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A trial to investigate whether a new medicine, KAND567, is well tolerated and if it can improve healing in patients who have had a heart attack

Submission date
24/06/2021

Recruitment status
No longer recruiting

Registration date
25/06/2021

Overall study status
Completed

Last Edited
16/07/2024

Condition category
Circulatory System

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Coronary heart disease is a condition in which the supply of blood and oxygen to the heart is reduced due to the narrowing of the arteries (blood vessels) supplying the heart. A heart attack is caused when one of the arteries becomes blocked. Modern treatment for heart attacks involves opening the blocked artery with a balloon and placing a stent (a small metal scaffold) in the artery to hold it open. This treatment is called primary percutaneous coronary intervention (PPCI).
Recently, research has shown that after opening the artery, inflammation develops within the heart. This inflammation is generated by the immune system. Studies have suggested that certain immune system cells (T cells) with the chemokine receptor CX3CR1 may be involved in causing much of the damage that occurs in the heart following a heart attack. The drug KAND567 inhibits CX3CR1, and thus temporarily inhibits the immune system.
The aim of this study is to investigate whether KAND567 can be safely used in patients with an acute heart attack, and whether KAND567 inhibits the adverse reaction of the immune system that causes hyperinflammation.

Who can participate?
Patients aged 18 - 75 years with an ST-elevation myocardial infarction (heart attack) who agree to undergo PPCI

What does the study involve?
Participants will receive an infusion of either KAND567 medicine or placebo (dummy drug) into a vein at the start of their PPCI procedure. This infusion will continue for 6 hours. Participants will then receive 8 doses of oral capsules of either KAND567 or placebo, each dose 8 hours apart from the previous dose. Participants are then followed up for 90 days as they would normally be for routine care, as well as having two additional cardiac MRI scans.

What are the possible risks and benefits of participating?
There are always risks with taking a trial medicine and all treatments can lead to side effects. KAND567 has previously been given in tablet form to healthy volunteers (young and old) every

day for up to 7 days. Based on these previous studies, no specific side effects are expected with the dose of medicine used in this study.
In previous studies with KAND567 at a higher dose, elevated liver values were reported. These levels returned to normal when KAND567 was stopped.
In a study where KAND567 was given as an infusion at a higher concentration and rate than this study, some inflammation was seen in the blood vessel into which the medicine was given. No such symptoms appeared in a second study when the medicine was administered at the same concentration and rate as this trial.
As with all medicines, allergic reactions can occur. There are also risks of bruising where the medicine is administered into a vein.
During the trial and follow up, participants will be closely monitored by the trial team and safety bloods will be taken up to day 90. It may be that you will have a positive outcome from receiving the medication but this is currently not known.

Where is the study run from?
The Freeman Hospital in Newcastle and the James Cook University Hospital, Middlesbrough (UK)

When is the study starting and how long is it expected to run for?
January 2021 to July 2023

Who is funding the study?
Kancera AB (Sweden)

Who is the main contact?
Karen Nicholson and Jaki Begum
Fractal@newcastle.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Ioakim Spyridopoulus

Contact details
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN
+44 (0)191 241 8675
ioakim.spyridopoulos@newcastle.ac.uk

Type(s)
Public

Contact name
Dr Karen Nicholson

Contact details
Newcastle Clinical Trials Unit
1-4 Claremont Terrace
Newcastle upon Tyne
United Kingdom
NE2 4AE
+44 (0)191 208 2519
Fractal@newcastle.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2021-001354-53

Integrated Research Application System (IRAS)
1003810

Protocol serial number
Sponsor ID: 09603

Study information

Scientific Title
A Phase IIa, randomized, two-arm parallel-group, placebo-controlled, double-blind, multi-centre trial to evaluate the safety, tolerability, anti-inflammatory and cardio-protective effects after intravenous and oral administration of KAND567 in ST-elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention

Acronym
FRACTAL

Study objectives
This trial will address whether KAND567 can be safely used in patients with an acute heart attack, and whether KAND567 inhibits the adverse reaction of the immune system that causes hyperinflammation when compared with a placebo.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/07/2021, Haydock REC (North West Centre of Research Ethics Committees, 3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)161 625 7835; haydock.rec@hra.nhs.uk), REC ref: 21/NW/0178

Primary study design
Interventional

Study design
Multicentre interventional double-blinded randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
ST-elevation myocardial infarction (STEMI)

Interventions
The safety and efficacy of KAND567 vs placebo will be investigated in ST-elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention.

Participants who are suitable for the trial will be randomised using the Sealed Envelope system into either the active arm or the placebo arm. This is a double-blinded trial.

As participants begin to undergo a PCI procedure to open a blocked artery, they will be given an IV infusion of either KAND567 or placebo for a total of 6 hours (total dose 134 mg KAND567, if given active drug). This is then followed by eight oral capsule doses of 200 mg of KAND567 or placebo, each dose 8 hours after the previous dose. The participants are then followed up for a further 90 days and to gather safety and efficacy information. This includes collecting data from two cardiac MRIs and well as the usual follow up for this patient group.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
KAND567

Primary outcome(s)
The safety and tolerability of KAND567 will be assessed on the following:
1. Occurrence of adverse events (AEs) during the 90 days trial participation
2. Changes in vital signs between baseline and 90 days
3. Any change in safety bloods including blood chemistry, haematology and urinalysis will be measured over the period that the participant is in hospital.

