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A 2-part study in healthy volunteers to assess the safety and tolerability of the test medicine and explore how it is taken up by the body following single and multiple doses with an optional third part and to compare how the test medicine is taken up by the body when compared to an existing formulation (recipe)

Submission date
26/10/2022

Recruitment status
No longer recruiting

Registration date
25/11/2022

Overall study status
Completed

Last Edited
13/07/2023

Condition category
Urological and Genital Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
The Sponsor is developing a new test medicine, UNI-494, for the potential treatment of acute kidney injury (AKI). AKI is a sudden loss of kidney function over hours or days, where the kidneys stop working properly, causing loss of kidney function, from relatively minor to complete kidney failure.

This up to three-part, First-in-Human healthy volunteer study will try to identify the safety and tolerability of single and multiple doses of the test medicine. It may also compare the test medicine to the licenced product, nicorandil, which is available for doctors to prescribe (optional).

Who can participate?
This study will take place at one non-NHS site, enrolling up to 64 male and female (not of childbearing potential) volunteers aged between 18 and 55 years of age.

What does the study involve?
In Part 1, 32 volunteers will be split into 4 groups and will receive a single dose of the test medicine or placebo, at different dose levels. One group may be required to return for an additional study visit to receive a single dose of the test medicine in the fed state, or at a higher dose level.
In Part 2, 20 volunteers will be split into 2 groups and will receive a single oral dose of the test medicine or placebo once or twice a day for 5 days in either the fed or fasted state.

Part 3 is optional, and if utilised, 12 volunteers in a single group will receive a single oral dose of the test medicine and a single oral dose of the reference product (nicorandil), one at each study visit.

In Part 1 and Part 3, volunteers will be discharged on Day 3 of each study and in Part 2, volunteers will be discharged on Day 8.
In all parts, volunteers will return to the clinic for a follow-up visit 7 to 10 days after final dose.

Volunteer's blood and urine will be taken throughout the study for analysis of the test medicine and for their safety.

Volunteers are expected to be involved in this study for 7 (Part 1 or 2) or 6 (Part 3) weeks from screening to the follow up visit.

What are the possible benefits and risks of participating?
Benefits:
Participants will get no medical benefit from taking part in this study. We hope that the development of a product to improve the treatment of acute kidney injury will be of benefit to patients with this condition.
Risks:
1. As this is a Phase I study, the most relevant population is healthy volunteers, as recommended by the US FDA and the European Medicines Agency (EMA). Fertility and teratology studies with UNI-494 have not yet been conducted; therefore, females of childbearing potential will not be enrolled in this study. Based on the listed considerations and target population female subjects of non-childbearing potential (WONCBP) and healthy male subjects, aged 18 to 55 years are considered suitable for this study.
2. There is always a risk that the stipend in healthy volunteer studies could represent coercion. The time spent in the clinic, travel, inconvenience and other expenses factor in calculating the stipend. Perception of risk is not considered in this calculation.
3. When investigating new medicines there is always a risk of unexpected side effects and occasionally allergic reactions. Volunteers will be closely monitored during the study.
4. Volunteers may experience side effects from the test medicine in this study. Full information on possible side effects is provided to volunteers in the Participant Information Sheet and Informed Consent Forms.
5. There will be an extended period of fasting for the volunteers taking part in this study. To ensure an adequate fluid intake, the volunteers will be allowed water until one hour pre- and post-dose, then ad libitum fluids will be allowed. Volunteers will be monitored for signs of dehydration and fatigue.
6. Blood samples will be collected during the study. Collection of these samples can cause soreness and bruising of the arms but these problems usually clear up within a few days to a few weeks.
7. ECG stickers on volunteers' chests and limbs may cause some local irritation and may be uncomfortable to remove but volunteers will be closely monitored to ensure any local irritation does not persist.
8. The test medicine could affect the way a volunteer's body reacts to direct sunlight. Once dosed, volunteers will be advised to minimise exposure to sunlight for example by spending a reduced amount of time outdoors/remaining inside the clinical unit during the residential periods of the study. They will also be advised not to use sunbeds. This restriction will be advised from first dose until 5 days post-final dose

Where is the study run from?
Quotient Sciences Limited (UK)

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

Who is funding the study?
Unicycive Therapeutics Inc. (USA)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2022-003223-17

IRAS number
1006558

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
UNI-494-101, IRAS 1006558

Study information

Scientific Title
A two-part phase 1 study to assess the safety, tolerability and pharmacokinetics of UNI-494 with an optional third-part to assess the relative bioavailability compared to nicorandil in healthy male and female subjects

