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Investigating whether regadenoson is safe and can improve patient outcomes following severe injury and bleeding

Submission date
26/01/2021

Recruitment status
Recruiting

Registration date
04/05/2021

Overall study status
Ongoing

Last Edited
19/08/2026

Condition category
Injury, Occupational Diseases, Poisoning

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

Plain English summary of protocol

Background and study aims
This study aims to investigate whether giving one injection of regadenoson in addition to standard care following injury and bleeding is safe and can improve participant outcomes. In animals, giving regadenoson following injury and bleeding improved heart function, decreased markers associated with cell stress and reduced the need for fluid transfusion.

Who can participate?
Male patients aged 18 to 70 years who have suffered a major injury, are bleeding, and are being attended to by London's Air Ambulance

What does the study involve?
Participants are randomly allocated to receive standard care for a bleeding trauma patient or one injection of regadenoson in addition to standard care. Patients who receive regadenoson will get one injection only, given to them by London's Air Ambulance at the scene of their injury. Participants will then be taken to hospital as usual, and the in-hospital research team will monitor the patient for up to 28 days whilst in hospital. Data will be collected on how participants' heart and body are responding to treatment. Blood samples will also be taken up to 7 days after injury to monitor how the heart is functioning and ensure safety tests can be conducted.

What are the possible benefits and risks of participating?
Regadenoson is generally well-tolerated but as there is little experience of using this drug at this dose in injured patients, there is a risk that participants could develop an adverse reaction. Regadenoson has a number of side effects, most of which occur shortly after the drug is injected. Common side effects include flushing, dizziness, nausea, chest pain, and shortness of breath. More uncommon side effects include changes to the rhythm of the heart, low blood pressure and other disturbances to the heart and blood vessels. Very rarely the medication could cause a stroke. A full list of side effects can be found in the information sheet. The air ambulance doctors are trained to look after patients should any of these side effects occur. Patients receiving standard care should experience no additional risks. Blood sampling should

not pose any serious risks to health, specific risks include temporary discomfort from the needle stick and bruising.

Where is the study run from?
London's Air Ambulance and the four major trauma centres it delivers patients to (UK)

When is the study starting and how long is it expected to run for?
July 2017 to August 2027

Who is funding the study?
1. Bart's Charity (UK)
2. JP Moulton Charitable Foundation (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-003284-62

Integrated Research Application System (IRAS)
252963

Central Portfolio Management System (CPMS)
41273

Study information

Scientific Title
A randomized, blinded, controlled, Phase 2a study to evaluate the safety and efficacy of administering Regadenoson to patients with critical injury and signs of haemorrhagic shock

Acronym
ReWiRe

Study objectives
Through agonism of/binding to the adenosine A2A receptor (A2AR), injection of regadenoson in the acute post-injury phase will improve coronary perfusion, support the maintenance of cardiac function and reduce the development of shock as measured by circulating lactate.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 18/07/2019, London – Harrow Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8154; harrow.rec@hra.nhs.uk), ref: 19/LO/0329

Primary study design
Interventional

Study design
Randomized; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Critical injury and signs of haemorrhagic shock

Interventions
The researchers wish to carry out a Phase 2a study aimed at testing the safety and potential effectiveness of regadenoson in a randomised controlled trial in the adult trauma-haemorrhage population.

ENVIRONMENT: This multi-site study will be performed through a single prehospital advanced medical service that serves the four major trauma centres across London as part of an integrated urban trauma system. This trauma network has extensive experience in successfully conducting trauma clinical trials. Operational procedures will be managed by the Centre for Trauma Sciences.

DURATION: The trial will recruit eligible patients, 24 hours a day, 7 days a week for a total period of 12 months. Subjects will be randomized to receive either regadenoson administered within 1 hour of emergency doctors arriving at the scene of the injury or standard care. Study blood samples will be drawn up to 24 hours. Adverse events will be monitored up to 28 days or discharge (whichever is soonest). Subjects will be followed up in critical care and/or trauma wards on a daily basis until hospital discharge, day 28 or death whichever is soonest. Data cleaning and analysis will be completed four months after the conclusion of trial recruitment

CONSENT: In the first instance, there will be a waiver of consent due to the nature of the setting of randomization. Subsequently consent will be obtained from the patient when appropriate, the Personal Legal Representative or a Professional Legal Representative.

