain stable throughout study participation (from screening through the post-study follow-up visit).
9. Supplements and/or Traditional Medicines: The use of herbal supplements and other natural products is allowed provided doses have been stable for at least 90 days prior to the screening visit. Increases in dose/frequency during the study are prohibited. Use of all such agents should be captured on the prior/concomitant medication CRFs.

Drug-drug interaction considerations

No formal drug-drug interaction studies in humans have been conducted with K-757 or K-833.

[redacted]

Contact the Sponsor if there any questions about potential drug interactions with concomitant medications.

11. STUDY RESTRICTIONS AND REQUIREMENTS

11.1. Dietary and Physical Activity Requirements and Restrictions

Fasting Prior to Study Visits

1. Participants must attend visits V2, V6, V9, V12, and V13 in the fasted state. These visits should be scheduled in the morning.
2. Fasting is defined as at least 8 hours before the visit without food or liquids, except for water.
3. At fasted visits, the morning doses of study medication should be withheld until blood samples have been obtained (except V12 and V13 where there is no dosing).

Diet and Physical Activity Counseling

All participants will receive nutritional and physical activity counseling according to the SOA (Table 2). This counseling will be provided by a dietician or similar qualified healthcare professional.

Nutritional counseling will focus on calorie-reduction with an energy deficit of approximately 500 kcal/day based on the total energy expenditure (TEE) estimated once based on the weight at V2. Physical activity will also be encouraged (minimum 150 min of physical activity per week, e.g. walking or use of the stairs). **Note**: To minimize potential for variability in counseling between study sites, diet and activity counseling must be limited to that specified for the study and occur only at the site visits specified in Table 2. No diet or activity counseling may occur at other site visits or outside of site visits (e.g. by phone, text, email).

If a BMI $\leq$22.5 kg/m^2 is reached, the recommended energy intake should be recalculated with no kcal deficit (maintenance diet) for the remainder of the trial. As necessary, the investigator may consult with the Kallyope Clinical Director to discuss when a maintenance diet should be initiated.

Calculation of Estimated TEE

The TEE is calculated by multiplying the estimated Basal Metabolic Rate (BMR) (Table 10) with a Physical Activity Level value of 1.3.

Table 10: Equation for Estimated BMR

Sex	Age (years)	BMR (kcal/day)
Men	18 to 30 31 to 60 >60	15.057 x weight at randomization in kg + 692.2 11.472 x weight at randomization in kg + 873.1 11.711 x weight at randomization in kg + 587.7
Women	18 to 30 31 to 60 >60	14.818 x weight at randomization in kg + 486.6 8.126 x weight at randomization in kg + 845.6 9.082 x weight at randomization in kg + 658.5

11.1.1. Alcohol Restrictions

Participants are permitted to consume alcohol, as long as the amount is lower than 14 drinks/week for men and >7 drinks/week for women, where l drink= 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor.

11.1.2. Caffeine Restrictions

Participants should avoid caffeine at least 30 minutes prior to measuring blood pressure.

11.1.3. Smoking Restrictions

Smoking is permitted during the study; however, participants will refrain from smoking >10 cigarettes per week. In addition, no other forms of nicotine (e.g. other forms of tobacco, nicotine patch, e-cigarettes, vapes) are permitted during the study.

Participants should avoid cigarette use at least 30 minutes prior to measuring blood pressure.

11.1.4. Activity Restrictions

See activity counseling above (Section 11.1).

11.2. Contraceptive Requirements

Male study participants:

Must not donate sperm from the first dose of study drug until 14 days after the last dose of study drug.

If the partner is a non-pregnant female of child-bearing potential, they must use an appropriate method of contraception, which must include a condom with spermicidal cream or jelly, from the first dose of study drug until 14 days after the last dose of study drug which is more than 5 times the estimated half-life of K-757 and K-833. A male subject who has had a vasectomy must use a condom but is not required to use spermicidal jelly.

If a partner is pregnant, they must use a condom.

Note: Contraception/condom requirements are waived if partner is NOT of child-bearing potential (i.e. is male or is a female who is post-menopausal or surgically sterile [post-hysterectomy, post-bilateral oophorectomy, and/or post-bilateral salpingectomy]).

Female study participants of reproductive potential

Must agree to not donate eggs from the first dose of study drug until 14 days after the last dose of study drug.

Must agree to not donate eggs from the first dose of study drug until 14 days after the last dose of study drug.

Must either agree to remain abstinent from heterosexual activity[a] or use (or have their partner use) a birth control method that is highly effective and has low user dependency. Acceptable methods of birth control are:

- Progestogen-only implant (e.g. etonogestrel implant)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner

[a] Abstinence can be used as the sole method of contraception if it is in line with the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ethics committees. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

The criteria specified in Section 8.1, Inclusion Criterion #8 must be met for a female subject to be considered not of reproductive potential for the purpose of this study.

12. RANDOMIZATION AND BLINDING

12.1. Randomization and Blinding

12.1.1. Randomization Code Creation and Storage

Randomization personnel of the Sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

12.1.2. Clinical Study Drug Blinding

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

12.1.3. Clinical Trial Blind Maintenance/Unblinding Procedure (Blinded Studies Only)

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.

Unblinding will be performed per the standard operating procedures of the study site. Any intentional or unintentional unblinding will be documented in the unblinding log and Clinical Study Report (CSR).

13. STUDY DRUG MATERIALS AND MANAGEMENT

13.1. Study Drug

In this protocol, the term study medication refers to all or any of the drugs defined below and in Table 11 and Table 12.

Details regarding the dosage form description and strengths of the active drug and placebo can be found in the Pharmacy Manual or equivalent manual. Study drug will be packaged to support enrollment and replacement of participants as required.

