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A study to evaluate the efficacy and safety of inhaled carbon monoxide on kidney function in patients who have received kidney transplants

Submission date
18/05/2023

Recruitment status
Recruiting

Registration date
05/04/2024

Overall study status
Ongoing

Last Edited
05/04/2024

Condition category
Urological and Genital Diseases

[ ] 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 purpose of this study is to determine if inhaled carbon monoxide (iCO) is safe to use as a therapy in people who are receiving a kidney transplant from a deceased donor. Delayed graft function (DGF) is the failure of a transplanted kidney to function immediately following transplantation. When DGF occurs, dialysis is still needed for a period of time after the transplant. The study aims to determine if the risk of DGF developing after surgery can be reduced through the use of iCO, without causing harmful side effects. This research is important because there are currently no effective therapies for the prevention of DGF. Benefits to participating in the study may include improved kidney function after transplant and the generation of new information that could help other kidney transplantation patients in the future.

Who can participate?
Patients aged 18-75 years old who are planned to be kidney-only transplant recipients (from a deceased kidney donor)

What does the study involve?
There will be two parts to the study: Part A, which will be an initial safety trial for the planned iCO dosing regimen, followed by Part B, which will evaluate the safety of iCO as well its efficacy (how well it works) to reduce DGF in patients who have received a kidney transplant from a deceased donor. Study participants will be chosen at random to receive the study drug (inhaled CO) or a control “placebo” (inhaled medical air) on three occasions: Once during the kidney transplant surgery and two further doses 24 and 48 hours after surgery. Participants will be followed up for 3 months after surgery. Outcomes that will be studied will include whether iCO causes any side effects and whether it improves the function of the transplanted kidney. The study will last for approximately one year and participants will have an initial Screening period (duration 7 days), followed by Day 0 (randomization and kidney transplant surgery), Days 1, 2, 3, 7, 14, 28, 56 and 84.

Full visit procedures and inclusion and exclusion criteria are outlined in the study protocol.

What are the possible benefits and risks of participating?
Risks of Inhaled CO Administration
Administration of inhaled CO may cause participants to have headaches or an elevated heart rate (tachycardia)
In cases of overdose, participants may experience nausea, vomiting, seizures, weakness, problems thinking, coma, cardiopulmonary arrest, and death. In other research, these adverse effects have only been observed in doses significantly higher than the study dose. Risk will be minimized by administering a low dose of the study drug to patients for a short period of time. Patients will be closely monitored during iCO administration and routinely observed for signs and symptoms of CO. If CO levels in blood rise above the intended range for an unforeseen reason, the study drug will be stopped until CO levels return to an acceptable range.
There may be other risks of inhaled CO that are currently unknown.
As with any drug, an allergic reaction can occur and participants may experience rash, itching, skin problems, swelling of the face and throat, or trouble breathing.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant
The effect of inhaled CO on a foetus or breastfeeding infant is unknown and may be harmful. We therefore ask all participants of child-bearing potential to use an acceptable method of birth control during the study and for one month after completing the study drug administration.

Risks of Blood Draws
Patients may experience bruising or discomfort at the site where the needle is inserted to collect blood samples. There is also a small risk of infection, lightheadedness, and/or fainting.

Risk of Kidney Biopsy
In many kidney transplant centers, a kidney biopsy is performed as a routine part of the transplant surgery. In this study, a kidney biopsy will be obtained at the time of surgery. The site of the biopsy will be closed with sutures to stop any bleeding. However, there is a small risk of bleeding from the biopsy site at a later time. If this happens, the bleeding usually stops spontaneously, but may rarely require another operation.

Where is the study run from?
Proterris Inc (UK)

When is the study starting and how long is it expected to run for?
May 2023 to February 2027

Who is funding the study?
Proterris Inc (UK)

Who is the main contact?
Dr. Kourosh Saeb-Parsy, Kourosh.saeb-parsy@proterris.com

Contact information

Type(s)
Public, Scientific

Contact name
Dr Kourosh Saeb Cooke

Contact details
20 The Causeway
Bishop's Stortford
United Kingdom
CM23 2EJ
+44 (0) 7713 641416
Kourosh.saeb-parsy@proterris.com