Key secondary outcome(s)
1. CD3+CX3CR1+ effector memory T-lymphocytes, quantified in non-coronary arterial or venous blood and measured by the BD TruCount assay and flow cytometry, from baseline up to 4 days
2. Levels of inflammatory markers including high-sensitivity CRP and IL-6 measured using laboratory analysis of blood samples at timepoints from baseline up until 90 days
3. CX3CR1 receptor density on the cell surface of T cells, monocytes and NK-cells measured using laboratory analysis of blood samples at baseline, and at set timepoints until the end of IMP administration
4. The following outcomes will be measured at 72 hours and 90 days using cardiac MRI:
4.1. The myocardial salvage index (MSI) (area at risk/absolute infarct size) (72 hours only)
4.2. Infarct size
4.3. Ejection fraction
4.4. Potential Improved left ventricular remodelling (lower delta end systolic volume and delta end diastolic volume, separately)
5. The pharmacokinetic parameters steady-state concentration (Css) and minimum plasma

concentration (Cmin) measured using laboratory analysis of blood samples at time points from immediately prior to reperfusion up to 4 days
6. ST-segment resolution measured by ECG 60 minutes post reperfusion
7. Microvascular obstruction (MVO) and intramyocardial haemorrhage (IMH) measured by cardiac MRI performed at 72 hours
8. Neutrophil and leukocyte counts from full blood analysis conducted at 24 hours, 48 hours and 72 hours

Completion date
19/07/2023

Eligibility

Key inclusion criteria
1. Reperfusion of anterior MI expected within 5 hours of onset of acute chest pain
2. Diagnosis of acute myocardial infarction with ST elevation at the J-point in two contiguous leads by ECG (V1-V4 at least two contiguous leads STE 2.0 mm in men and 1.5 mm in women)
3. Agreement to undergo routine procedure of PPCI
4. Aged ≥18-75 years
5. Willingness and ability to comply with trial procedures, visit schedules, trial restrictions and requirements
6. Confirmation of anterior STEMI (TIMI 0-2 flow) by angiography and occlusion of proximal or mid LAD (segments 5 or 6)
7. Verbal consent to take part in the trial is given

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
All

Total final enrolment
61

Key exclusion criteria
1. Anyone with known cognitive impairment or unable to provide verbal consent
2. Serious co-existing medical condition, including known hepatic failure and known renal failure with known eGFR <30 ml/min/m^2 or severe mental disorder, known at the time of randomisation

3. Cardiogenic shock, non-compensated acute heart failure and/or pulmonary edema
4. Previous known major vascular intervention within the last 4 weeks
5. History of previous myocardial infarction (MI) in the LAD
6. Documented left ventricular systolic dysfunction (EF <40%)
7. Previous coronary artery bypass grafting (CABG)
8. Patients unable to tolerate or undergo MRI scanning including patients with claustrophobia, cardiac pacemaker/defibrillator, ferromagnetic metal implants unless approved for use in MRI scanners or excessive body weight
9. Known planned hospitalisations (e.g. elective surgery), or other scheduled treatment for pre-existing conditions during the course of the trial that could interfere with clinical assessment
10. Known allergy to contrast agent or other contraindications for angiography
11. Any known previous diagnosis of invasive cancer within the last 5 years except for treated basal cell carcinoma of the skin
12. Current use of steroids or immunosuppressants
13. Current use of benzodiazepines
14. Current use of ticagrelor (unable to switch to Prasugrel on trial entry)
15. Known pre-existing severe liver disease, including chronic hepatitis or alcohol-dependent liver cirrhosis
16. Other medical or social reasons for exclusion at the discretion of the investigator
17. Administration of any investigational drug within 3 months of trial medication, as far as known to the patient
18. Current use of drug sensitive to CYP3A4 inhibition which cannot be paused or switched to an alternative from the same class of medication for the period of IMP administration, including:
18.1. Certain P2Y12 inhibitors (clopidogrel)
18.2. Certain statins (lovastatin and simvastatin)
19. Women of child-bearing potential who are sexually active who are not using a contraceptive method with a failure rate of <1% to prevent pregnancy prior to trial entry. Postmenopausal women must be amenorrhoeic for at least 12 months prior to randomisation to be considered of non-childbearing potential
20. Women of child-bearing potential who are not willing to use a contraceptive method with a failure rate of <1% to prevent pregnancy throughout the trial
21. Male patients with female partners of childbearing potential not willing to use effective contraception
22. Male patients must agree to refrain from donating sperm whilst participating in the trial

Date of first enrolment
15/11/2021

Date of final enrolment
28/02/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

Freeman Hospital
Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Road
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
James Cook University Hospital
South Tees Hospitals NHS Foundation Trust
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Industry

Funder Name
Kancera AB

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Funder report results			16/07/2024	No	No
HRA research summary			26/07/2023	No	No