The study site will be supplied to the study site / Investigator by the Sponsor with the following medication in a double-blind manner:

- K-757 30-mg and 60-mg capsules and placebo capsules. Capsules will be provided in polyvinyl chloride (PVC)/polyvinylidene chloride (PvDC) blisters with aluminum base as a primary package. Blister strips are then secondary packaged into wallet cards to meet the required dosing regimen. Participants are blinded as to the study treatment they receive.
- K-833 100-mg capsules and placebo capsules. Capsules will be provided in PVC/PvDC blisters with aluminum base as a primary package. Blister strips are then secondary packaged into wallet cards to meet the required dosing regimen. Participants are blinded as to the study treatment they receive.

Blister packs will be labeled with a single-panel label that will contain, but will not be limited to, the following: Sponsor's name and address, protocol number, packaging job/lot number, caution statement and storage conditions.

Table 11: K-757 Investigational Product

	Investigational Product
Product Name:	K-757
Dosage Form:	[redacted]
Unit Dose	Capsules: placebo, 30-mg and 60-mg potencies
Route of Administration	Oral
Physical Description	30 mg or 60 mg of K-757 and placebo [redacted] primary packaged in PVC/PvDC blisters with aluminum base and secondary packaged into wallet cards based on dosing regimen.
Manufacturer	[redacted]
Packaging / Distribution	[redacted]

Additional reference information and administration instructions can be found in the Pharmacy Manual.

Table 12: K-833 Investigational Product

	Investigational Product
Product Name:	K-833
Dosage Form:	[redacted]
Unit Dose	Capsules: placebo, 100-mg potencies
Route of Administration	Oral
Physical Description	100 mg of K-833 and placebo [redacted] primary packaged in PVC/PvDC blisters with aluminum base and secondary packaged into wallet cards based on dosing regimen.
Manufacturer	[redacted]
Packaging / Distribution	[redacted]

13.2. Study Drug Packaging and Labeling

A clinical label will be affixed to study drug containers in accordance with local regulatory requirements.

13.3. Study Drug Storage

Study drug must be stored in a secure, limited-access location under the storage conditions specified on the label and must remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained.

K-757 and K-833 capsules should be stored in well-closed containers at room temperature (15 to 25 °C / 59 to 77 °F). The temperature excursion information can be found in the pharmacy manual or in the referenced compounding manual when applicable. Receipt and dispensing of study drug must be recorded by authorized personnel at the study site.

13.4. Administration

Participants will be blinded to treatment assignment and dose level at all times.

Study medication may be taken without regard to food.

13.4.1. Dose Timing

The morning dose should be taken between 6 and 10AM.

The evening dose should be taken approximately 10 hours after the morning dose.

There should always be at least 6 hours in between doses.

13.4.2. Missed Doses

If a subject did not take their scheduled dose:

1. If a morning dose is not taken by 12 noon, it should not be taken.

2. If an evening dose is not taken by 12 midnight, it should not be taken.
3. If a dose is missed, that dose should not be taken at a later time. It should be left in the blister pack and returned to the study site at the next site visit.

13.4.3. Dosing Interruptions

If multiple days of dosing are missed due to subject error, the participant may resume QD dosing for 3 days under PI discretion before returning to the BID regimen. If less than 2 days (4 consecutive doses) are missed, the subjects should resume the BID regimen.

If study medication is missed for ≥7 consecutive days, for any reason, the decision to resume should be based on discussion between the PI and Sponsor Clinical Director.

All dosing interruptions should be documented in the case report forms.

13.5. Study Drug Accountability

The Investigator is responsible for keeping accurate records of the study drug received from the Sponsor or designee, the amount dispensed to and returned by the participants, and the amount remaining at the end of the study. For all study sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for study drug accountability, return, and destruction.

All ancillary supplies will be provided by either the study site or the Sponsor or designee, depending upon availability. The list of ancillary supplies and source information can be found in the Pharmacy Manual or in the referenced compounding manual when applicable. If provided by the Sponsor, unused ancillary supplies will be accounted for and disposed of as directed by the Sponsor or designee.

13.6. Study Drug Handling and Disposal

For all study sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for study drug accountability, return, and destruction.

13.7. Treatment Compliance

Treatment compliance will be monitored throughout the duration of the study. Study medication will be reconciled at each visit, when new treatment wallets are administered to participants. A system to support subject adherence to BID dosing will be used at participating sites during the study. Dosing reminder texts and capture of anonymized subject AM/PM dosing will be done via a smart phone application and monitored centrally. No data from the application-based tool will be collected during the study. Actual dosing compliance is to be confirmed between the site staff and subjects at each study visit and upon return of the subject IMP blister cards. Missed doses will be quantified within the eCRF and tracked within the site drug accountability logs.

14. EFFICACY ASSESSMENTS

14.1. Body Measurements

Body weight should be measured at all site visits where indicated in the SOA, in the fasted state.

The scale should be calibrated prior to study start. A recalibration is not needed if calibration occurred within 3 months prior to the study start.

Body weight will be measured, in kilograms (kg) or pounds (lbs), using a standardized, digital scale. The scale must provide body weight in kg or lbs (unit conversion from pounds to kilograms by site staff is not permitted). The weighing process is as follows:

- The same scale should be used for each patient at all study visits where weight is measured.
- Weight will be taken in duplicate throughout the trial at approximately the same time of day, after voiding (i.e., forced void) and while wearing only a gown and underwear (no street clothes or shoes; socks do not need to be removed).
- Participants should be instructed to step gently onto the scale, place both feet together in the center of the scale and stand straight with eyes directed ahead. Participants should be instructed to stand still and not sway. Measurement will be recorded after the weight has stabilized.
- Body weight should be reported with precision to one decimal place (i.e., 0.1 kg or lbs). The 2 measurements should be recorded in the source documents. If the 2 measurements differ by more than 0.2 kg or lbs, a second set of duplicate measurements must be obtained as follows: (1) check the subject to ensure proper positioning as indicated above and (2) re-measure weight in duplicate. This process should be repeated, as needed until duplicate measurements that agree within 0.2 kg or lbs are obtained. This set of measurements should be recorded in the source documents and in the clinical database.