Type(s)
Principal investigator

Contact name
Dr Rajesh Sivaprakasham

Contact details
9 Prescot Street
London
United Kingdom
E1 8PR
+44 (0)7968185510
Rajesh.sivaprakasam@gmail.com

Type(s)
Principal investigator

Contact name
Dr Rajesh Sivaprakasham

Contact details
9 Prescot Street
London
United Kingdom
E1 8PR
+44 (0)7968185510
rajesh.sivaprakasam@nhs.net

Additional identifiers

Integrated Research Application System (IRAS)
1007335

Protocol serial number
PRO-K-001

Study information

Scientific Title
A Phase 2 randomized, prospective, partially double-blind, placebo-controlled trial to evaluate the preliminary efficacy and safety of inhaled carbon monoxide upon kidney function in kidney transplant recipients

Acronym
PRO-K-001

Study objectives
Part A: To generate an initial controlled assessment of safety regarding potential frequently occurring safety events of the planned iCO dosing regimen (Part A), followed by an overall safety assessment of iCO in patients receiving a kidney transplant from a deceased donor (Part B).

Part B: To assess the effect of iCO on the rate of delayed graft function (DGF) in kidney transplant recipients, as defined by the need for at least one dialysis treatment within 7 days of transplant, as well as overall assessment of safety of iCO in kidney transplant recipients.

Part B: To assess the effect of iCO in improving kidney function after transplantation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, ref: 23/WA/0177

Primary study design
Interventional

Study design
Randomized prospective partially double-blind placebo-controlled trial

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Prevention of delayed graft function in kidney transplant recipients

Interventions
Participants will be randomised (3:1 for Part A, and 1:1 for Part B) to receive 3 doses of inhaled CO (iCO) or placebo (medical air), with the aim of achieving (but not exceeding) a peak carboxyhaemoglobin (COHb) concentration of 10% (using an online tool to guide dosimetry). The iCO will be administered for a maximum of 90 minutes at 450 ppm (dose 1) or 300 ppm (doses 2 and 3). Dose 1 will be administered intra-operatively at the time of kidney transplantation via the anesthesia circuit. Doses 2 and 3 will be administered post-operatively via a respiratory mask. Dose 2 will be administered 18-30 hours after dose 1, and; dose 3 will be administered 18-30 hours after dose 2. Participants will be followed for 84 days.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)

Inhaled carbon monoxide

Primary outcome(s)
Primary Outcome Measure (Safety):
Part A and Part B: The safety of iCO will be defined by the incidence of all reported adverse effects (AEs) including reported seriousness and relatedness as well as events leading to discontinuation of treatment or withdrawal from the trial at 84 days. The occurrence of AEs will be detected by monitoring vital signs, blood oxygenation, serum hematology and chemistry, urinalysis, and cardiac status by both telemetry and electrocardiograms (ECGs). AEs will be coded using MedDRA. The severity of AEs will be graded for severity (mild, moderate, severe or life-threatening) based on the investigator's assessment. The safety assessment will have an additional focus on pre-specified administration-associated events defined as recipient death, graft loss, and acute cardiovascular, respiratory and neurological adverse event reactions.

Primary Efficacy Objective (Part B only):
The rate of delayed graft function (DGF) in kidney transplant recipients with DGF, defined by the need for at least one dialysis treatment within 7 days of transplant, at 84 days.

Key secondary outcome(s)
Part B:
1. Total number, timing and purpose of any dialysis required during the 84-day period posttransplant
2. Trajectory of change in serum creatinine, estimated glomerular filtration rate (eGFR) over the first 72 hours and 7 days post-reperfusion of a donor kidney
3. Creatinine Reduction Ratio: [(Creatinine Post-Operative Day 1-Creatinine Post-Operative Day 2) / Creatinine Post-Operative Day 1] x 100 (Post-operative Day 1 = Day after transplant date)
4. Daily urine volume post-transplant prior to discharge from the hospital
5. Urinary marker of kidney injury (NGAL and KIM-1) up to discharge from hospital

