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A study to test the safety and effectiveness of using mutant pro-urokinase and low-dose alteplase to unblock blood vessels in heart attack patients before receiving treatment at a hospital with PCI capability

Submission date 25/07/2023	**Recruitment status** Stopped	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 27/12/2023	**Overall study status** Stopped	
Last Edited 06/03/2025	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims

Heart attacks are the end result of a blockage of an artery of the heart, and according to the World Health Organisation, heart attacks are one of the leading causes of death worldwide. This study concerns a type of heart attack called STEMI. The treatment of a patient who has suffered a heart attack, as quickly as possible, gives them the best chance of survival and recovery from their heart attack. One of the main treatments is a PCI (primary percutaneous coronary intervention) which is a way of inserting a tube (stent) into the blocked artery or a balloon into the blocked artery or other mechanical means to help restore the blood flow through the blocked artery quickly. Delays in receiving this treatment and/or being transferred to a hospital where this treatment can be performed has a negative impact on the outcome for patients suffering a heart attack. If a patient suffering a heart attack arrives at a hospital that cannot perform PCI then a treatment called fibrinolysis is recommended. Fibrinolysis breaks down the clot that has caused the blockage but is limited by possible bleeding issues for the patient. Previous studies have indicated that a treatment called “sequential fibrinolysis therapy” has the potential to be safer. This is giving two fibrinolysis treatments one after another. Thrombolytic Science LLC, a US based company, have developed HisproUK which is a fibrinolytic medication, meaning that it is a treatment used to dissolve blood clots. The aim of this study is to assess the safety and effectiveness of “sequential fibrinolysis” (a low dose of a fibrinolysis drug called alteplase by injection followed by an infusion into the patient’s vein of HisproUK).

Who can participate?

Patients who have suffered a heart attack and are also expected to have a delay of at least 1 hour before being able to receive the PCI treatment.

What does the study involve?
The study will compare patients treated with the “sequential fibrinolysis therapy” with patients who receive the normal standard care.

What are the possible benefits and risks of participating?
The anticipated clinical benefits are:
- Improved myocardial salvage
- Limited infarct size
- Improved patient outcomes

Risks:
Adverse events noted in a phase I, randomised, double blind, healthy volunteer trial in 26 healthy male volunteers who received a single dose of HisproUK or placebo intravenously or a single dose of HisproUK or placebo preceded by a single mini bolus of tPA predominantly included mild and moderate gastro-intestinal disturbances. Adverse events included:
• Diarrhoea
• Nausea
• Vomiting
• Abdominal discomfort
• Blood fibrinogen decreased (0.7 g/L) at 50 mg mproUK
• Nausea and pyrexia (same subject) at 50 mg mproUK
• Syncope, which occurred during an episode of vomiting at 65 mg mproUK
• Leukocytosis in one patient that received 50 mg mproUK on Day 1 of receiving study drug.

No residual risks have been identified from the healthy volunteer trial. For this trial all adverse events will be collected and reviewed by the DSMB but events of note will be related to bleeding events, ischaemic events such as stroke, and measures of changes in fibrinogen (a measure of systemic fibrinolysis – depletion will increase the risk of bleeding) and fibrin D-dimer (fibrin degradation product – a measure of fibrin lysis and therefore efficacy of the drug).
There is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures and it is expected that the procedural risks in this study and existing stenting procedure will not be significantly different. No additional discomfort is anticipated other than the risks described by the clinical professional ahead of the PCI procedure before enrolment into the trial.
Known adverse events that may result from stent intervention include, but may not be limited to:
• Allergic reaction or hypersensitivity to device material and its degredants (everolimus, platinum, chromium, poly-lactide-co-glycolide (PLGA))
• Shortness of breath/dyspnea
• Distal embolism (air, tissue, or thrombotic)
• Nausea/Vomiting
• Coronary and stent thrombosis
• Coronary and stent embolism
• Coronary dissection
• Total coronary occlusion
• Abrupt coronary closure/threatened abrupt closure
• Coronary injury
• Coronary spasm
• Coronary perforation
• Coronary rupture
• Pseudoaneurysm
• Angina (stable or unstable)
• Urgent or non-urgent coronary artery bypass graft surgery
• Vascular complications including at the entry site which may require vessel repair and vessel

dissection
• Hematoma
• Respiration cease
• Hypertension
• Death
• Bleeding
• Bleeding complication (that may require transfusion)
• Shock
• Myocardial ischemia
• Cardiac enzyme level elevation
• Myocardial infarction
• Cardiac tamponade
• Cardiac arrest
• ECG change
• Heart failure
• Renal failure
• Stent implanted in unintended location
• Restenosis of lesion/vessel treated with stent
• Access site infection or pain
• Access site hematoma or bleeding
• Cerebral stroke/cerebral vascular accident (CV A)
• Hypotension
• Palpitation
• Aneurysm
• Arteriovenous fistula
• Pulmonary edema
• Fever
• Arrhythmia (atrial or ventricular)
• Peripheral ischemia (due to vascular injury)
• Adverse reaction to drug (to everolimus, antiplatelets or contrast agent)

At the end of the primary PCI procedure, a coronary physiology study is carried out for the study. The drugs administered during the coronary physiology study (nitrates and adenosine) may induce transient low blood pressure, low heart rate, headaches which will likely clear up without requiring further treatment.