Height is measured without shoes in centimeters (one decimal). BMI will be calculated from screening data and must agree with inclusion criterion no. 4. Height will be measured at Screening only and will not need to be reassessed at subsequent visits where weight is required per the SOA. Body mass index equals a subject' s weight in kilograms divided by the square of the height in meters (body mass index=kg/m^2). Body mass index will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4, round down, and 0.5 to 0.9, round up.

14.2. Blood Pressure and Heart Rate

Vital sign measurements include a triplicate measurement of sitting blood pressure and heart rate. Blood pressure and heart rate will be measured using an automated, oscillometric blood pressure measuring device at time points noted in the SOA (Table 2). Site personnel should use the same blood pressure measuring device throughout the study for each subject. The following method should be used to record sitting blood pressure and heart rate for participants in triplicate:

- Participants will refrain from nicotine-containing products and/or ingesting caffeine for at least 30 minutes preceding the measurements.
  - Participants should be seated in a chair with their back supported, feet flat on the floor and arm bared (free of restrictions such as rolled up sleeves) and supported at heart level.
  - The appropriate cuff size must be used to ensure accurate measurement. Each subject's cuff size should be noted in his/her source file to assure the same cuff size is used throughout the trial.
  - Measurements should be taken on the same arm at each visit (preferably the non-dominant arm).
  - Measurements should begin after at least 5 minutes of rest.
  - The three measurements of both the blood pressure and heart rate must be taken approximately 2 minutes apart with the triplicate set recorded in the source document and eCRFs.
  - Assessment of heart rate can be manual (rather than using an automated device); however, when done manually, heart rate must be measured in the brachial/radial artery for at least 30 seconds.
  - Other procedures should not be performed during the time of the blood pressure and heart rate measurements.

14.3. Blood Sample Collection

Blood samples for determination of K-757 and K-833 will be collected according to times noted in the SOA. Also refer to Section 17.6.

14.3.1. Blood for Plasma PK Measurements

Refer to the Operations Manual for plasma PK collection, handling, storage, and shipping information.

Actual sampling times will be involved in the final computations of plasma PK parameters for final and preliminary analyses, if available. Preliminary analyses may use nominal sampling times to characterize the PK parameters for dose escalation meetings.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing (trough). The actual time of sample collection and the most recent dosing time both prior to and after each sample collection will be recorded on the source document and electronic case report form.

14.3.2. Blood for Plasma PD and DNA Measurements

Refer to the Operations Manual for plasma PD collection, handling, storage, and shipping information. Trough samples will be collected and analyzed for disease related markers such as gut hormone levels (eg, GLP-1, PYY). Additionally, archived samples may be used for analysis of additional gut hormones, such as GIP, active GIP, active GLP-1, or other markers relevant to the investigation (such as bile acids).

Refer to the Operations Manual for the collection, handling, storage, and shipping information pertaining to the optional blood sample for DNA. A one-time blood sample will be collected in consenting participants. DNA may be isolated from these samples and analyzed for genetic markers related to obesity and diabetes. These may include factors predicting response to treatment with the investigational agents or other types of obesity treatments.

15. ASSESSMENT OF SAFETY

15.1. Safety Parameters

15.1.1. Demographic/Medical History

Qualified site personnel will collect subject significant medical history (past and concurrent medical conditions), per the clinical site' s standard of care and appropriate clinical judgment, and subject demographics.

Qualified site personnel will review subject prior and concomitant medication use. Medications are defined as prescription and over-the-counter drugs, vaccines, supplements, nutraceuticals, and oral herbal preparations.

15.1.2. Vital Signs

Refer to Section 14.2 for details pertaining to heart rate and blood pressure measurements.

Body temperature will be measured with either an oral (temperature taken at floor of the mouth) or tympanic thermometer. The same method (ie, oral or tympanic) must be used for all measurements for each individual subject and should be the same for all participants.

15.1.3. Physical Examination (PE)

Qualified site personnel will conduct full PE during visits noted in the SOA.

The PE will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim PEs will be performed at the discretion of the Investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

15.1.4. Electrocardiogram (ECG)

A triplicate 12-lead ECG will be collected at all the timepoints specified in the Schedule of Assessments following a rest period of at least 5 minutes.

The Investigator will interpret the Safety ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The time that the ECG was performed will be recorded.

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.

The Investigator will be responsible for providing the interpretation of all safety ECGs (normal/abnormal). These results will be reviewed by the Investigator for subject safety and will be provided in an appropriate format with the clinical study report.

An electronic copy of the 12-lead ECG, which includes the Investigator’s approval or a copy of the 12-lead ECG with the Investigator's signature and date of assessment, will be filed with the source and captured in the appropriate eCRF where required. If the original ECG is printed on

thermal paper, the ECG report must be photocopied and signed by the Investigator or archival quality paper can be utilized for ECG printouts, with a 25-year (or more) guarantee from the manufacturer (assuming appropriate storage conditions are satisfied). If a photocopy is made, it will be filed with the original ECG in the source.

15.1.5. Laboratory Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Except for screening safety laboratory samples, safety laboratory samples will be collected at the time points and observing fasting requirements where stipulated in the Schedule of Assessments.

