ISRCTN43650325 https://doi.org/10.1186/ISRCTN43650325

Participants undergoing coronary artery bypass graft will receive veins removed from legs treated with gene therapy and a placebo for grafting. Vein segments are treated at random with either gene therapy or a placebo.

Submission date 15/11/2024	**Recruitment status** Recruiting	[_] Prospectively registered [_] Protocol
Registration date 18/02/2025	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 18/02/2025	**Condition category** Surgery	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims

Coronary artery bypass graft (CABG) is recommended in clinical guidelines for the treatment of multivessel and/or left main obstructive coronary atherosclerosis (fatty plaque). Typically, the CABG operation involves three ‘bypass grafts’. The surgeon will harvest a saphenous vein from the leg, and divide the vein into two or three segments for use as grafts. The surgeon will also dissect the internal mammary artery to use as an additional graft. During the surgery, the saphenous veins are connected to the aorta and the coronary arteries to ‘bypass’ blockages in the right coronary artery and the left obtuse marginal coronary artery. The mammary artery is grafted to the left anterior descending artery which is the main branch of the left coronary artery. The CABG operation is routinely undertaken in cardiothoracic centres worldwide. In the West of Scotland, cardiac surgery services are provided by the NHS Golden Jubilee National Hospital as part of a regional model of integrated care. Patients with ischaemic symptoms, such as angina and myocardial infarction, are referred by cardiologists to the multidisciplinary team meeting where a consensus-based care plan is established for individual patients. Patients who undergo CABG surgery have an appreciable likelihood of developing recurrent angina and experiencing a heart attack in the longer term. Although the artery graft works well life-long, on exposure to arterial levels of blood pressure, the vein grafts undergo maladaptive remodelling in the longer term. The mechanism involves neointima formation, wall thickening, lumen loss and progressive occlusion limiting the flow of blood from the aorta to the heart. Despite intensive biomedical research and clinical trials during the past three decades, there are no preventive treatments for vein graft disease and vein graft failure post-CABG presents an unmet therapeutic need. The purpose of this study is to investigate the safety of a new gene therapy (Adenovirus tissue inhibitor of matrix metalloproteinase-3 or Ad5.CMVTO.TIMP-3) to help keep vein grafts open. This study will also help to find the right treatment dose that could be used in any future studies.

Who can participate?
Adult patients referred for planned CABG surgery anticipated to involve one mammary artery graft and two or more saphenous vein grafts.

What does the study involve?
Each of the two vein segments will be exposed for 30 minutes to either the gene therapy or placebo media. Participants will receive both treated and placebo veins, acting as their own control in the study.

What are the possible benefits and risks of participating?
This study will provide information on a possible new treatment to prevent vein graft failure after bypass surgery.

Ad5.CMVTO.TIMP-3 is an unlicensed gene therapy. The known and potential risks to human participants include the occurrence of vein graft failure and immune activation with clinically important systemic effects. These include allergy, myocarditis, pericarditis, hepatitis, nephritis, pneumonitis, and vasculitis. The clinical risk to participants is mitigated in several ways. First, the gene therapy will be administered to SVG ex vivo (outside of the body), minimising the risk of systemic exposure to the individual. Second, patients with a systemic health problem that would increase the risk of an immune reaction will not be eligible to participate. Third, women of child-bearing potential (i.e. pre-menopause) or breastfeeding will not be enrolled. Fourth, education and training of the staff, including members of the research teams and NHS staff providing patient care, will be prioritised. Fifth, willingness to comply with the protocol is an inclusion criterion. Sixth, in the immediate post-surgery period, participants will be managed within an ICU or HDU clinical area and thereafter, the protocol involves scheduled follow-up visits for a clinical review. Lastly, the standard care surgical approach should not change.