Patients will be required to be transferred from a non-PCI hospital to a PCI hospital, whilst receiving the IMP via infusion in the ambulance. In order to minimise risk during the transfer, ambulance teams will be provided with the details of back-up medics who can be contact in the case of any adverse events.

We anticipate minimal burden for participating in the trial but acknowledge participants are being asked to attend one additional hospital visit, to have two MRI scans, to complete a medication diary, and to complete 3 questionnaires at the follow up visit. The visits outside of usual care will be organised by the research nurse and completion of the questionnaires will also be supported by the research team.

Where is the study run from?
Thrombolytic Science LLC (USA)

When is the study starting and how long is it expected to run for?
July 2023 to November 2025

Who is funding the study?
Thrombolytic Science LLC (USA)

Who is the main contact?
Dr Vasim Farooq, Vasim.Farooq@wales.nhs.uk

Contact information

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Principal Investigator

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1006643

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
SALVAGE_1, IRAS 1006643, CPMS 54066

Study information

Scientific Title
An open-label, randomised study to evaluate the safety and efficacy of sequential 'physiological' fibrinolysis with mutant pro-urokinase and low-dose alteplase to establish early epicardial and microvessel patency in patients presenting with an ST-elevation myocardial infarction with an expected delay of at least one hour before undergoing mechanical reperfusion at a PCI-capable hospital

Acronym
SALVAGE_AMI

Study objectives
The primary objective is to assess the safety of the study drug in patients who attend hospital with a heart attack, with an expected delay of at least 1 h before being treated at a PCI capable hospital with a stent.

Secondary objectives are to:
1. Assess the final size of damaged area via an MRI scan at Day 30
2. Assess mortality, readmission for heart failure and acute bleeding rates at 30 days
3. Assess quality of life, angina status and disease outcome at Day 30 by the use of patient questionnaires; the HeartQOL, the Seattle Angina Questionnaire (SAQ) and the Medical Outcome Study 36-item Short-Form Health Survey MOS SF-36)
4. Assess the acute response to the study drug. Assess the safety of the study drug.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 20/07/2023, Wales REC 5 (Health and Care Research Wales Support and Delivery Centre, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 2922 941106; Wales.REC5@Wales.nhs.uk), ref: 23/WA/0225

Study design
Interventional randomized parallel group controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Participants presenting with ST-elevation myocardial infarction

Interventions
Patients randomised into the intervention arm will receive sequential fibrinolysis consisting of an alteplase bolus dose followed by an infusion of the study medication.
Patients randomised into the standard of care arm will receive either:
1. No fibrinolytic therapy if the anticipated delay to the cardiac cath lab is <2 h
2. Conventional, full-dose, fibrinolytic therapy if the anticipated delay to the cardiac cath lab is >2 h

Randomisation – Randomisation activity will be performed via the use of an online electronic case report form. Patients will be centrally allocated by the eCRF system, stratified by site, to the interventional arm or the standard of care arm.

Follow up activity:-
Patients will be followed up with ECGs and coagulation tests for the 24-h period following the PCI procedure which include the primary study endpoint. MRIs will be performed at Day 2-4 and at the end of the study (Day 30) to assess the Salvage Index.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase II

Drug/device/biological/vaccine name(s)
HisproUK [Recombinant mutant prourokinase]

Primary outcome measure
Change from baseline serum fibrinogen levels to 6 h after administration of the IMP

Secondary outcome measures
1. Reperfusion, thrombus, epicardial patency (coronary angiography) pre and post PCI, and microvascular patency (coronary physiology: index of microcirculatory resistance [IMR]) will be assessed at the end of the index primary PCI procedure. These measures will be analyzed centrally at an independent CoreLab.
2. Coronary angiography measures of reperfusion and thrombus (pre- and post-primary PCI procedure) will include TIMI flow, TIMI myocardial blush grade, TIMI frame count, and TIMI thrombus grade.
3. Epicardial patency will be evaluated using parameters like reference vessel diameter, minimum lumen diameter, and percentage diameter stenosis from coronary angiography before (immediately after coronary angiogram) and after the PCI procedure. The analysis will be done centrally at a selected independent CoreLab.
4. Microvascular patency (coronary physiology - index-of-microcirculatory resistance [IMR]) will be assessed at the end of the index primary PCI procedure, with the site reporting the results.
5. Percentage ST segment resolution on ECG will be measured at baseline, immediately before the primary PCI procedure, and 1 h after the primary PCI.