15.1.5.1. Hematology

Hematology includes the following assessments:

White blood cell (WBC) count[a]	Hemoglobin
Red blood cell (RBC) count[b]	Hematocrit
Platelet count	HbA1c

[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).

15.1.5.2. Blood Chemistry

Blood chemistry testing includes the following assessments:

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)
Glucose	Magnesium
TSH (Screening)	Multiple biochemical analysis (MBA)[a]
	Amylase
	Lipase

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

Please refer to Section 8.3 for subject discontinuation criteria related to abnormal liver test results, and Appendix A for details on management and follow-up of LFT elevations.

15.1.5.3. Urinalysis

Urinalysis includes the following assessments (Screening Visit only):

Dipstick:	Microscopic:
Nitrite	WBC
Protein	RBC
Glucose	Epithelial cells
pH	Casts (specify)
Specific gravity	
Ketones	
Bilirubin	
Urobilinogen	
Leucocyte Esterase	
Blood	

15.1.5.4. Virus Serology

Human immunodeficiency virus antibody, hepatitis B surface antigen, and hepatitis C virus antibody will be assessed at screening.

15.1.5.5. Drug Screen

The urine drug screening assessment will include the following tests:

Amphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol (THC), cocaine/metabolites, 3,4-methylenedioxy-methamphetamine, methadone/metabolite, opiates.

15.1.5.6. Pregnancy Screen

Serum and urine hCG tests as per SOA.

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

The PHQ-9 is the 9-item depression module of the patient health questionnaire, which is a self-administered diagnostic tool used for assessment of mental disorders. The questionnaire takes approximately 10 minutes to complete. The PHQ-9 will be assessed at screening. The questionnaire is located in Appendix C.

Referral to a mental health professional (MHP)

If a participant's screening PHQ-9 score is 10-14 (inclusive) the participant should be referred to a MHP if this is considered appropriate by the investigator. If a referral is not considered appropriate, the reason for this decision must be documented in the subject's medical records.

If a participant has a screening PHQ-9 score of ≥15 **or** has a score >0 for Question # 9 (Thoughts that you would be better off dead or of hurting yourself), they will be excluded from the study. However, they must be referred to a MHP.

At any point during the study, MHP referral is required if a participant has any suicidal behavior or if the investigator considers referral necessary for the safety of the participant for any reason.

If any of the referral criteria are met, the reason for referral should be explained to the participant. If the participant refuses the referral, this should be documented.

15.2. Adverse Events and Serious Adverse Events

15.2.1. Definition of Adverse Events (AEs) and Serious Adverse Events (SAEs)

15.2.1.1. Adverse Event (AE)

An Adverse Event/Experience 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 [ICH E2A].

The following can be considered AEs:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected or diagnosed after the initiation of treatment with study medication, even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen after informed consent or following the initiation of treatment with study medication.
- Laboratory values and ECG findings: Changes in laboratory values or ECG parameters may be considered AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). If the value results in a discontinuation of investigational study drug, then the occurrence should be reported as an AE.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE. Any laboratory AE should be recorded in the eCRF, whether or not it is related to study drug.
- Any change in vital signs that are considered clinically significant by the Investigator may be recorded as an AE. If the value results in a discontinuation of investigational study drug, then the occurrence should be reported as an AE.

15.2.1.2. Serious Adverse Event (SAE)

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

- 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.

Additional details and clarifications for AEs and SAEs are in Appendix B.

15.2.2. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from time of consent through the Poststudy/End of Trial visit.

15.2.3. Identifying AEs and SAEs

Adverse events spontaneously reported by the patient/subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site.

15.2.4. Recording of AEs and SAEs

All AEs that occur after any patient/subject has been consented, before treatment, during treatment, during all visits, and within 14 days following the cessation of treatment, whether or not they are related to the study drug, must be recorded on the eCRFs provided by Kallyope, Inc.

Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s) and updated once the information becomes available.

The following information will be documented for each event:

- Event term
- Start and end date and time
- Pattern of AE (frequency)
- Severity/intensity
- Causality Assessment (Investigator's opinion of the causal relationship between the event and administration of study drug[s])
- Action taken with trial drug
- Outcome of event
- Seriousness

Event Term

The AE term should be reported in standard and current medical terminology (e.g., MedDRA) when possible.

Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the patient/subject and/or Investigator.

End Date

The end date of the AE is the date at which the patient/subject recovered, the event resolved but with sequelae, or the patient/subject died.

Pattern of AE (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of non-consecutive days are intermittent. All other events are continuous.

Severity/Intensity

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 15.2.1.2. An AE of severe intensity may or may not be considered "serious."

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

For assessment of the severity of GI AEs, the grading scales below may be taken as a reference per investigator discretion (Table 13):

Table 13: Severity Grading of GI AEs

AE	Mild	Moderate	Severe
Nausea/ Vomiting*	-No interference with activity -1-2 episodes/24 hours**	-Some interference with activity -3-5 episodes/24 hours**	-Prevents daily activity -6 or more episodes/24 hours** -Requires IV hydration -More severe (e.g. hypotensive shock)
Diarrhea*	-2-3 loose stools -<400gms/24 hours	-4-5 stools -400-800 gms/24 hours	-6 or more watery stools -> 800 gms/24 hours -Requires IV hydration -More severe (e.g. hospitalization indicated)
Constipation***	-Occasional or intermittent symptoms -Occasional use of stool softeners, laxatives, dietary modification or enema	-Persistent symptoms with regular use of laxatives or enemas -Limiting instrumental activities of daily living	-Obstipation with manual evaluation indicated -Limiting self-care activities of daily living -more severe (e.g. urgent intervention indicated)

*Based on the Guidance for Industry-Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007); https://www.fda.gov/media/73679/download
Individual episodes separated by at least 5 min.* Table is based on the Constipation Grading Scale National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0)

Causality Assessment

An Investigator who is qualified in medicine must make the determination of relationship to the study drug for each AE.