Where is the study run from?
BHF Glasgow Cardiovascular Research Centre, University of Glasgow

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

Who is funding the study?
1. Medical Research Council
2. The British Heart Foundation

Who is the main contact?
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Contact information

Type(s)
Public, Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1010338

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
GN10CA195

Study information

Scientific Title
A randomised Placebo-contROlled Trial of Ad5.CMVTO.TIMP-3 to prEvent Coronary artery bypass grafT failure

Acronym
PROTECT

Study objectives
Heart bypass surgery relieves chest pain (angina) symptoms and lowers the chance of a heart attack in the longer term. However, the veins may block – one in ten may be blocked by one year after surgery and two thirds may be blocked by ten years. The main reason for vein grafts blocking is because blood pressure causes the veins to thicken. There are no preventive treatments for vein graft disease.

The purpose of this study is to investigate the safety of a new gene therapy to help keep vein grafts open. Our study will also help to find the right treatment dose that could be used in any future studies.

The primary objective is to determine a tolerable dose of Ad5.CMVTO.TIMP-3 to be used in future studies by evaluating safety and dose-limiting toxicity (DLT).

Safety
Secondary endpoints at 12 months:
1. SVG occlusion by CTCA at 12 months;
2. SVG with diameter stenosis >50%
3. SVG with diameter stenosis >50% or occlusion
4. SVG revascularisation

Major adverse cardiovascular events: MACCE (death, re-hospitalisation for cardiovascular events including recurrent MI, heart failure); repeat revascularization of a native coronary artery or graft, as adjudicated by the SRC, until the end of the trial.

Withdrawal rate
SAEs
Efficacy
The within-subject difference between active therapy- and placebo-treated SVG including all available assessments.
Patient reported outcome measures: EQ5D, Seattle Angina Questionnaire, DASI

Ethics approval required
Ethics approval required

Ethics approval(s)
Submitted 12/11/2024, North East - York - 6th Dec; South Central - Oxford A - 6th Dec; South Central - Berkshire B - 10th Dec (-, -, -, United Kingdom; -; not@available.com), ref: 24/SC/0395

Study design
Randomised placebo-controlled open-label parallel-group study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Vein graft blocking in those having a Heart Bypass Surgery to address Heart Disease symptoms, such as chest pain and shortness of breath

Interventions
Coronary artery bypass graft (CABG) is recommended for the treatment of multivessel and/or left main obstructive coronary atherosclerosis (fatty plaque). Typically, the CABG operation involves 'bypass grafts'. The surgeon will harvest a saphenous vein from the leg, and divide the vein into two or three segments for use as grafts. During the surgery, the saphenous veins are connected to the aorta and the coronary arteries to 'bypass' blockages. Patients who undergo CABG surgery have an appreciable likelihood of developing recurrent angina and experiencing a heart attack in the longer term. Although the artery graft works well life-long, on exposure to arterial levels of blood pressure, the vein grafts undergo maladaptive remodelling in the longer term. Each of the 2 Vein segments will receive 30 min exposure to either; gene therapy - Adenovirus tissue inhibitor of matrix metalloproteinase – 3 or placebo media. Saphenous vein segments will be treated depending on the cohort the participant is recruited to. This means that each participant that receives a vein treated with active gene therapy will also receive a vein treated with a placebo, therefore each participant acts as their own treated versus placebo comparison.

Intervention Type
Drug

Pharmaceutical study type(s)
Dose response, Therapy

Phase
Phase I

Drug/device/biological/vaccine name(s)
Ad5.CMVTO.TIMP-3 [Ad5.CMVTO.TIMP-3]

Primary outcome measure
Incidence of treatment-emergent adverse events (TEAE) measured using an assessment of physical examinations (if indicated), changes in vital signs and ECGs, and analysis of clinical laboratory samples by the end of the study

Secondary outcome measures
1. The following saphenous vein graft (SVG) measures will be assessed at 12 months:
1.1. SVG occlusion by CTCA at 12 months
1.2. SVG with diameter stenosis >50%
1.3. SVG with diameter stenosis >50% or occlusion
1.4. SVG revascularisation
2. Major adverse cardiovascular events: MACCE (death, re-hospitalisation for cardiovascular events including recurrent MI, heart failure); repeat revascularization of a native coronary artery or graft, as adjudicated by the SRC, measured using data collected in Case Report Forms until

the end of the trial
3. Withdrawal rate, serious adverse event (SAE) rate measured using measured using data collected in Case Report Forms until the end of the trial
4. Efficacy - The within-subject difference between active therapy- and placebo-treated SVG including all available assessments measured using clinical data until the end of the trial
5. Patient-reported outcome measures (PROMs) measured using the EuroQol 5 Dimension (EQ-5D), Seattle Angina Questionnaire and the Duke Activity Status Index (DASI) at V2 (Pre CABG) and at V6 (6 weeks post-procedure)

