ISRCTN64669648 https://doi.org/10.1186/ISRCTN64669648

NLRP3 and SASP in Vazkepa therapy in patients with heart disease with or without type 2 diabetes

Submission date
06/03/2025

Recruitment status
Recruiting

Registration date
31/03/2025

Overall study status
Ongoing

Last Edited
31/03/2025

Condition category
Circulatory System

[ ] 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
Vazkepa is a medicine which works by lowering a type of fat in the blood, known as triglycerides. In clinical trials, Vazkepa has demonstrated an ability to reduce the risk of serious complications such as heart attacks and strokes in people who have heart disease with or without type 2 diabetes, which are responsible for the majority of deaths associated with heart disease. However, these benefits extend beyond the ability of the medicine to lower triglycerides, meaning exactly how Vazkepa works is currently unknown.
When individuals have heart disease, immune cells in the body can behave more aggressively, promoting a specific form of inflammation which is associated with poor outcomes in heart disease.
This study aims to determine whether Vazkepa can cause these immune cells in our body to behave less aggressively, therefore reducing inflammation, which we think may explain the significant reduction in heart attacks and strokes observed when people with heart disease take Vazkepa.

Who can participate?
Patients aged 18 to 85 years who have heart disease with or without type 2 diabetes who, despite taking statins, still have high levels of triglycerides in their blood.

What does the study involve?
The study involves blood samples being taken from participants who are enrolled in the trial over a 6-month period. Patients will be randomised to either arm A (where they receive Vazkepa at the beginning of the study) or arm B (where patients receive Vazkepa 3 months into the study).
Using these blood samples, the researchers will isolate the immune cells and determine whether after taking Vazkepa, they behave in a more controlled manner. They will also use blood samples to check the participant's overall health as part of the standard of care associated with starting this medicine.

What are the possible benefits and risks of participating?
The researchers involved in this study aim to understand how Vazkepa may reduce a type of inflammation which predisposes individuals to a greater risk of serious secondary complications. Whilst Vazkepa is already prescribed to reduce blood triglycerides, understanding how this medicine works will allow us to identify more patients who may also benefit from taking Vazkepa, in addition to developing new therapies to treat heart disease.
Vazkepa is already licensed and recommended by NICE for individuals with established heart disease and elevated triglycerides, this is not a clinical trial to investigate the safety or efficacy of the drug as this has already been established. Instead, this trial aims to understand the mechanisms of the medicine, allowing researchers to better understand the significant benefits associated with taking Vazkepa.
Vazkepa is well tolerated among patients, with very few side effects. However, should the patients enrolled on the trial experience any side effects, they can be discussed with a cardiologist at any of their follow-up appointments, and participants will be monitored for any such events. A key benefit of participating in the study is the increased clinical access associated with study participation. When patients are initially enrolled into the study, then after both 3 and 6 months of the study duration, they will see a cardiologist to discuss any areas of concern, which would allow for any further investigations of issues they may raise.
The small risk of taking part in the study is associated with blood sampling, which is aligned with the standard of care for receiving Vazkepa outside of the clinical trial. To minimise this risk, the research clinics will be run by experienced clinicians to reduce any discomfort associated with blood taking.
Finally, participants will be reimbursed for any research visits which occur outside of the normal standard of care, which should avoid any additional financial burden associated with participating in the study.

Where is the study run from?
The study is run from Lincoln County Hospital and the University of Lincoln (UK)

When is the study starting and how long is it expected to run for?
February 2024 to March 2027

Who is funding the study?
The study is funded by Amarin Pharmaceuticals and the University of Lincoln (UK)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
335916

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 59736

Study information

Scientific Title
Does Vazkepa mitigate the negative effects of metabolic memory in monocyte-derived macrophages isolated from patients with cardiovascular disease +/- type 2 diabetes?

Study objectives
This study, through the use of monocyte-derived macrophages isolated from individuals with established atherosclerotic cardiovascular disease (ASCVD) with or without type 2 diabetes mellitus, will elucidate triglyceride-lowering independent mechanisms which are responsible for the significant cardiovascular benefit observed with Vazkepa therapy. It is hypothesised that Vazkepa may produce such benefits through the regulation of three independent mechanisms:
1. Vazkepa targets and blunts the priming/activation of the NOD-like receptor protein 3 (NLRP3) inflammasome
2. Which may lead to a decrease in inflammation and senescence
3. In addition to affecting cell behaviour and signalling through inhibition of aberrant connexin hemichannel activity

Ethics approval required
Ethics approval required

Ethics approval(s)

approved 13/02/2024, East of Scotland Research Ethics Service (EoSRES) (Tayside Medical Science Centre, Residency Block Level 3, George Pirie Way, Ninewells Hospital and Medical School, Dundee, DD1 9SY, United Kingdom; +44 (0)1382383848; tay.eosres@nhs.scot), ref: 24/ES/0006

Study design
Single-centre prospective open-labelled observational cohort study with randomisation

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Atherosclerotic cardiovascular disease with or without type 2 diabetes mellitus

Interventions
This is a single-centre prospective open-labelled observational cohort study with randomisation, involving human blood samples and data collection from patients randomised to one of two groups to ensure no selection bias into either group.