TRIAL DESIGN: This is a single provider, multisite Phase 2a study looking for safety and effectiveness data with which to appropriately power a subsequent definitive international 2b trial. The study will comprise the randomised, blinded administration of intravenous regadenoson versus standard care, in addition to current resuscitation practice. The study will occur in two parts. The first will be conducted by the prehospital physicians, and the second will commence following admission of the patient to the major trauma centre.

An initial cohort of participants will receive a safety dose escalation of regadenoson as follows:

Part One:
Phase One: Safety dose escalation
Dose 1: 3 participants to be recruited to the current therapeutic dose of regadenoson, equivalent to 1 vial = 0.4 mg
Dose 2: 3 participants to be recruited to a weight-based dose (~15 ug/kg) of regadenoson: <60 kg = 0.8 mg, 60-80 kg = 1.2 mg, >80 kg = 1.6 mg
Dose 3: 3 participants to be recruited to a weight-based dose (~30 ug/kg) of regadenoson: <60 kg = 1.6 mg, 60-80 kg = 2.0 mg, >80 kg = 2.4 mg

This phase of the study will follow a 3+3 dose-escalation design. At each safety dose, three participants will be dosed with the stage appropriate concentration of regadenoson as outlined above. Safety data will be submitted to the DMC for review. If they deem none of the three participants has experienced the intolerable safety outcomes, then the next three participants will receive the subsequent concentration of the escalation of the dose. If one of the three participants triggers the safety concern criteria then an additional three participants will be

tested at that dose. If at any dose-escalation stage 2 or more participants trigger the safety concern criteria that dose will be deemed unsafe. The full trial will only continue if safety dose 3 is safely completed.

Phase Two:
49 participants will be randomized to receive high-dose regadenoson (at Dose 3 only)

Comparator arm: to receive standard care only
49 participants will be randomized to receive standard care only throughout the recruitment schedule. Taking into consideration the logistics of pre-hospital care, the participants randomised to receive the IMP will be estimated to be in one of three weight categories (<60 kg, 60-80 kg, >80 kg). The dose of the trial drug that the participant received will be based on these weight categories. Those randomized to receive standard care will receive no IMP intervention. The time of dosing will be recorded alongside completion of standard documentation including fluid administration and on-scene observations.

Randomization codes will be generated by the trial statistician and made available to a GMP certified clinical trial supply company for the treatment packs to be created in accordance with the randomisation list. Patients will be randomized in a 1:1 manner. Once a participant is determined eligible for the study, participants will be enrolled as soon as possible by opening the next available, lowest consecutively numbered randomisation card. The randomization number of the opened envelope will be used as the participant's study ID throughout the trial and will be documented on the enrolment log. Randomization must take place within 1 hour of the pre-hospital physician arriving at the scene of the injury.

Part 2
The participant will be transported to one of the four major trauma centres (MTCs), at which point trial procedures and data recording will be conducted by the local research team at the admitting MTC. Whilst in the care of the pre-hospital advanced medical service, the participant remains under the responsibility of Barts Health NHS Trust. Once admitted to one of the four MTCs, the responsibility for the participant will be with the receiving hospital.

Data variables will be collected from hospital admission through to day 28 as per the schedule of events (see Section 12.6).

Adverse events (AEs) and serious adverse events (SAEs) will be reviewed by the research team on a daily basis from the point of hospital admission through till day 7 of the subjects' participation in the trial.

Barts Health NHS Trust pharmacy department will hold and dispense the treatment packs to the out of pharmacy storage area within the Trauma Research laboratory and the prehospital care team offices.

Following admission to one of the four major trauma centres, trial procedures and data recording will be the responsibility of the research teams. Teams will collect data from admission to the department until day 28, or death (whichever is soonest).

An admission blood sample will be taken alongside those used for routine clinical bloods. It is not anticipated that the samples taken will have any adverse effect on clinical outcomes.

RESEARCH SAMPLES: Admission blood samples will be processed and plasma will be prepared and stored frozen for future measurement of h-FABP. These samples will be sent to the Blizard Institute (Queen Mary, University of London) for analysis at the end of the recruitment period.