The relationship of each AE to study drug will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of study drug (including the course after withdrawal of the study drug), or for which a causal relationship is at least a reasonable possibility that the study drug caused the AE, ie, it is medically plausible. "Reasonable possibility means" there is evidence to suggest a causal relationship between the study drug and the AE.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of study drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and/or concurrent treatments.

Action Taken with Study Treatment

- Drug withdrawn (ie, discontinuation due to an AE) - a study medication is stopped due to the particular AE.
- Dose not changed - the particular AE did not require stopping a study medication.

- Unknown - only to be used if it has not been possible to determine what action has been taken.
- Not applicable - a study medication was stopped for a reason other than the particular AE, e.g., the study has been terminated, the subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.
- Dose reduced - the dose was reduced due to the particular AE.
- Dose increased - the dose was increased due to the particular AE.
- Drug interrupted - the dose was interrupted due to the particular AE.

Outcome

- Recovered/resolved - subject returned to first assessment status with respect to the AE.
- Recovering/resolving - the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved - there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs /symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae - the subject recovered from an acute AE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal - an AE that is considered as the cause of death.
- Unknown - the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

Seriousness

- See Section 15.2.1.2 for the criteria for an SAE. Seriousness is a factor in determining regulatory obligations.

15.2.5. Follow-Up of AEs and SAEs

All participants/participants experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside (the patient’s/subject’s health has returned to baseline status) and any clinically relevant changes in laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, regardless of whether the patient/subject is still participating in the study. The exception are

nonserious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, which need not be followed-up for the purposes of the protocol.

All appropriate therapeutic measures will be undertaken and recorded. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

15.2.6. Reporting Serious Adverse Events (AEs) to the Sponsor

The study designated SAE form (or equivalent) must be completed, in English, and signed by the Investigator immediately or within 24 hours of first onset or notification of the event.

The SAE must also be entered into the EDC within 24 hours of the Investigator's (or other study personnel's) initial knowledge of the event. A paper form may be used as back-up.

The SAE form should be transmitted within 24 hours of awareness by email to the safety mailbox address listed below and in Table 1.

[redacted]

The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name/site
- Name of the study medication(s)
- Causality assessment

The Investigator must verify the accuracy of the information recorded on the SAE pages with the corresponding source documents. Supporting documents (e.g. discharge summaries, imaging reports, ECGs, laboratory tests, autopsy reports, etc.) should also be provided with the SAE or as soon as obtained.

Additional follow-up information, if requested or becomes available at a later date, should be transmitted to Kallyope, Inc. and its designated contact address within 24 hours of receipt. The investigator should complete a follow-up SAE form. All SAE information, including initial and all follow-ups, should be kept with the appropriate section of the CRF and/or study file.

All SAEs should be followed up as described in Section 15.2.5. The timelines and procedure for follow-up reports are the same as those for the initial report.

15.2.7. Reporting AEs to Regulatory Authorities and IRBs/IECs

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements for safety reporting to regulatory authorities, IRBs/IECs, and investigators.

A SAE may qualify for expedited reporting to regulatory authorities if it is determined to be a sudden unexpected serious adverse reaction (SUSAR). A SUSAR is an AE associated with the use of the study drug which is serious, unexpected, and assessed as related to the study drug. An

AE is considered “unexpected” if the nature of the AE is not consistent with what is not listed in the Reference Safety Information section of the Investigator Brochure. Reports that add significant information on specificity or severity of a known, already documented serious adverse event constitute unexpected events. The Sponsor is responsible for determining whether a SAE is expected or unexpected for the purpose of regulatory reporting.

The Sponsor or its designated representative will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor' s designee, SUSARs will be submitted within 7 days for fatal and life-threatening SUSARs and 15 days for non-fatal and non-life-threatening SUSARs, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial.

It is the Principal Investigator’s responsibility to promptly notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all SUSARs (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs, in accordance with its regulations and guidelines.

15.2.8. Adverse Events of Special Interest (AESI)

An AESI is an AE (serious or non-serious) of scientific and medical interest to the Sponsor’s product or program. Ongoing monitoring and rapid communication to the Sponsor is requested as such an event might warrant further investigation in order to further characterize it.

AESIs and any follow-up information must be reported to the Sponsor within 24 hours of first awareness (Section 15.2.6).

- For this study, there are no AESIs.

15.2.9. Pregnancy and Lactation

Although pregnancy and lactation are not considered an AE, it is the responsibility of the Investigator to report the pregnancy/lactation in either a female subject or the partner of a male subject to the Sponsor and its designee during the trial (within 24 hours) up until the post-study Visit. All participants and partners of participants who become pregnant must be followed to the completion or termination of pregnancy.

Should a pregnancy occur, it must be recorded on the eCRFs and designated pregnancy form and reported within 24 hours to the designated safety mailbox at:

[redacted]

Pregnancy, in itself, is not regarded as an AE unless a negative or consequential outcome occurs in the participant or child/fetus, or there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Pregnancy outcomes (e.g. spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, ectopic pregnancy, pre-eclampsia, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as SAEs (important medical events). If the pregnancy continues to term, the outcome (health of infant) must also be followed up and documented even if the patient was discontinued from the study. All reports of congenital abnormalities/birth defects are SAEs. SAEs should be reported as per Section 15.2.6.

16. STATISTICS

16.1. General Statistical Considerations

A Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe details of the summaries and analyses to be performed. Any changes in the planned analyses will be reported in the CSR.