This study will be performed at Lincoln County Hospital, where the research team will screen eligible patients to be then approached for their consent to participate. These participants involve those with established atherosclerotic cardiovascular disease +/- type 2 diabetes mellitus, with elevated triglycerides despite maximally tolerated statin therapy who are eligible for Vazkepa therapy.

This is not a clinical trial of an investigational medical product to prove its efficacy or safety since this has already been established for Vazkepa. This medication has licensed indication and is already prescribed to treat individuals with atherosclerotic heart disease. Patients who are eligible for Vazkepa as part of their recommended standard of care will be randomised into either Arm A (Vazkepa initiated at time =0) or Arm B (Vazkepa initiated at time = 90) at their randomisation visit (time=0). To ensure equal distribution of patients with/without type 2 diabetes in each arm, patients will be randomised based on their diabetic status. All patients will receive Vazkepa as part of the study.

1. Arm A: patients will be initiated on Vazkepa therapy (oral administration, 1.996 g twice daily) at time = 0 with subsequent follow-up appointments at time = 30, time = 90 and time = 180. The total follow-up duration will be 6 months.
2. Arm B: patients will have baseline blood samples taken at time=0 and time=30, prior to initiation of Vazkepa therapy (oral administration, 1.996 g twice daily) at time = 90, with subsequent follow-up appointments at time = 120 and time = 180. The total follow-up duration for the entire study will be 6 months.

At the end of trial visit (time = 180), a cardiologist will decide whether Vazkepa therapy will be continued for the patient based on their response to the drug in the study.

This study involves only blood sampling from the participants, with samples taken from those in Arm A at T=0, T=30, T=90, T=180, and for those in Arm B at T=0, T=30, T=90, T=120, T-180.

Participants will be reimbursed for their travel expenses for visits which are for research purposes only and are outside of the standard of care (T=30 and T=120). The participant's participation in the study will end after their final study visit at 6 months.

Pseudo-anonymised patient data, demographics, clinical data, measurements of interest and clinical results will be collected for correlation and analysis in the study. Blood samples will be transferred through an approved cold chain process to the laboratories at the University of Lincoln where further analysis will take place as per the study protocol. These analyses will assess levels of pro-inflammatory pathways which are known to lead to cell degeneration and increased inflammation.

Key aspects of study design:
1. 68 patients with complete blood sampling will be recruited to the study, this accounts for over-recruitment from the initial target of 60 patients to ensure enough participants in the event of dropout or withdrawal from the study.
2. Each participant will be involved in the study for 6 months.
3. Patients are randomised to one of two arms to ensure there is no selection bias in blood sampling for either group.
4. The study will not affect the patient's treatment, prescribing practice, clinical management or follow-up.
5. Patients will be commenced on Vazkepa therapy as part of the established standard of care. Any adverse events (AEs) and serious adverse events (SAEs) will be managed as per the usual standard of care.
6. As part of the study, patients will have increased clinical access and more frequent contact with the clinical team to allow for early assessment, review, investigation, referral or management.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Vazkepa (icosapent ethyl)

Primary outcome(s)
Measured in blood samples taken from patients with Vazkepa-IPE prescribed (Arm A, 34 patients, blood sampled at day 0, 30, 90 and 180), (Arm B, 34 patients blood sampled at day 120, 180) vs without Vazkepa (Arm B (control), 34 patients, blood sampled at day 0, 30 and 90).