SAFETY BLOOD SAMPLING: As part of the study's safety analysis the researchers will monitor and record the patient's clinical blood r esults (for instance the full blood count, urea and electrolytes, liver function tests) to detect derangements that may potentially be attributable to the study drug. This analysis is being undertaken because regadenoson has not been studied in the trauma cohort previously. They will record patients blood results daily during the first 7 days of admission, and then weekly until day 28 (a total of 10 blood tests). The majority of these blood tests will be taken routinely by the clinical team as part of the patient's clinical management on the intensive care unit (approximately 7) and therefore will not require extra sampling for research purposes. However, there may be instances where routine clinical bloods are not taken, and provided the patient is still in hospital and gives consent, an extra sample (comprising approximately 10 ml) will be taken on those days for safety monitoring purposes. It is not anticipated that these samples will have any adverse effect on patient outcomes.

SAFETY REPORTING: All serious adverse events (SAE) will be reported up to 28 days or discharge (whichever is soonest).

DATA ANALYSIS: The final analysis of the trial cohort (total = 98) will be performed according to standard trial best-practice criteria. Preliminary data analysis will be performed before the breaking of the randomization code. Standard tests of two-group comparison will be used throughout.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
Shock (lack of blood flow to the body's tissues) measured by collection of a blood sample and measurement of lactate (a shock biomarker) at 2 hours post IMP administration

Key secondary outcome(s)
1. Change in lactate (a marker of lack of blood flow to the tissues) measured using blood sample following admission to hospital to 2 hours after the intervention
2. Measurement of damage to the heart muscle after the intervention through measurement of h-FABP, a protein released by damaged heart muscle, measured using blood sample on admission and 24 hours after the intervention
3. Amount of fluid transfused to the patient recorded in medical notes within 24 hours of the intervention
4. Lactate measured using blood sample on hospital admission and at 24 hours after admission
5. Blood pressure recorded by the patient's clinical team in medical notes on admission to hospital
6. Mean arterial blood pressure recorded by the patient's clinical team in medical notes on admission to hospital

7. Difference between lowest systolic blood pressure recorded by the patient's clinical team in medical notes before hospital admission and at hospital admission
8. Number of adverse cardiac events: abnormal heart episodes defined as rhythm or ECG changes recorded by the patient's clinical team in medical notes during hospital stay
9. How the patient's organs are performing, measured using the Sequential Organ Failure Assessment score and composite time to complete organ failure recovery, for 7 days
10. The total number of days the patient receives drugs that support the hearts function (vasopressor/inotrope) including the type and dose recorded in medical notes for a maximum of 28 days
11. Total length of hospital stay recorded in medical notes for a maximum of 28 days
12. Scoring of the patient's health outcome using the GOS-E at discharge, day 28 or death - whichever is soonest
13. Total length of critical care stay recorded in medical notes for a maximum of 28 days
14. Survival status recorded in medical notes up to 28 days

Completion date
31/08/2027

Eligibility

Key inclusion criteria
1. Male
2. Deemed to be aged ≥18 and ≤70 years
3. Activated pre-hospital code-red criteria (activation criteria are: systolic blood pressure <90 mmHg AND suspected haemorrhage)
4. Started transfusion of at least 1 unit of packed red blood cells (PRBCs) (or blood component equivalent)
5. Is intubated and ventilated
6. Patient has suffered a traumatic injury
7. Is able to be randomised within 1 hour of the pre-hospital physician arriving at the scene of the injury

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
70 Years

Sex
Male

Total final enrolment
0

Key exclusion criteria
1. Patient suffered a traumatic cardiac arrest prior to screening
2. Patients who are suspected to have shock due to a non-haemorrhagic cause, as assessed by the pre-hospital care team
3. Unable to administer IMP within pre-hospital phase of care
4. Presence of obvious catastrophic traumatic brain injury or other non-survivable injury, suspected by the pre-hospital team
5. Known or suspected pre-injury cardiac disease
6. Known allergy to Regadenoson

Date of first enrolment
01/08/2020

Date of final enrolment
31/01/2027

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The Royal London Hospital
Barts Health NHS Trust
Whitechapel
London
England
E1 1BB

Study participating centre
St Mary's Hospital
Imperial College Healthcare NHS Trust
Praed Street
London
England
W2 1NY

Study participating centre
St George's Hospital
St George's University Hospitals NHS Foundation Trust

Blackshaw Road
Tooting
London
England
SW17 0QT

Study participating centre
King's College Hospital
King's College Hospital NHS Foundation Trust
Denmark Hill
London
England
SE5 9RS

Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Charity

Funder Name
Barts and the London Charity and Related Charities

Funder Name
J P Moulton Charitable Foundation

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

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