All summaries and analyses will be presented in tabular or graphical form. Continuous data will be summarized by reporting number of observations, mean, standard deviation (SD), median, minimum, and maximum by treatment and visit. Categorical data will be summarized using frequency tables reporting the number and percentage of participants falling within each category by treatment and by visit.

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

Baseline will be taken as the last available observation prior to dosing during the double-blind treatment period.

16.2. 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.

16.3. Analysis Populations

The modified Intent-to-Treat (mITT) analysis set will 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, efficacy analyses.

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

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

16.4. Disposition

The number and percentage of participants who were randomized, and randomized but did not receive the study product as randomized will be summarized by treatment group. The number and percentage of participants who completed the double-blind treatment and/or the study, prematurely discontinued to treatment and/or study, and primary reason for discontinuation will be summarized by treatment group.

16.5. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group. Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (e.g., age, height, weight, and BMI). The number and percentage of participants in each class of the categorical demographic variables and baseline characteristics variables (e.g., gender, ethnicity, race) will be summarized. Individual subject demographic and baseline characteristics data will be listed.

16.6. Efficacy Analyses

16.6.1. Primary Endpoints

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

Primary Estimand

For the primary endpoints, the primary estimand for the percentage change from baseline in body weight is defined as the average treatment effect of K-757 alone and the combination of K-757 + K-833 relative to placebo in the mITT analysis population, had they remained on their randomized treatment for the entire planned duration of the trial (“hypothetical” estimand).

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 or until first discontinuation of randomized treatment. An unstructured covariance will be used. If the unstructured covariance structure leads to nonconvergence, Akaike’s information criteria will be used to select the best covariance structure.

Secondary Estimand

The secondary Estimand for the percentage change from baseline in body weight is defined as the average treatment effect of K-757 alone and the combination of K-757 + K-833 relative to placebo in the mITT analysis population regardless of adherence to treatment (“treatment policy” estimand).

All available data at Week 13 including the participants who have discontinued treatment but completed week 13 visit ("retrieved dropouts”) are used for the analysis of the secondary estimand. 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. Additional imputation for missing data at Week 13 may be performed using multiple imputation approach.

16.6.2. Secondary Endpoints

The confirmatory secondary continuous endpoints will be analyzed to address the primary estimand using the same MMRM described for the primary endpoint.

For the secondary categorical endpoint of proportion of subject achieving ≥5% weight reduction after 13 weeks, the same MMRM described for the primary endpoints will be used to address the primary estimand. The missing data will be imputed using MMRM assuming missing at random

(MAR) and the imputed 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.

16.6.3. Exploratory Endpoints

The exploratory endpoints will be analyzed using the same approach described for the secondary endpoint.

16.7. Safety Analyses

Safety analyses will be based on the Safety Analysis Set. No formal statistical tests or inference will be performed for safety analyses. All summaries will be summarized by treatment.

16.7.1. Treatment-emergent Adverse Events (TEAE)

Safety analyses will be based on the Safety Analysis Set. No formal statistical tests or inference will be performed for safety analyses.

Adverse events will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect at the start of the study. AEs will be summarized as TEAEs (defined as events that are newly reported after randomization or reported to worsen in severity from baseline). The incidence of participants with at least 1 TEAE and the incidence of TEAEs by preferred term and system organ class will be presented by treatment group. The frequency and percentage of TEAEs will be presented. The incidence of participants with at least 1 TEAE assessed as related to the study drug will be summarized by treatment group. All SAEs will be listed by patient. If a sufficient number of SAEs are reported, summaries will be included. Discontinuations to study and study drug due to TEAEs will be summarized by treatment group. All adverse events will be listed by patient.

16.7.2. Clinical Laboratory Evaluation

Baseline, post baseline measurements and changes from baseline for clinical laboratory evaluations will be summarized by treatment and timepoint. Individual measurements of laboratory tests from hematology, chemistry, and urinalysis that meet KALLYOPE, Inc.'s abnormal criteria will be summarized.

16.7.3. Vital Signs

Baseline, post baseline measurements and changes from baseline for vital sign data will be summarized by treatment and timepoint.

16.7.4. Electrocardiogram

Baseline, post baseline measurements and changes from baseline for electrocardiogram data will be summarized by treatment and timepoint. QTc values and changes form baseline that reach the threshold of clinical concern will be summarized. All electrocardiogram data will be provided in the data listings.

16.7.5. Prior and Concomitant Medications

Prior and concomitant medications will be summarized by treatment group.

16.8. Pharmacokinetics

16.8.1. Sample Analysis

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

16.8.2. Plasma PK

Plasma concentrations will be summarized for K-757 for K-757 alone and the combination of K-757 + K-833. Plasma concentrations will be summarized for K-833 for the combination of K-757 + K-833.

Mean plasma concentrations measured over time will be displayed graphically by treatment.

16.9. 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 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.

16.10. Interim Analysis

No interim analysis is planned for this study.

17. ADMINISTRATIVE AND REGULATORY DETAILS

17.1. Direct Access to Source Data/Documents

17.1.1. Study Monitoring

Study progress will be monitored by the Sponsor or its representative as frequently as necessary to perform source document verification, ensure a accurate data collection, protocol compliance, and study conduct in accordance with accepted regulatory requirements. The Principal Investigator must make all the subject data available to the monitor for review during the planned site monitoring visits. Arrangements for monitoring visits will be made in advance, except in emergency cases.

17.1.2. Audits and Inspections

Authorized representatives of Kallyope, Inc., a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Sponsor -- medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Sponsor -- access to records, facilities, and personnel for the effective conduct of any inspection or audit.

17.2. Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

17.3. Written Informed Consent

The Principal Investigator(s) at each center will administer an IRB/EC approved informed consents to all subjects who are screened on this trial. The subject's/patient's signed and dated informed consent must be obtained before conducting any study procedures.