Overall study start date
13/11/2024

Completion date
18/12/2026

Eligibility

Key inclusion criteria
1. Referral for planned CABG surgery anticipated to involve one mammary artery graft and two or more saphenous vein grafts.
2. Willingness to comply with all trial-related procedures and visits as defined in the protocol
3. Written informed consent

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
12

Key exclusion criteria
1. Requirement for immunosuppressive drug therapy at any time during the past 3 months; whether administered orally, subcutaneously or intravenously. This would include corticosteroids (but not inhaled or topical), drugs used following transplantation (e.g. tacrolimus, cyclosporine), anti-metabolite therapies (e.g. mycophenolic acid (Myfortic), azathioprine, leflunomide (Arava)), and immunomodulators including biologics (e.g. adalimumab, etanercept, aldesleukin), and conventional and targeted synthetic DMARDs (cyclophosphamide, methotrexate, baracitinib etc). Please note this list is not exhaustive and a requirement for other immunosuppressive drugs not listed would also exclude the patient and must be discussed with the Sponsor.
2. Active or prophylactic treatment with oral or parenteral antibiotic, antifungal or antiviral therapy to treat or prevent infection.
3. Anti-cancer treatment (excluding surgery) at any time during the past 3 months including chemotherapy, radiotherapy and treatment with biologics such as Vascular Endothelial Growth Factor Receptor (VEGFR) inhibitors (e.g. bevacizumab, pazopanib), targeted chemotherapy drugs

e.g. protein kinase inhibitors, and cell-based therapy e.g immunotherapy. This list is not exhaustive and sponsor or CI should be contacted for advice if required.
4. Previously enrolled in a gene therapy or cell therapy trial.
5. Liver disease with a Child-Pugh score of A (5-6 points) or higher. See Appendix 3*
6. Women who are pregnant, breast-feeding or of child-bearing potential (WoCBP).
7. Men who are sexually active with a WoCBP who are unwilling to use condoms or other highly effective methods of contraception for the duration of study treatment and for 12 weeks after dosing.
8. Participation in another intervention study involving a drug within the past 90 days or 5 half-lives whichever is longer (co-enrolment in observational studies is permitted).
9. Incapacity or inability to provide informed consent.
10. Unwillingness to comply with all trial related procedures and visits defined in the protocol.

Date of first enrolment
01/01/2025

Date of final enrolment
31/10/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Golden Jubilee National Hospital
Agamemnon Street
Clydebank
United Kingdom
G81 4DY

Sponsor information

Organisation
NHS Greater Glasgow and Clyde

Sponsor details
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Sponsor type
Hospital/treatment centre

Website
https://www.nhsggc.scot/

ROR
https://ror.org/05kdz4d87

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Sponsor type
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ROR
https://ror.org/00vtgdb53

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
British Heart Foundation

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer reviewed scientific journals
2. Internal report
3. Conference presentation
4. Submission to regulatory authorities

Intention to publish date
18/12/2027

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

During the trial and in the period prior to publication of the main study results as described in the protocol, only the Glasgow CTU will have access to the full dataset. After that period, the Trial Steering Committee will conduct further data analyses for a period of approximately three years. After that time the Trial Steering Committee will consider requests from external parties for further analyses of the study data.
Such transfer will require assurances on information security systems at the sites that data are

to be transferred to and will involve a legal data transfer agreement. A log of all data requests and subsequent data transfers will be held at the Glasgow CTU.
Participants are asked to consent to the sharing of deidentified data.

IPD sharing plan summary

Data sharing statement to be made available at a later date