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Effect of Icosapent ethyl on inflammation in the vessel wall assessed by the Fat Attenuation Index Score (IRIS-FAI)

Submission date 22/06/2024	**Recruitment status** Stopped	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 22/08/2024	**Overall study status** Stopped	
Last Edited 31/10/2025	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Cardiovascular disease is a general term for conditions affecting the heart or blood vessels. Although there have been improvements in the prevention and treatment of cardiovascular disease, it continues to be a major health concern globally. Icosapent Ethyl (IPE), also known as 'Vazkepa', is an approved medication in the UK. This medication is given to people who have their cholesterol levels under control with statins but may still be at risk of cardiovascular disease for other reasons, such as high triglycerides (a type of fat in the blood). The risk that remains after statin use is known as "residual risk". People with high triglyceride levels are at greater risk of having a cardiovascular event, such as a heart attack or stroke. Clinical trials have shown that IPE can help lower this risk in people who are known to have cardiovascular disease and who have raised triglycerides. However, the way IPE works is not fully understood. This trial aims to understand how IPE works by assessing the effect of IPE on a marker known as the Fat Attenuation Index (FAI) score. FAI can detect inflammation in the coronary arteries using images from a CT scan (also known as a coronary CT angiography). Testing the effect of IPE on the FAI score will provide a better understanding of how IPE works and how it can be used to improve the health of people who are at risk of having a cardiovascular event.

Who can participate?
High-risk adults aged ≥18 years old with established cardiovascular disease and raised triglyceride levels who are already receiving statins.

What does the study involve?
The research will be carried out across approximately 6 different NHS hospital sites in the UK. The hypothesis is that targeted treatment of participants with high vascular inflammation taking IPE reduces vascular inflammation to a greater extent than standard-of-care treatment. Participants randomised to the treatment arm will be asked to take two capsules of IPE twice daily for 52 weeks.

What are the possible benefits and risks of participating?
The study has the potential to provide important insights into the use of IPE as an adjunct

therapy for reducing cardiovascular risk in high-risk, statin-treated patients with established CVD and elevated plasma triglycerides (TGs).
As IPE is an approved medication with an established safety profile, there is a low risk of side effects. The most commonly reported adverse events are gastrointestinal disturbances and skin reactions. However, in rare cases, IPE has been associated with an increased risk of bleeding, particularly in patients receiving concomitant anticoagulant therapy. Therefore, patients receiving anticoagulants will be excluded from the study. Undesirable effects will be noted in the participant information leaflet for the patient's review and consideration, before consenting to the study.
The study involves a low risk of radiation exposure, as it uses computed tomography (CT) imaging to assess coronary fat attenuation index. The radiation dose associated with coronary CT angiography is generally low. The risk of radiation exposure will be minimized by using low-dose CT imaging protocols and limiting the number of scans to only those necessary for the study at follow-up as baseline measurements have already been obtained as part of routine clinical practice. If a participant has had a routine CTCA scan within 3 months before the Week 52 visit, a repeat CTCA at Week 52 scan will not be required to avoid repeated exposure to radiation.
There is a limited amount of data on the use of IPE in pregnant women, and it is not known whether the drug is excreted in human milk. Therefore, women of childbearing potential will be asked to undertake a urine pregnancy test at the randomisation clinic visit. Results must be reviewed, and eligibility confirmed before dispensing trial medication. If a participant becomes pregnant during the study, trial medication should be discontinued immediately. This information will be clearly stated in the PIS.
Blood tests may cause some redness, swelling of the vein, infection or fainting and this is explained to participants in the PIS.
Participants will be asked to travel to the clinic more regularly than they normally would, which could interfere with everyday plans. Participants will be compensated for their travel costs. To reduce the burden on the participant, 5 out of the 9 visits will be conducted by telephone rather than in the clinic.
The participants will be given the option to download a free digital health app (such as ELFIE) on their mobile phones as a tool to increase medication compliance. The app can push reminder notifications to the participant's mobile phone when they are required to take their medication. This is an optional tool, and will not be mandatory for any participant.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
June 2024 to November 2026

Who is funding the study?
Amarin UK Limited

Who is the main contact?
Imperial Clinical Trials Unit

Contact information

Type(s)
Public, Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
1009727

Protocol serial number
24IC8850

Study information

Scientific Title
Effect of icosapent ethyl on coronary Fat Attenuation Index score in high-risk, statin treated patients with established cardiovascular disease and elevated plasma triglycerides

Acronym
IRIS-FAI

Study objectives
To evaluate the impact of IPE treatment on coronary inflammation (assessed by Fat Attenuation Index-Score).