6. Acute infarct characteristics on contrast-enhanced cardiac MRI will be evaluated at Day 2-4, including myocardial salvage index as a surrogate measure of therapeutic benefit and late gadolinium enhancement (LGE, % LV mass) volume (acute infarct size).
7. Incidence and extent of microvascular obstruction (MVO) and/or hemorrhage will be expressed as a percentage of left ventricular mass.
8. Left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular ejection fraction will be assessed as part of the final infarct size on contrast-enhanced cardiac magnetic resonance imaging (MRI) at Day 30 (range 23-44 days).
9. The Selvester score of 30-day infarct size on the ECG taken at day 30 will be calculated. The Selvester score translates subtle changes in ventricular depolarization on ECG to a surrogate measure of infarct size, with a maximum score of 32 points, where 1 point corresponds to 3% of the left ventricle.
10. 30-day mortality, readmission for heart failure, and acute bleeds (BARC ≥3) will be recorded as outcomes.
11. Changes in fibrinogen and D-Dimers levels will be monitored from baseline, immediately pre- and post-primary PCI, 6 hrs, and 24 hrs post randomization. The primary endpoint is the change in fibrinogen from baseline to 6 hours post randomization.
12. Outcomes will be stratified by transfer times and the dose of the IMP administered.
13. Patient-reported outcomes for Heart Related Quality of Life (HRQoL), Medical Outcome Study 36 Item Health Survey (MOS SF-36), and the Seattle Angina Questionnaires (SAQ) will be collected at Day 30.
14. Other endpoints will include outcomes stratified by anatomical complexity.
15. Baseline and residual SYNTAX Scores from pre- and post-primary PCI procedures will be calculated. The score will be determined centrally at a selected independent CoreLab.

Overall study start date
20/07/2023

Completion date
30/11/2025

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. Presentation to an investigational site with an acute ST-elevation myocardial infarction (symptom onset 0-6 h) requiring mechanical reperfusion with primary PCI to one or more lesions
2. Visually assessed ST-segment elevation (measured at the J-point) in at least two contiguous leads with ST-segment elevation. ≥ 2.5 mm in men <40 years; ≥2 mm in men ≥40 years ≥ 1.5 mm in women in leads V2–V3 and/or ≥ 1 mm in the other leads In the absence of left ventricular hypertrophy or left bundle branch block (LBBB) and associated with ongoing ischaemic symptoms
3. Aged ≥18 years
4. Anticipated delay to primary PCI of at least 1 hour from presentation to being able to be treated with emergency mechanical reperfusion at a PCI-capable centre
5. Able in person, or with the support of a Next of Kin or legal guardian, to provide informed verbal assent prior to randomisation.
6. Radial artery access for primary PCI procedure

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
48

Key exclusion criteria
1. Left bundle branch block (LBBB) or ventricular pacing
2. Currently taking a P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel)
3. High bleeding risk patients – one major, or two minor criteria on the ARC-HBR criteria
4. Prior percutaneous coronary intervention in the last 3 months
5. Known contraindications to primary PCI or cardiac MRI
6. Cardiogenic shock (Killip Class IV)
7. NYHA Class 3-4 heart failure
8. History of intracranial haemorrhage
9. Known intolerance/hypersensitivity to aspirin, ticagrelor, heparin, limus drugs
10. Patients with current concomitant oral anticoagulant therapy, including vitamin K antagonists (warfarin) and non-vitamin K antagonist oral anticoagulants (NOACS)
11. Recent administration of any intravenous or subcutaneous anticoagulation within 12 h, including unfractionated heparin, enoxaparin, and/or bivalirudin
12. Severe hepatic impairment
13. Non-cardiac co-morbidity with expected survival <1 year
14. Patients of child-bearing potential with either a confirmed positive pregnancy test or those unable to have a pregnancy test conducted prior to inclusion in the study

Date of first enrolment
10/10/2024

Date of final enrolment
30/11/2025

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre

Cardiff ECMC
Cardiff University
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XN

Study participating centre
The Royal Glamorgan Hospital
Ynysmaerdy
Pontyclun
United Kingdom
CF72 8XR

Study participating centre
Prince Charles Hospital Site
Prince Charles Hospital
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Sponsor information

Organisation
Thrombolytic Science LLC

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Sponsor type
Industry

Funder(s)

Funder type

Industry

Funder Name
Thrombolytic Science LLC

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Submission to regulatory authorities
Access of source records and study will be required to staff outside of the healthcare team for monitoring purposes, and this will be agreed upon via the model clinical trials agreement in place with the investigator site.
Data transfer agreements will be in place between the CRO and Sponsor, and CRO and vendors, and this will define the process for data transfer.
It will be made clear in the Participant Information Sheet and Consent Form that data rendered anonymous will be sent outside the UK or the EEA, and patients will provide consent for their data to be transferred.

Intention to publish date
30/11/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available as it is proprietary information for registration of a patented product.

IPD sharing plan summary
Not expected to be made available