Acronym
QSC207400

Study objectives
Primary objectives:
Part 1: To assess the safety and tolerability of single ascending doses (SAD) of UNI-494 Capsule administered to healthy male and female subjects
Part 2: To assess the safety and tolerability of multiple ascending doses (MAD) of UNI-494 Capsule administered to healthy male and female subjects
Part 3 (optional): To assess the relative bioavailability (the proportion of the active ingredient that enters the body compared in two forms) of nicorandil following dosing of UNI-494 Capsule compared to the nicorandil tablet in the fasted state

Secondary objectives:
Part 1:
1.1. To characterise the pharmacokinetics (what the body does to the test medicine, PK) of UNI-494, nicorandil and 1-cyclohexylethylamine after SAD of UNI-494 Capsule administered to healthy male and female subjects
1.2. To assess the PK of UNI-494 Capsule at the same dose in the fed versus the fasted state in healthy male and female subjects (optional)
Part 2: To characterise the plasma PK of UNI-494, nicorandil and 1-cyclohexylethylamine after MAD of UNI-494 Capsule administered to healthy male and female subjects
Part 3 (optional):
3.1. To characterise the PK of UNI-494, nicorandil and 1-cyclohexylethylamine after single dose of the nicorandil marketed product administered to healthy male and female subjects
3.2. To provide further safety and tolerability data of UNI-494 at the selected dose

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/12/2022, North East - York REC (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 2071048079; york.rec@hra.nhs.uk), ref: 22/NE/0189

Study design

Parts 1 and 2 are double-blind placebo controlled, Part 3 is an open-label two-way cross-over study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Other

Participant information sheet

Health condition(s) or problem(s) studied
Acute Kidney Injury (AKI)

Interventions
Parts 1 and 2 are randomised, double-blind and placebo controlled assessing single and multiple ascending doses.
Optional Part 3 is a randomised open-label assessment comparing the test medicine to a reference product.
Volunteers are expected to be involved in this study for seven (Part 1 or 2) or six (Part 3) weeks from screening to the follow up visit.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
UNI-494, nicorandil

Primary outcome measure
Safety and tolerability will be assessed throughout the study, from dosing to follow up visits (Day 1 to Day 11 in Part 1 and Part 3, Day 1 to Day 15 in Part 2)
Part 1: To provide safety and tolerability information for UNI-494 by assessing: incidence of adverse events (AEs), physical examination findings and change from baseline for vital signs, electrocardiograms (ECGs), and laboratory safety tests
Part 2: To provide safety and tolerability information for UNI-494 by assessing: incidence of AEs, physical examination findings and change from baseline for vital signs, ECGs, and laboratory safety tests

Part 3 (optional): Nicorandil relative bioavailability (Frel) based on a within subject comparison for Cmax, AUC(0-last) and AUC(0-inf) of the UNI-494 Capsule compared to the nicorandil marketed product (tablet) through measurement of plasma samples taken in Part 3 from dosing to discharge, across both periods.

Secondary outcome measures
Pharmacokinetic parameters will be measured using analysis of plasma samples taken from pre-dose to 48 hours post-dose in all Parts. Relative bioavailability will be assessed through measurement of plasma samples taken in Regimen E, should this be utilised. Samples will be taken from pre-dose to 48 hours post-dose in both periods. Safety and tolerability will be assessed throughout the study, from dosing to follow up visits (Day 1 to Day 11 in Part 3).

Part 1:
1.1. Following PK parameters for UNI-494, nicorandil and 1-cyclohexylethylamine will be calculated (where possible and appropriate): Tlag, Tmax, Cmax, C24, AUC(0-24), AUC(0-last), AUC (0-inf), AUCextrap, Lambda-z, T1/2, metabolite to parent ratios (MPR) based on AUC and Cmax, CL/F, Vz/F and MRT
1.2. Relative bioavailability based on a within cohort comparison for Cmax, AUC(0-last) and AUC (0-inf) for UNI-494, nicorandil and 1-cyclohexylethylamine following dosing of the UNI-494 capsule in the fed versus the fasted state

Part 2: Following PK parameters for UNI-494, nicorandil and 1-cyclohexylethylamine will be calculated (where possible and appropriate) Tlag, Tmax, Cmax, C24, AUC(0-tau), AUC(0-last), Lambda-z, T1/2, metabolite to parent ratios (MPR) based on AUC and Cmax, accumulation ratios based on Cmax and AUC, CL/Ftau, Vz/Ftau and MRT

Part 3 (optional)
3.1. Following PK parameters for UNI-494, nicorandil and 1-cyclohexylethylamine will be calculated (where possible and appropriate): Tlag, Tmax, Cmax, C24, AUC(0-24), AUC(0-last), AUC (0-inf), AUCextrap, Lambda-z, T1/2, metabolite to parent ratios (MPRs) based on AUC and Cmax, CL/F, Vz/F and MRT
3.2. To provide further safety and tolerability information for UNI-494 by assessing: incidence of AEs, physical examination findings and change from baseline for vital signs, ECGs, and laboratory safety tests

