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Safety, tolerability, pharmacokinetics and pharmacodynamics of KNS366

Submission date	**Recruitment status**	[X] Prospectively registered
21/10/2022	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
22/12/2022	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
29/01/2024	Other	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
KNS366 (the study medicine) is an experimental treatment for preventing damage to the kidneys caused by heart surgery. It is hoped that the study medicine will work by blocking a protein known as KMO. KMO makes a substance called 3HK which is harmful in high levels and can damage organs such as the kidneys. People who've had heart surgery sometimes have kidney damage caused by increased blood levels of 3HK. By blocking KMO, it is hoped that the study medicine will protect patients having heart surgery from kidney damage. This is a two-part study (Parts A and B). The researchers will test single doses of the study medicine in Part A and a single dose followed by a continuous slow injection in Part B. They aim to find out the study medicine's side effects, blood levels, and whether it reduces the blood levels of 3HK. The study medicine has never been given to humans before, so in each part they will start with a low dose and increase the dose as the study progresses.

Who can participate?
Healthy men and women aged 18–55 years

What does the study involve?
In Part A, two groups of up to 12 participants will have three study sessions. In each session they' ll have a single dose of the study medicine or placebo as a slow injection over 30 minutes. In Part B, up to four groups of eight participants will have a single dose of the study medicine or placebo injected into a vein over 30 minutes, followed by a continuous slow injection for 7 days. Participants will take up to 9 weeks to finish the study. They'll make up to two outpatient visits and will stay on the ward three times for four nights each in part A or once for 11 nights in part B.

What are the possible benefits and risks of participating?
The researchers don't expect the participants to get any medical benefit from the study medicine. The screening tests may be of benefit if an important medical problem is found, but they could reveal something people would prefer not to know about.
To date, no humans have taken KNS366, so its side effects are unknown. The highest dose in this study has more than a 25-fold safety margin from the highest repeated dose tested in laboratory animals that was considered safe.
The researchers will monitor the participants closely and won't increase the dose of KNS366

unless the previous dose causes no important side effects. If a participant is withdrawn, they are asked to consent to a final follow-up.
During their stay, participants must follow HMR's 'house rules'. An information leaflet is given to volunteers at screening.
If a participant, or their partner, becomes pregnant during the study, they are asked to contact their GP about the pregnancy and this is documented using a generic form.
If the researchers find any medically important problem at screening, the physician will tell the participant in person and pass on the results to the participant's GP.
The researchers will contact the participants' GPs to inform them that their patient has volunteered to take part in a study and provide the GP with a study summary. For first-in-human studies, they ask the GP if there's any medical problem that might compromise the volunteer's safety during the study.
Please refer to the informed consent form for details on procedural risks, lifestyle and fasting restrictions, COVID-19 vaccine restrictions, and contraception requirements.

Where is the study run from?
HMR, London (UK)

When is the study starting and how long is it expected to run for?
October 2022 to January 2024

Who is funding the study?
Kynos Therapeutics Ltd (UK)

Who is the main contact?
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Contact information

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Scientific

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Clinical Trials Information System (CTIS)
2022-003179-41

Integrated Research Application System (IRAS)
1006658

Protocol serial number
KNS366_002

Study information

Scientific Title
A randomized, double-blind, placebo-controlled dose escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single (intravenous infusion) and multiple (continuous intravenous infusion over 7 days) doses of KNS366 in healthy adult participants

Study objectives
Primary objective:
To assess the safety and tolerability of KNS366 administered as a single intravenous (IV) infusion (Part A) and as an IV loading dose followed by continuous IV infusion over 7 days (Part B) in healthy participants.

Secondary objectives:
1. To find out the levels of KNS366 in the bloodstream, and how long the body takes to process and remove it.
2. To find out the effects of KNS366 on kynurenine 3 monooxygenase (KMO) inhibition in healthy participants.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/12/2022, London-Westminster (Meeting held by video-conference via Zoom; +44(0) 207 104 8066, (0)207 1048236; westminster.rec@hra.nhs.uk), ref: 22/LO/0757

Primary study design
Interventional

Study design
Randomized double-blind parallel-group cross-over placebo-controlled trial

Study type(s)
Other

Health condition(s) or problem(s) studied
Healthy volunteers. The intended indication for the product under development is damage to secondary organs during a systemic inflammatory response.

Interventions
The study is in two parts: Part A (single doses) and Part B (a single dose followed by a continuous slow injection).

In Part A, up to 24 participants will be enrolled in two groups of up to 12 (called Groups A1 and A2). Participants will have three study sessions. In each session, they will receive a single dose of KNS366 or placebo by a slow injection into a vein. The dose participants receive will depend on their group; we plan to increase the dose as the study progresses. The researchers plan to give the following doses: Group A1 will receive 0.05 mg in their first study session, 0.25 mg in their second session, and 1 mg in their third session; Group A2 will receive 2.5 mg in their first study session, 7.5 mg in their second session, and 20 mg in their third session. Subsequent higher doses will only be tested if the previous dose causes no important side effects. At each dose level participants will be randomized to KNS366 or placebo in a ratio of 2:1.