-To evaluate the impact of Icosapent Ethyl (IPE) treatment on cardiovascular risk (assessed by CaRi-Heart®) plaque morphology and biochemical lipid and inflammation parameters.
-Evaluating the effect of IPE on lipid parameters, including plasma Triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non-

HDL-C.
• Assessing the safety and tolerability of IPE in high-risk, statin-treated patients with established cardiovascular disease and elevated plasma TGs.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 12/08/2024, South Central - Hampshire A Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8120, 207 104 8210, 2071048135; hampshirea.rec@hra.nhs.uk), ref: 24/SC/0231

Primary study design
Interventional

Study design
Randomized controlled open-label parallel-group trial

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Cardiovascular disease, hypertriglyceridemia

Interventions
This trial has an open-label treatment arm with Icosapent Ethyl (IPE) and a usual care arm. 50 participants will be randomised to IPE plus usual care, and 50 will be randomised to usual care only.

Participants in the IPE arm will be given standard advice that is consistent with usual clinical practice i.e. to take two 998mg capsules, orally, twice daily at a similar time each day and to take the medication with or following a meal.

Eligibility for inclusion in the trial will be confirmed at the randomisation visit. The randomisation sequence will be created by Sealed Envelope and will be incorporated into the EDC. Randomisation will be performed using random permuted blocks of size 4 and 6. To aid concealment the block size will be randomly chosen for each block.

All participants will be followed up for 52 weeks from randomisation.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Vazkepa [Icosapent Ethyl]

Primary outcome(s)

Median change in coronary artery inflammation measured using the Fat Attenuation Index-Score from screening to 12 months, IPE vs standard of care, including all randomized participants (Intention to treat)

Key secondary outcome(s)
1. Median change in CaRi-Heart® Risk, and the associated predicted 8-year risk of cardiac mortality and major adverse cardiovascular events, with IPE vs standard of care (comparison by change from screening to 12 months, IPE vs standard of care)
2. Median change in non-calcified plaque volume and total atherosclerotic plaque burden between screening CTCA and 12-month CTCA, IPE vs usual care
3. Median change in plasma lipid parameters, from screening to 12 months

Completion date
21/10/2025

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
Current inclusion criteria as of 07/05/2025:
1. Adult aged ≥18 years
2. Participants will come from one of the following groups:
2.1. enrolled in the ORFAN registry OR
2.2. Undergone CTCA with CaRi-Heart® analysis performed
3. CTCA performed ≤4 months prior to screening visit
4. FAI score ≥75th percentile in the left anterior coronary or right coronary artery or with FAI score ≥95th percentile in the circumflex coronary artery; OR CaRi-Heart Risk >5%
5. Evidence of established coronary artery disease defined by the presence of at least one of the following:
5.1. Established cardiovascular disease
5.2. Or diabetes with at least one other cardiovascular risk factor
6. Fasting or non-fasting serum triglycerides ≥1.7 mmol/L within the last 9 months, either on ORFAN baseline blood sample or blood sample taken from routine care, whichever measurement is available and/or most recent
7. Stable dose of statin therapy for at least 4 weeks prior to randomization
8. Able to undergo CT imaging of the coronary arteries at 12 months follow-up.
9. Women of childbearing potential willing to use an acceptable method(s) of birth control during the study and for 30 days after the end of treatment, including combined hormonal contraception (oral contraceptive pills, contraceptive patch, vaginal ring), progestogen-only contraception (oral contraceptive pills, injectable, implant, intrauterine device [IUD], hormonal intrauterine system [IUS]), barrier methods with spermicide (condoms, diaphragm with spermicide), intrauterine device (IUD) without hormones, and sterilization (surgical sterilization of the participant or partner). There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.
10. Willing and able to provide written informed consent to participate in the study.

Previous inclusion criteria:
1. Adults aged ≥18 years old

2. Participants will come from one of the following groups:
2.1. Enrolled in the ORFAN registry OR
2.2. Undergone CTCA with CaRi-Heart® analysis performed
3. CTCA performed ≤2 months before screening [defined as screening]
4. FAI score ≥75th percentile in the left anterior coronary or right coronary artery or with FAI score ≥95th percentile in the circumflex coronary artery; OR CaRi-Heart® Risk >5%
5. Evidence of established coronary artery disease defined by the presence of at least one of the following:
5.1. Evidence of coronary artery plaques (evaluable, pre-randomization CTCA with quantifiable, non-calcified plaque in an unstented segment)
5.2. Coronary artery Calcium Score (CAC) >100
6. Fasting or non-fasting serum triglycerides ≥1.7 mmol/L within the last 6 months, either on ORFAN baseline blood sample or blood sample taken from routine care, whichever is available and/or most recent
7. Stable dose of statin therapy for >30 days before randomization
8. Able to undergo CT imaging of the coronary arteries at 12 months follow-up
9. Women of childbearing potential willing to use an acceptable method(s) of birth control during the study and for 30 days after the end of treatment, including combined hormonal contraception (oral contraceptive pills, contraceptive patch, vaginal ring), progestogen-only contraception (oral contraceptive pills, injectable, implant, intrauterine device [IUD], hormonal intrauterine system [IUS]), barrier methods with spermicide (condoms, diaphragm with spermicide), intrauterine device (IUD) without hormones, and sterilization (surgical sterilization of the participant or partner). There are no protocol-specific birth control requirements for men with partners who can become pregnant.
10. Willing and able to provide written informed consent to participate in the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
2