To elucidate the role of Vazkepa-IPE in regulating (reducing) specific inflammatory responses in patients with established ASCVD, the researchers shall determine the ability of Vazkepa (vs no Vazkepa) to:
1. Blunt the priming/activation of specific inflammatory responses (the NLRP3 inflammasome complex) in activated monocyte-derived macrophages isolated from peripheral blood mononuclear cells. Measured using quantitative real-time PCR and a caspase assay at time=0, 30,90,180 (Arm A) (n = 34) and time=120,180 (Arm B) compared to no Vazkepa time=0, 30, 90 (Arm B) (n = 34).
2. Determine whether this leads to a decrease in accelerated cell aging and sustained tissue damage by measuring a decrease in senescent cell accumulation and a decrease in the

accumulation of the senescence-associated secretory phenotype (SASP). Measured using quantitative real-time PCR and plasma/serum biomarkers at time=0, 30,90,180 (Arm A)(n=34) and time=120,180 (Arm B) compared to no Vazkepa time=0, 30, 90 (Arm B) (n=34).
3. Examine cell-cell communication by measuring if Vazkepa suppresses connexin-43 hemichannel mediated ATP release in activated monocyte-derived-macrophages. Measured through ATP release at time=0, 30,90,180 (Arm A) (n = 34) and time=120,180 (Arm B) compared to no Vazkepa time=0, 30, 90 (Arm B) (n = 34).

Key secondary outcome(s))
1. The difference in baseline activity in the chronic stable disease phase of ASCVD (before Vazkepa-IPE therapy) of the Primary Outcome Measures above: of NLRP3 (Measure1), SASP (Measure2) and Cx43 (Measure3) to T2DM status (with T2DM vs without), by measuring caspase-1, ATP release and mRNA expression in PBMC-derived macrophages isolated and differentiated from blood samples taken from patients before starting their Vazkepa-IPE medication (T2DM patients in Arm A Day 0 and in Arm B Day 0, 30 and 90 [n = 34], vs non-diabetics in Arm A Time = 0 and in Arm B Time = 0, 30 and 90 [n=34]).
2. Correlate the magnitude of effect with Vazkepa-IPE therapy of the Primary Outcome Measures above: of NLRP3 (Measure1), SASP (Measure2) and Cx43 (Measure3) to T2DM status (with T2DM vs without), by measuring caspase-1, ATP release and mRNA expression in PBMC-derived macrophages isolated and differentiated from samples taken from patients starting their Vazkepa-IPE medication during the initial 3 months (T2DM patients in Arm A Time = 0, 30 and 90 and in Arm B Time=90, 120 and 180 [n = 34], vs non-diabetics in Arm A Time=0, 30 and 90 and in Arm B Time=90, 120 and 180 [n = 34]).
3. The variation/difference in the baseline activity of NLRP3 (Measure 1), SASP (Measure 2) and Cx43 (Measure 3) in patients without Vazkepa therapy, by measuring caspase-1, ATP release and mRNA expression in the series of pair-wise blood samples taken over 3 months from patients without Vazkepa therapy (Arm B Time = 0, 30 and 90, n = 34)
4. Determine whether the effect of Vazkepa on NLRP3 (Measure 1), SASP (Measure 2) and Cx43 (Measure 3) correlates and extends to day 180 of Vazkepa therapy by measuring caspase-1, ATP release and mRNA expression (Arm A Time = 0, 30, 90 and 180, n = 34).

Completion date
31/03/2027

Eligibility

Key inclusion criteria
1. Patients with established ASCVD
2. Previous event of acute myocardial infarction (AMI)
3. Previous percutaneous coronary intervention (PCI)
4. With or without known T2DM
5. If diabetic, is established and stable on diabetes oral medication
6. Established and stable on statin and/or ezetimibe therapy
7. Low-density lipoprotein cholesterol (LDLC) levels above 1.04 mmol/litre and below or equal to 2.60 mmol/litre
8. Raised fasting triglycerides (1.7 mmol/litre or above)
9. Eligible for Vazkepa therapy within licenced indication and NICE guideline criteria
10. Able to provide informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
85 years

Sex
All

Key exclusion criteria
1. Contraindications to Vazkepa therapy
2. Concurrent or planned bempedoic acid or inclisiran or PCSK9 therapy
3. Pregnancy or breastfeeding
4. Severe end-stage kidney failure
5. Severe end-stage liver disease
6. Other conditions that would reduce the expected life span of a patient to less than 2 years
7. Unable to provide informed consent
8. Acute renal failure
9. Cardiogenic shock
10. Severe valvular heart disease
11. Recent acute cardiac event, revascularisation, or surgery (within 3 months)
12. Recent infective event (within 3 months)
13. Active inflammatory-related conditions, including infection, cancer, or autoimmune disease

Date of first enrolment
26/04/2024

Date of final enrolment
30/04/2026

Locations

Countries of recruitment
United Kingdom

England

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Sponsor information

Organisation
University of Lincoln

ROR
https://ror.org/03yeq9x20

Funder(s)

Funder type
Industry

Funder Name
Amarin Global

Funder Name
University of Lincoln

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date