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K757 and K833 multiple-dose study in healthy subjects

Submission date 06/02/2024	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 21/02/2024	**Overall study status** Completed	
Last Edited 10/07/2024	**Condition category** Other	

Plain English summary of protocol

Background and study aims
K-757 and K-833 are novel gut-restricted small molecules which are full agonists of the G-protein coupled receptor 40 (GPR40) and G-protein coupled receptor 119 (GPR119), respectively, that are being investigated as oral treatments for weight loss. This is a randomized, double-blind (sponsor open), placebo-controlled, 14-day multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of a combination of K-757 and K-833 in healthy volunteers.

Who can participate?
Healthy volunteers between 18 to 55 years of age

What does the study involve?
Participants are randomly allocated in a 3:1 ratio to receive the active drug or a placebo. A review of safety, tolerability, and available PK data occurs before the administration of the next dose level in each subsequent panel. The study phases are comprised of Screening (up to 28 days before the first dose of the study drug), Treatment, and Follow-Up Periods (about 14 days after the last dose). The total duration of the study for each participant was about 8 weeks. Safety and tolerability are assessed through physical examinations, vital sign assessments, 12-lead electrocardiograms (ECG), clinical laboratory assessments (blood chemistry and hematology biomarkers), and the collection of adverse events (AEs). Plasma (blood) is obtained for PK and PD assessments pre-dose and for up to 72 hours after the last dose on Day 14.

What are the possible benefits and risks of participating?
There are no known health benefits to the healthy volunteers participating in the study. Participants were consented before participation and received an ethics-approved stipend. Risks to participation were defined in the informed consent and included adverse events (the most notable one related to abdominal discomfort).

Where is the study run from?
Kallyope Inc. (USA)

When is the study starting and how long is it expected to run for?
May 2022 to December 2022

Who is funding the study?
Kallyope Inc. (USA)

Who is the main contact?
Annemarie Vance, annemarie@kallyope.com

Contact information

Type(s)
Principal investigator

Contact name
Dr Rajkumar Chetty

Contact details
22-24 Lisburn Road
Belfast
United Kingdom
BT9 6AD
+44 (0)7828743979
rajkumar.chetty@celerion.com

Type(s)
Public

Contact name
Ms Annemarie Vance

Contact details
430 E 29th St #900
New York
United States of America
10016
+1 (908) 377-6454
annemarie@kallyope.com

Type(s)
Scientific

Contact name
Dr Brett Lauring

Contact details
430 E 29th St #900
New York
United States of America
10016

+1 9083776454
brett@kallyope.com

Additional identifiers

Clinical Trials Information System (CTIS)
2022-001578-78

Integrated Research Application System (IRAS)
1005721

Protocol serial number
K-757 P003-02

Study information

Scientific Title
A multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of combination K-757 and K-833 in healthy volunteers

Study objectives
To characterize the safety and tolerability of multiple oral doses of the combination of K-757 and K-833 in healthy subjects

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 27/07/2022, Fast track REC (Holland Drive, Newcastle, NE2 4NQ, United Kingdom; +44 (0)207 104 8012; fasttrack.rec@hra.nhs.uk), ref: 22/FT/0084

Primary study design
Interventional

Study design
Randomized double-blind (Sponsor-open) placebo-controlled multiple-ascending-dose study

Study type(s)
Safety

Health condition(s) or problem(s) studied
Healthy subjects

Interventions
This is a randomized, double-blind (sponsor open), placebo-controlled multiple ascending doses of combination K-757 and K833. Site staff and study participants were blinded to the treatment assignment. The Sponsor and unblinded pharmacists at the Phase I clinic were unblinded to treatment assignment. 12 subjects per panel were enrolled in Panels A, B and C. Subjects were randomized (3:1) to receive the active drug or a placebo. Dose escalation proceeded for each panel in sequential form (Panel A initiated in advance of Panel B and Panel B initiated in advance

of Panel C).
1. Panel A consisted of oral administration in the clinic of K-833 100 mg x 14 days QD or matching placebo.
2. Panel B consisted of oral administration in the clinic of K-757 20/40 mg (K-757 20 mg was administered on Days 1 through 5, followed by 40 mg on Days 6 through 14.) + K-833 100 mg x 14 days QD or matching placebo.
3. Panel C consisted of oral administration in the clinic of K-757 30/60 mg (titration of K-757 30 mg was administered on Days 1 through 5, followed by 60 mg on Days 6 through 14.) + K-833 100 mg x 14 days QD b or matching placebo.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
K757, K833

Primary outcome(s)
Safety measures consisted of the collection of the following parameters:
1. Physical examination findings at screening, check-in, Day 13, and the 14-day post last dose follow-up visit
2. Vital signs collection of blood pressure, heart rate, and body temperature at Check in, Day 1 pre-dose, 2, and 6 h post dose; Days 3, 5, 8, and 11 pre-dose, Day 13 check-in; Day 14 pre-dose, 2, 6, and 24 h post-dose and the 14-day post last dose follow up visit.
3. 12-lead electrocardiograms (QTc) at Check in, Day 1 pre-dose, 2, and 6 h post dose; Days 3, 5, 8, and 11 pre-dose; Day 14 pre-dose, 2, 6, and 24 h post-dose
4. Blood chemistry and hematology at Check in, Day 1 8 and 24 h post-dose; Days 3, 5, 8, and 11 pre-dose; Day 13 check-in; Day14 pre-dose, 8, 24 h post-dose, and the 14-day post last dose follow up visit.
5. Collection of adverse events (AEs) following the signed information consent through the 14-day post last dose follow-up visit.