17.4. Data Handling and Recordkeeping

17.4.1. Data Collection and Reporting

Data for this study will be collected using eCRFs. The Investigator and study site staff will receive system documentation, training, and support for the use of the eCRF.

All protocol-required information collected during the study must be entered by the Investigator or designated representative in the source documents and eCRF. All data entry, modification, or deletion will be recorded automatically in an electronic audit trail indicating the individual subject, original value, the new value, the reason for change, who made the change, and when the change was made. All data changes will be clearly indicated with a means to locate prior values. The system will be secured to prevent unauthorized access to the data or the system. This

will include the requirement for a user identification (ID) and password to enter or change data. The Investigator will maintain a list of individuals who are authorized to enter or correct data and their system ID.

The Investigator or designated sub-Investigator, following review of the data in the eCRF, will confirm the validity of each subject's data by electronic signature.

17.5. Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents. Refer to (Refer to ICH E6 (R2) Good clinical practice Section 8 Essential documents for the conduct of a clinical trial).

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Kallyope, Inc. or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

17.6. PK and PD Sample Retention

Blood samples collected in this study will be used for analysis of K-757 and K-833 PK and PD levels, as outlined in Section 9. Any leftover samples, if not used, will be preserved and retained at the Sponsor-selected long-term storage facility for up to 5 years from the end of the study to conduct additional analyses, as mentioned above.

17.7. Publication Policy

The Investigator is obliged to provide the Sponsor with complete test results and all data derived information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

Investigators will be asked to review primary publications. The Sponsor may publish any data and information from the study (including data and information generated by the Investigator). Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

Investigators must seek approval from the Sponsor prior to publishing information from this trial. The Sponsor must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

17.8. Financial Disclosure

Investigators who participate on this study will be required to provide the sponsor and/or its designees financial disclosure documentation as required per regulatory requirements. Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54).

17.9. Compliance with Law, Audit, and Debarment

By signing this protocol, the Investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The Investigator agrees not to seek reimbursement from participants, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the Investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate trial documentation in compliance with GCP standards and applicable federal, state, and local laws, rules, and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the Investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The Investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The Investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, Investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the Investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine

the minimum retention period and notify the Investigator when documents may be destroyed. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The Investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

ICH GCP guidelines recommend that the Investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The Investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The Investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

17.10. Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. KALLYOPE, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. KALLYOPE entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the Investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

17.11. Confidentiality

17.11.1. Confidentiality of Data

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the Investigator, except to the extent

that it is included in a publication as provided in the Publications section (Section 17.7) of this protocol.

17.11.2. Confidentiality of Subject Records

By signing this protocol, the Investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. The subject is informed about this process within the Informed Consent Form. Participants will be identified in CRFs and other documents submitted to the Sponsor only in a pseudonymized form (eg, by a subject number and/or birth year, but not by name).

By signing this protocol, the Investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules, and regulations.

17.11.3. Confidentiality of Investigator Information

By signing this protocol, the Investigator recognizes that certain personal identifying information with respect to the Investigator, and all sub-Investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.
5. financial information such as the declaration of financial interests, if applicable, and other financial information collected for the purpose of payment and reporting of payments in connection with the conduct of trials.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates, and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the Investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other Investigators. By signing this protocol, the Investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between Investigators, the Sponsor may share an Investigator's name and contact information with other participating Investigators upon request.

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19. APPENDICES

APPENDIX A. MANAGEMENT OF PARTICIPANTS WITH ELEVATED LIVER ENZYMES (ALT OR AST >/=3X ULN)

If baseline ALT/AST is normal (below the laboratory ULN), increases to ≥3X ULN are defined as clinically significant in this study. If baseline ALT/AST is elevated (> the laboratory ULN), increases that are both ≥3X ULN ***and*** ≥2X baseline are defined as clinically significant in this study. The Investigator will review safety labs and determine if an ALT/AST meets either of these thresholds. In studies where a central laboratory is used, the central lab will also alert the Investigator if these thresholds are met.

When a randomized subject who is receiving IMP has an ALT or AST elevation beyond these thresholds, the Investigator should select the appropriate set of instructions (A or B below), depending on 1. whether the baseline (pre-dose Day 1) ALT/AST value is normal or elevated, 2. the magnitude of ALT/ALT elevation, 3. the presence or absence of symptoms of potential liver injury, and 4. whether there is a corresponding increase in bilirubin. **Note:** ALT and AST should be evaluated against these criteria independently.

A. Criteria for starting close observation: If the criteria noted here are met and there is no immediately obvious alternate cause of the ALT/AST elevation, **close observation (see below) must initiate.** IMP dosing may continue **if** no criteria for dosing interruption are met (see B below).

If the participant's baseline (predose Day 1) ALT/AST value is normal (≤ lab ULN)

- ALT/AST is ≥3X the ULN

If the participant's baseline (predose Day 1) ALT/AST value is elevated (> lab ULN)

- ALT/AST is ≥3X the ULN **and** ≥2x baseline.

B. Criteria for interrupting IMP administration: If **any** of the criteria noted here are met and there is no immediately obvious alternate cause of the ALT/AST elevation, **IMP dosing must be interrupted, and close observation (see below) must initiate, unless already ongoing.** IMP dosing may **not** resume unless/until criteria for resumption (see below) are met and both the investigator and the Sponsor medical monitor agree this is appropriate.