Key exclusion criteria
Current exclusion criteria as of 07/05/2025:
1. Use of other omega-3 fatty acid medicines, either prescription or over the counter within the previous 28 days
2. Known allergy or hypersensitivity to icosapent ethyl or fish, shellfish, soya, or peanuts.
3. History of pancreatitis or uncontrolled diabetes mellitus (HbA1c >8% or 64 mmol/mol).
4. Use of PCSK9 inhibitors within the previous 90 days.

5. Use of Bile Acid sequestrants within the previous 7 days
6. Serum triglycerides ≥5.63 mmol/L
7. Serum calculated or directly measured LDL-C ≥2.6 mmol/L
8. Current use of anti-coagulant therapy.
9. Prior history of permanent or persistent atrial fibrillation (patients with a history of paroxysmal atrial fibrillation are eligible)
10. Any condition that, in the opinion of the study investigator, would make a patient ineligible for icosapent ethyl as per the SmPC, or for CTCA
11. Active chronic treatment with any anti-inflammatory agents (e.g. NSAIDs, systemic corticosteroids) within the previous 28 days
12. Severe chronic kidney disease (estimated glomerular filtration rate <30 ml/min/1.73 m² and /or serum creatinine >2.5 mg/dL or 220 µmol/l).
13. Hepatic dysfunction (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >3 × the upper limit of normal [ULN] measured on local labs in the last 6 months)
14. Participants who have participated in another research study involving a treatment intervention or an investigational product in the past 12 weeks.
15. Contraindication to iodinated contrast media for CTCA.
16. Pregnant or unwilling to take a pregnancy test at the randomisation visit or lactating women.

Previous exclusion criteria:
1. Use of other omega-3 fatty acid medicines, either prescription or over the counter within the previous 28 days
2. Known allergy or hypersensitivity to icosapent ethyl or any of its components
3. History of pancreatitis or uncontrolled diabetes mellitus (HbA1c >8% or 10.1 mmol/L)
4. Use of PCSK9 inhibitors within the previous 90 days
5. Use of Bile Acid sequestrants within the previous 7 days
6. Serum triglycerides >5.63mmol/L
7. Serum calculated or directly measured LDL-C ≥2.6mmol/L
8. Current use of anticoagulant therapy
9. Prior history of permanent or persistent Atrial Fibrillation. Patients with a history of paroxysmal atrial fibrillation are eligible
10. Any condition that, in the opinion of the study investigator, would make a patient ineligible for icosapent ethyl as per the SmPC, or for CTCA
11. Active chronic treatment with any anti-inflammatory agents (e.g. NSAIDs, systemic corticosteroids)
12. Severe Chronic kidney disease (estimated glomerular filtration rate <30 ml/min/1.73 m² and /or serum creatinine >2.5 mg/dL or 220 µmol/l).
13. Hepatic dysfunction (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3 × the upper limit of normal [ULN] measured on local labs in the last 6 months)
14. Participants who have participated in another research study involving a treatment intervention or an investigational product in the past 12 weeks.
15. Contraindication to iodinated contrast media for CTCA.
16. Pregnant or unwilling to take a pregnancy test at the randomisation visit or lactating women.

Date of first enrolment
26/03/2025

Date of final enrolment
21/10/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Industry

Funder Name
Amarin UK Limited

Results and Publications

Individual participant data (IPD) sharing plan
The Sponsor and trial funder made the decision to terminate the IRIS-FAI trial early due to low patient recruitment. Unfortunately, there is no further funding available to extend the recruitment period again. Despite significant screening efforts from all participating sites, it has become clear that the participant profile required to answer the scientific question cannot be achieved via the small number of sites and limited funding available. Given these challenges, the decision was made collaboratively with the study team that continuation of the study was not operationally viable. Consequently, no datasets will be produced or shared as part of this project.

IPD sharing plan summary
Not expected to be made available