Completion date
01/02/2027

Eligibility

Key inclusion criteria
1. Male and female adult subjects (age 18-75) undergoing deceased kidney-only transplants, including machine-perfused kidneys.
2. Recipients of both donation after brainstem death (DBD) and donation after circulatory death (DCD) kidney transplants will be included.
3. Clinically stable in the opinion of the Investigator.
4. Willing and able to comply with the requirements of the study protocol (including required study visits).
5. Able to provide written informed consent (including consent for the use and disclosure of research-related health information).
6. A female subject is eligible to enter the study if she is:
6.1. Not pregnant or nursing
6.2. Female subjects of childbearing potential must have a negative serum pregnancy within 48 hours prior to transplant surgery and must use a highly acceptable method of contraception for at least 3 months prior to the first administration of trial drug and for 28 days after the last administration of trial drug, as defined in the protocol.
6.3. In order to be considered "not of childbearing potential," female subjects must be

postmenopausal for at least 1 year at Screening and 1 year of amenorrhea, or have been irreversibly surgically sterilized by complete hysterectomy, oophorectomy, or bilateral tubal ligation for at least 6 months prior to the first administration of the trial drug.
7. Male subjects whose female partners are of childbearing potential (defined as above) must agree to use an acceptable method of birth control for the duration of trial treatment and for 28 days after the last administration of trial drug.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
75 Years

Sex
All

Key exclusion criteria
1. Age less than 18 years or greater than 75.
2. Patients who lack mental capacity to give informed consent.
3. Multi-organ transplant recipients.
4. Subjects who are currently or, in the past 60 days, have been on experimental or unapproved medications, or who have been actively enrolled in a clinical trial investigating new therapies. Subjects enrolled in other observational (non-interventional) studies will not be excluded.
5. Subjects with significant pre-transplant anemia, whose serum Hb is < 7.8 g/dl at screening. Subjects who drop below a Hb of 7.8 g/dL would receive a blood transfusion to maintain Hb >7.7 g/dL and therefore remain in the trial.
6. Subjects who are Jehovah's witnesses or other subjects who will not accept blood transfusions.
7. Subjects who, in the opinion of the investigator, have unstable medical issues rendering them at significantly greater risk for adverse events in the peri-operative period, and specifically patients with a recent new-onset (<6 months from screening) history of one or more of the following:
7.1. myocardial infarction (MI)
7.2. transient ischemic accident (TIA)
7.3. cerebrovascular accident (CVA)
7.4. clinically significant abnormal ECG changes
8. New focal neurological signs at screening or Day 0 (Visit 1).
9. Abnormal neuro-psychological test at screening.
10. Patients with significant pulmonary gas exchange compromise or conditions, such as interstitial lung disease or severe emphysema, and all subjects who have baseline oxygen saturations on room air of <90%.
11. Subjects with baseline carboxyhemoglobin [COHb] levels ≥ 2%.

12. Subjects who do not have a central venous catheter placed pre- or intra-operatively that may be used for venous blood sampling.
13. BMI > 40 kg/m2
14. Subjects who are being transplanted pre-emptively (not yet on dialysis)
15. Are pregnant, plan to become pregnant during this trial, are nursing mothers or are unwilling to use an acceptable method of contraception for the duration of the trial.
16. Have any serious or active medical or psychiatric illness, which in the opinion of the Investigator, would interfere with subjects' treatment, assessment, or compliance with the protocol.
17. Have a history or suspicion of unreliability, poor cooperation, or non-compliance with medical treatment.
18. Have previously been randomized in this trial.
19. Have any other condition that, in the opinion of the Investigator, would prohibit the subject from participating in the trial.

Date of first enrolment
01/04/2024

Date of final enrolment
01/12/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
80 Newark Street
London
United Kingdom
E1 2ES

Study participating centre
University College London Hospital
235 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre

St George's University Hospitals
St Georges
Uni of London
Cranmer Terrace
London
United Kingdom
SW17 0RE

Sponsor information

Organisation
Proterris Inc

Funder(s)

Funder type
Industry

Funder Name
Proterris Inc

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr. Kourosh Saeb-Parsy; [email: Kourosh.saeb-parsy@proterris.com; Tel: +44 (0) 7713 641416]. The trial contact will make available upon written request from accredited universities or transplant centers, anonymised participant demographic data (during and after the course of the trial), and outcome (endpoint) data (after the close of the trial). Consent from participants will be obtained for the sharing of anonymized data. The sponsor may elect to publish trial data.

IPD sharing plan summary
Available on request