Overall study start date
21/10/2022

Completion date
25/02/2024

Eligibility

Key inclusion criteria
1. Must provide written informed consent
2. Must be willing and able to communicate and participate in the whole study
3. Subjects must be willing and able to swallow multiple capsules
4. Aged 18 to 55 years inclusive at the time of signing informed consent
5. Must agree to adhere to the contraception requirements defined in the clinical protocol
6. Healthy males or healthy females of non-childbearing potential

7. Body mass index (BMI) of 18.0 to 32.0 kg/m² as measured at screening
8. Weight ≥50 kg at screening
9. Must have a normal blood pressure defined as a systolic BP between 100 and 140 mmHg, diastolic BP between 40 and 90mmHg after 5 mins supine
10. No evidence of postural hypotension (defined as a dizziness / light headedness or a drop is systolic BP >20mmHg or drop in diastolic BP >10 mmHg when assessed 3 minutes after standing

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Both

Target number of participants
64

Key exclusion criteria
1. Serious adverse reaction or serious hypersensitivity to any drug or formulation excipients
2. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active
3. History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or gastrointestinal disease, neurological or psychiatric disorder, as judged by the investigator
4. Subjects with a history of cholecystectomy or gall stones
5. Subjects with any past history of gastrointestinal ulceration (e.g. peptic ulcer disease), gastrointestinal haemorrhage, diverticular disease or recent (within 6 months) symptoms of dyspepsia lasting 2 weeks or more
6. Recurrent and recent history of simple faints, vasovagal presyncope/syncope or blackouts
7. Subjects with glucose-6-phosphate dehydrogenase deficiency
8. Subjects with a history of conjunctival or corneal ulceration within the past 12 months.
9. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening
10. Evidence of current SARS-CoV-2 infection
11. Clinically significant abnormal clinical chemistry, haematology or urinalysis as judged by the investigator. Subjects with Gilbert's Syndrome are not allowed
12. Subjects with elevated potassium above the upper limit of the normal reference range
13. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) 1 and 2 antibody results
14. Females of childbearing potential including those who are pregnant or lactating (all female subjects must have a negative highly sensitive urine [or serum] pregnancy test). A woman is considered of childbearing potential unless she is permanently sterile (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) or is postmenopausal (had no menses for 12

months without an alternative medical cause and a serum follicle stimulating hormone [FSH] concentration ≥40 IU/L)
15. Subjects who have received any IMP in a clinical research study within the 90 days prior to Day 1, or less than 5 elimination half-lives prior to Day 1, whichever is longer
16. Subjects who have previously been administered IMP in this study. Subjects who have taken part in Part 1 are not permitted to take part in Parts 2 and 3. Subjects who have taken part in Part 2 are not permitted to take part in Part 3
17. Donation of blood or plasma within the previous 3 months or loss of greater than 400 mL of blood
18. Subjects who are taking, or have taken, any prescribed or over-the-counter drug or herbal remedies (other than up to 4 g of paracetamol per day or established HRT) in the 14 days before study medication administration. COVID-19 vaccines are accepted concomitant medications. Exceptions may apply, as determined by the investigator, if each of the following criteria are met: medication with a short half-life if the washout is such that no PD activity is expected by the time of dosing with IMP; and if the use of medication does not jeopardise the safety of the trial subject; and if the use of medication is not considered to interfere with the objectives of the study
19. Subjects who are using PDE5 inhibitors
20. History of any drug or alcohol abuse in the past 2 years
21. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type)
22. A confirmed positive alcohol breath test at screening or admission
23. Current smokers and those who have smoked within the last 12 months
24. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission
25. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
26. Confirmed positive drugs of abuse test result
27. Male subjects with pregnant or lactating partners
28. Subjects who are, or are immediate family members of, a study site or sponsor employee
29. For Part 1 Cohort SAD 3 and Part 2 only: Subjects who do not agree to eat a high fat breakfast
30. Failure to satisfy the investigator of fitness to participate for any other reason

Date of first enrolment
20/12/2022

Date of final enrolment
25/02/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre

Quotient Sciences Limited
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Sponsor information

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Sponsor type
Industry

Funder(s)

Funder type
Industry

Funder Name
Unicycive Therapeutics Inc.

Results and Publications

Publication and dissemination plan
Internal report
Submission to regulatory authorities
The findings of this Phase I study will be shared with the Sponsor, Unicycive, only. As these findings are confidential due to commercial sensitivity, it is not appropriate to share the results of this study with other researchers at this time.

Intention to publish date
25/02/2025

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to no regulatory requirement to do so.

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