If participant's baseline (predose Day 1) ALT/AST value is normal (≤ lab ULN)

1. ALT or AST is ≥ 3X ULN plus any of the following:
   - Total bilirubin is ≥ 2X ULN* *or*
   - INR is >1.5** *or*
   - There are symptoms of potential liver injury (ie. severe fatigue, nausea, vomiting, and/or RUQ pain
2. ALT or AST is ≥ 8X ULN
3. ALT or AST is ≥ 5X ULN for ≥ 2 weeks

If participant's baseline (predose Day 1) ALT/AST value is elevated (> lab ULN)

1. ALT or AST is ≥ 3X ULN **and** ≥2X baseline plus any of the following:

- Total bilirubin is ≥ 2X ULN* *or*
- INR is >1.5** *or*
- There are symptoms of potential liver injury (ie. severe fatigue, nausea, vomiting, and/or RUQ pain

2. ALT or AST is ≥ 8X ULN
3. ALT or AST is ≥ 5X ULN **and** ≥3X baseline for ≥ 2 weeks

*If a participant has Gilbert's syndrome, a direct bilirubin ≥2X baseline will be used instead of total bilirubin.

**INR criteria is not applied if a participant is on therapeutic anticoagulation.

Criteria for considering resumption of IMP after interruption:

If any of these criteria for interruption of IMP are met, dosing may **not** resume unless/until all the following criteria are met:

1. Another etiology for the abnormal liver biochemistries leading to IMP interruption (e.g., active hepatitis with specific etiology demonstrated, cholecystitis, biliary obstruction) is established ***and***
2. Liver biochemistries have normalized or returned to ~ baseline for ≥2 weeks ***and***
3. The participant is able and willing to undergo close observation after resumption of IMP ***and***
4. Both the investigator and the Sponsor medical monitor agree that resumption of IMP is appropriate.

Close observation must be initiated at the resumption of IMP. Close observation may stop if liver biochemistries have remained normal or at ~baseline for ≥2 weeks ***and*** both the investigator and the Sponsor medical monitor agree this is appropriate.

Close observation

Close observation includes liver biochemistry monitoring and assessment of etiology as detailed below. **If monitoring requirements cannot be met for any reason, IMP dosing must be interrupted.**

Monitoring

- Repeat testing must occur within 48-72 hours. This should include liver biochemistries (ALT, AST, alkaline phosphatase, GGT, total bilirubin, INR) and creatinine phosphokinase (CPK)**.**
- Liver biochemistries (ALT, AST, alkaline phosphatase, GGT, total bilirubin, INR) should be repeated at least twice weekly.
  - Frequency can decrease to once weekly with approval of the Sponsor medical monitor if abnormalities are stable for ≥2 weeks.
  - Close monitoring may stop if abnormalities have normalized or returned to ~ baseline for ≥4 weeks, if both the investigator and the Sponsor medical monitor agree this is appropriate.
  - **Dosing must be interrupted if any criteria for interruption (see B above) are met.**

Etiology assessment

- **Questions to assess etiology:** Investigate potential causes for the subject's elevated liver enzymes using the questions below. Answers to questions should be recorded in the subject's source documents and appropriate eCRFs.

  1. Has the subject recently:
     a. Had a change in his/her pattern of alcohol use?
     b. Administered an illegal drug(s)?
     c. Been exposed to a chemical agent or other environmental toxin?
     d. Consumed any unusual food (e.g., mushrooms), seasonal foods, or initiated treatment with new herbal/nutritional supplements?
     e. Initiated a new diet regimen, started a rigorous exercise program, or experienced any form of severe physical exertion?
     f. Traveled to another country or region?
  2. Does the subject have a relevant concomitant illness (e.g., cholelithiasis, hepatitis, etc.) or has the subject had potential exposure to viral hepatitis (transfusion, tattoo, new sexual partner)?
  3. Does the subject have a relevant medical history (e.g., autoimmune disorder, cancer, Gilbert's syndrome, obesity, Wilson's disease, NASH, alcohol or infectious hepatitis, biliary tract disease, hemochromatosis)?
  4. Has the subject:
     a. recently been treated with a concomitant medication(s) with demonstrated or suspected effects on the liver (e.g., acetaminophen, amiodarone, aspirin, chlorpromazine, dantrolene, erythromycin, halothane, isoniazid, methyldopa, nitrofurantoin, oxyphenisatin, perhexiline maleate, phenytoin, propylthiouracil, rifampin, sulfonamides, tetracyclines)?
     b. initiated treatment with another new medication?

- **Additional Laboratory/Imaging Evaluations to assess etiology:** In participants for whom an etiology for the abnormal liver enzymes is unknown or whose elevated liver enzymes persist for >1 week:

  1. Consider performing serologic tests including: (a) Hepatitis A (Immunoglobulin M, IgM); (b) Hepatitis B (surface Antigen (Ag) and core IgM); (c) Hepatitis C (antibody); (d) Hepatitis E (Immunoglobulin G (IgG) and IgM). Obtain consent prior to testing, if required locally. Additional evaluations may be performed at the discretion of the Investigator.
  2. Consider an ultrasound of the subject's RUQ and additional scans [endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) if needed].

- Refer to the FDA Guidance for Industry on pre-marketing clinical evaluation for drug-induced liver injury (https://www.fda.gov/media/116737/download) for additional guidance on assessment of etiology.

APPENDIX B. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Further Details and Clarifications on the AE Definition

The following events are NOT considered Adverse Events

- Stable chronic conditions that are present prior to clinical trial entry and do not worsen. These will be accounted for in the subject's medical history.
- Laboratory values that are abnormal but not of clinical significance. This includes a laboratory re-test and/or continued monitoring of an abnormal value. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of a laboratory or ECG abnormality is not considered an AE.
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic surgery or elective surgery or social/convenience admissions)

APPENDIX C. PHQ-9 DEPRESSION SCALE

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

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 fidgety 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 in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

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
☐	☐	☐	☐