Key secondary outcome(s)
1. Pharmacokinetics measured by plasma PK parameters of K-757 and K-833 including: AUC0-∞, AUC0-last, Cmax, Tmax, t½, and volume of distribution (Vdss) and clearance (Cl). Timepoints included:
1.1. Day 1: 2 h pre-dose, 1, 2, 3, 4, 6, 8-, 12, 16, and 24-hours post-dose
1.2. Days 3, 5, 8, 11, 13 (pre-meal/predose)
1.3. Day 14: pre-dose, 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, 48, and 72 h post-dose
2. Pharmacodynamic measures consisted of plasma levels and changes from baseline of glucagon-like peptide 1 (GLP-1), peptide YY (PYY), glucose-dependent insulinotropic polypeptide (GIP) and other PD biomarkers (if available). Timepoints included:
2.1. Day 1: 2 h pre-dose 1, 2, 3, 4, 6, 8, 11, 12, 14, 16, and 24 h post dose
2.2. Days 3, 5, 8, 11, 13 (pre-meal/predose)
2.3. Day 14: premeal/pre-dose, 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, 48, and 72 h post-dose

Completion date
16/12/2022

Eligibility

Key inclusion criteria
1. Understand the trial procedures and agree to participate by providing written informed consent
2. Be willing and able to comply with all trial procedures and restrictions
3. Be healthy between 18 to 55 years of age, inclusive, at the Screening Visit
4. Have a Body Mass Index (BMI) ≥19.0 and <30.0 (kg/m2) at the Screening Visit
5. Be a nonsmoker who has not used tobacco or nicotine-containing products (e.g. nicotine patch) for at least 3 months before administration of the initial dose of the trial drug and agrees to abstain from smoking tobacco or the use of nicotine-containing products while on study
6. Be judged to be in good health by the Investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the Screening Visit and before administration of the initial dose of trial drug
7. Meet the following birth control requirements:
7.1. Is a male subject who agrees to use an appropriate method of contraception, including a condom with or without spermicidal cream or jelly, from the first dose of the study drug until 14 days after the last dose of the study drug. A male subject who had a vasectomy procedure must follow the same restrictions as a non-vasectomized man.
7.2. Is a male subject who agrees not to donate sperm from the first dose of the study drug until 14 days after the last dose of the study drug.
OR
7.3. Is a female who is of non-childbearing potential defined by at least 1 of the following criteria:
7.3.1. Postmenopausal (aged >45 years and with a minimum of 12 months of spontaneous amenorrhea with a Screening serum follicle-stimulating hormone level >30 mIU/mL).
7.3.2. Post hysterectomy, bilateral oophorectomy or bilateral salpingectomy, based on the subject’s recall of their medical history.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
All

Total final enrolment
36

Key exclusion criteria

1. Has participated in another investigational study within the following time period: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer or based on local regulations) before the Screening Visit. The window will be derived from the date of the last study procedure and/or AE related to the study procedure in the previous study to the Screening Visit of the current study.
2. Is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the Sponsor or study site
3. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food
4. Has a known hypersensitivity or contraindication to any component of K-757, K-833, related compounds or its excipients
5. Has a positive alcohol or drug screen at Screening or admission
6. Has a positive pregnancy test
7. Is a lactating/nursing female
8. Has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency antibody, at the Screening Visit. Note: Subjects 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.
9. Subject does not meet study site COVID-19 admission/study participation restrictions or has a fever (>38oC)
10. Had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the Screening Visit.
11. Is unable to refrain from the use of prescription or non-prescription drugs including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the first dose of study medication for each dosing period until two days after the last dose of study medication in each Panel, unless in the opinion of the Investigator and Kallyope Medical Monitor the medication will not interfere with the study procedures or compromise subject safety. Paracetamol (≤2 grams [g] per day) and COVID vaccination are acceptable.
12. Has regular consumption of alcohol within 6 months before screening (>14 drinks/week 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) or use of soft drugs (such as marijuana) within 3 months before Screening, or hard drugs (such as cocaine) within 6 months before Screening
13. Is unwilling or unable to refrain from study alcohol restrictions: Subjects will refrain from consuming alcohol from 7 days before the first and until the last PK blood sample has been collected and 7 days before the follow-up visit. At all other times, alcohol consumption is limited to no more than approximately 14 drinks/week 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.
14. Is unable or unwilling to refrain from consumption of Seville oranges, grapefruit, grapefruit juice, pomelos, exotic citrus fruits, and grapefruit hybrids from 2 weeks before administration of the first dose of study drug, throughout the study, and until the Follow-up Visit
15. Unwilling to refrain from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard) or charbroiled meats beginning approximately 48 hours before admission to the clinic, if possible (if the subject has consumed any of these items before admission, the subject may be included in the study and the food and amount should be recorded in the source documents). Subjects will not consume any of the above foods while in the clinical research unit and until the post-study visit.
16. Unable to refrain from g caffeinated beverages 24 hours before check-in and 24 hours post-last dose

17. Substance abuse disorder
18. Previous major psychotic disorder
19. Corrected QT interval to Fridericia's formula (QTcF) >450 milliseconds (msec) for males and >470 msec for females at screening and on Day 1 predose
20. Systolic blood pressure >140 mmHg and/or diastolic blood

Date of first enrolment
17/08/2022

Date of final enrolment
14/11/2022

Locations

Countries of recruitment
United Kingdom

Northern Ireland

Study participating centre
Celerion (GB) Ltd
22-24 Lisburn Rd
Belfast
United Kingdom
BT9 6AD

Sponsor information

Organisation
Kallyope (United States)

ROR
https://ror.org/01qvcpq30

Funder(s)

Funder type
Industry

Funder Name
Kallyope

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Stored in non-publicly available repository