In Part B, up to 32 participants will be enrolled in up to four groups of eight (called Groups B1–B4). Participants will have a single study session. They will receive KNS366 or placebo, first as a single dose given by injection over 30 minutes, and immediately after that as a continuous injection over 7 days. The dose participants receive will depend on their group. Doses will be decided after reviewing the results from earlier groups, including Part A of the study. At each dose level participants will be randomized to KNS366 or placebo in a ratio of 3:1.

Participants will be dosed in the clinical unit and will remain on the ward for follow-up until 3 days after their dose in each study session in Part A, and until 3 days after the end of injection in Part B. They will have a final follow-up about 4–11 days after their last dose in Part A, and at about 3 and 7 weeks after discharge from the ward for Part B.

A computer program will decide randomly whether a participant takes KNS366 or placebo.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
KNS366

Primary outcome(s)
1. Safety and tolerability of KNS366, including vital signs (blood pressure, heart rate, tympanic temperature, and respiratory rate), 12-lead electrocardiogram (ECG), physical examination, laboratory safety tests (haematology, clinical chemistry, and urinalysis), and local tolerability assessments, will be measured regularly by standard Phase I unit monitoring, at screening, Day -1 to Day 4 (Part A), Day -1 to Day 11 (Part B), and at follow-up visits.
2. Treatment-emergent adverse events (TEAEs) to assess tolerability of KNS366 will be collected by often asking volunteers how they are feeling, from the start of the trial until follow-up.
3. In Part B only, mood and cognition will be assessed using the Columbia-Suicide Severity Rating Scale questionnaires and cognitive assessments will be performed to evaluate cognitive and behavioural effects at screening, Days -1, 3, 7 and 11

Key secondary outcome(s)
1. Pharmacokinetic parameters of KNS366:
1.1. Plasma concentrations of KNS366 after single and repeated doses will be measured by liquid chromatography coupled with tandem mass spectrometry at the following timepoints: between Day 1 and Day 4 in each session in Part A; and between Day 1 and Day 11 in Part B.
1.2. Pharmacokinetics of KNS366 in urine after single and repeated doses will be measured by liquid chromatography coupled with tandem mass spectrometry. Urine samples will be taken at the following timepoints: on Day -1 to Day 4 in each session in Part A; before dosing and from Day 3 to Day 4 in Part B.
2. Pharmacodynamic parameters of KNS366: Blood samples for assay of kynurenine and metabolites will be taken on Day 1 to Day 4 in each session in Part A; and between Day 1 and Day 11 in Part B.

Completion date
23/01/2024

Eligibility

Key inclusion criteria
1. Male or female volunteers aged 18-55 years
2. Body mass index (BMI) of 18.5 to 32 kg/m²
3. Body weight >50 kg
4. Deemed healthy on the basis of medical history, clinical laboratory test results, vital sign measurements, ECG, and physical examination
5. Agree to follow the contraception requirements of the trial
6. Male participants must refrain from donating sperm during the treatment period and for at least 90 days following the last dose
7. Able to give fully informed consent

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
40

Key exclusion criteria
1. Not healthy (clinically significant abnormality in our screening tests, which include ECG, vital signs, physical examination, and laboratory safety tests of blood and urine)
2. A current or chronic history of liver disease or known hepatic or biliary abnormalities; history of or current evidence of cardiac arrhythmia, structural or mechanical heart disease, or cardiac conduction defect; a history or current evidence of depression, bipolar, suicidal ideation and behaviour; positive tests for hepatitis B and/or C, or human immunodeficiency virus (HIV)
3. Have used any prescription or over-the-counter medications (except paracetamol [up to 2 g per day]), including herbal or nutritional supplements, within 7 days (or 14 days if the medication is a potential enzyme inducer) before the first dose of study medicine; consumed grapefruit or grapefruit juice, Seville oranges or Seville orange-containing products (e.g., marmalade), exotic citrus fruits, red wine, or fruit juices from 7 days before the first dose of study medicine; consumed caffeine- or xanthine-containing products within 24 hours before the first dose of study medicine.
4. Have had a serious reaction to any medicine or have certain food allergies
5. Current smoker or used nicotine containing products within 6 months of screening; a history of alcohol abuse or drug addiction; strenuous activity within 48 hours of the first dose
6. Donated blood or have taken part in a study of an experimental medicine in the 3 months before first admission to the unit, or plan to do so in the 3 months after this study
7. Pregnant or lactating

Date of first enrolment
10/01/2023

Date of final enrolment
23/11/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
HMR
Cumberland Avenue
London

United Kingdom
NW10 7EW

Sponsor information

Organisation
Kynos Therapeutics Ltd

Funder(s)

Funder type
Industry

Funder Name
Kynos Therapeutics

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and analysed during the current study are not expected to be made available due to the study being a Phase I clinical trial in healthy volunteers. At this stage in the development of the study medicine, the study data are highly commercially confidential. They will be shared with others only as the sponsor regards as appropriate.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No