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Inhibiting white blood cell function as a new way to treat coronary heart disease

Submission date 17/02/2016	**Recruitment status** Stopped	[X] Prospectively registered [X] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 25/02/2016	**Overall study status** Stopped	
Last Edited 17/03/2023	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims

Atherosclerosis is an inflammatory disease of blood vessels, which gives rise to fatty deposits ('atheromatous plaques') and narrowing of those vessels. It is the commonest cause of death and disability in the Western world and its complications – which are mainly heart attack and stroke – can be caused by the splitting open (rupturing) of these plaques. If a plaque does rupture a blot clot can form on its surface that partially or completely stops blood flow through the blood vessel. White blood cells (in particular neutrophils) play an important part in this process. In this study, researchers will determine whether stopping neutrophils from migrating (moving) into plaques using the novel drug AZD5069 (which blocks a molecule important to the normal functioning of neutrophils) will improve the structure and function of coronary arteries in patients with coronary heart disease who are undergoing treatment for atherosclerosis involving balloon dilatation of the narrowed coronary arteries together with placement of a stent (so-called percutaneous coronary intervention, or PCI).

Who can participate?

Adults (aged at least 18) with coronary heart disease and being treated with PCI.

What does the study involve?

Participants are randomly allocated to one of two groups. Those in group 1 are given AZD5069 on top of their usual therapy for 6 months. Participants in group 2 are given a placebo on top of their usual therapy for 6 months. The structure and function of each participants coronary arteries are assessed at the start of the study and again after 6 months. This includes PET-CT scans, intravascular ultrasound (or IVUS - a method of seeing inside blood vessels) coronary angiography (a test that uses dye and special x-rays to show inside coronary arteries) and a number of blood tests.

What are the possible benefits and risks of participating?

AZD5069 is not a licensed medicine: it was originally developed for treatment of asthma and obstructive airways disease. Previous studies have shown that the drug is well tolerated but may occasionally cause a drop in the number of neutrophils in the blood, leading to a possible risk of infection. This risk, however, has been shown to be rare at the dose used for this study.

Where is the study run from?
St Thomas' Hospital, London (UK)

When is the study starting and how long is it expected to run for?
January 2016 to February 2022 (updated 07/08/2020, previously: December 2017)

Who is funding the study?
AstraZeneca (UK)

Who is the main contact?
Professor Albert Ferro

Contact information

Type(s)
Scientific

Contact name
Prof Albert Ferro

ORCID ID
https://orcid.org/0000-0002-5486-9145

Contact details
King's College London
3.07 Franklin-Wilkins Building
150 Stamford Street
London
United Kingdom
SE1 9NH

Additional identifiers

Clinical Trials Information System (CTIS)
2016-000775-24

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
AZ/KCL/5069

Study information

Scientific Title
CXCR2 inhibition: a novel approach to treating coronary heart disease

Study objectives

The primary objective of this trial is to determine whether CXCR2 inhibition, in patients following percutaneous coronary intervention for atherosclerotic coronary disease, will give rise to improvement in coronary endothelial function. The secondary objectives are to ascertain whether CXCR2 inhibition in this context gives rise to a change in plaque composition towards a more stable form and to a decrease in in-stent restenosis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central - Berkshire B Research Ethics Committee , 29/09/2016, ref: 16/SC/0478

Study design
Single centre interventional randomised double-blind placebo-controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Coronary heart disease

Interventions
The trial will be a randomised double-blind placebo-controlled parallel group study. Eligible patients (n=90) undergoing percutaneous coronary intervention (PCI) either for stable coronary disease or following admission to hospital with acute coronary syndrome (ACS), will be recruited from the Cardiac Catheterisation laboratories at St Thomas' Hospital. Once written informed consent has been obtained, patients will undergo coronary angiography with PCI as per normal clinical care, but will also undergo intravascular ultrasound (IVUS) using the Volcano system to provide virtual histology of all major coronary vessels (culprit and non-culprit, intervened and non-intervened). A subset of enrolled patients will be invited to have ComboWire assessment at the time of coronary angiography.

Four weeks later, subjects will re-attend the Cardiology department, at which time a full history and physical examination will be performed and inclusion criteria confirmed. Assessments will include 12-lead electrocardiogram, and blood tests (fasted) for blood count and biochemistry (renal, liver, lipid, glycaemic and thyroid profiles), high sensitivity C-reactive protein (hs-CRP, a well validated marker of cardiovascular risk) and homocysteine level. Screening blood test for disorders which may exclude patients from the study will be drawn as indicated (e.g. serum hepatitis B surface antigen, hepatitis C antibody, and HIV testing if prompted by history). Additionally, an aliquot of blood will be taken for measurement of circulating monocyte-platelet aggregates. In the case of women of child-bearing potential, pregnancy will be excluded by performing a pregnancy test on a spot urine. At the same visit, an ammonia PET cardiac scan will be performed to measure coronary flow reserve (CFR). PET scans will be performed sequentially at rest and during pharmacological stress using an infusion of 140 µg/kg/min adenosine with intravenous administration of 13N-ammonia at rest and again during peak stress to measure myocardial perfusion. CT scans will be performed prior to the PET for attenuation correction and to measure calcium score. The first 10 of these subjects will receive a second PET scan (at rest

and during pharmacological stress) within 5 days of the first, to measure intra-subject (test-retest) repeatability of CFR measurement.

After randomization, subjects will be allocated 2:1 to receive either AZD5069 or matched placebo, orally, for the succeeding 24 weeks (pending safety review). At different time points (day 1 of dosing and weeks 1, 2, 4, 8, 12, 16, 20 and 24: the projected end point of the study), patients will attend for repeat visits prior to their morning dose, at which time they will undergo repeat physical examination and further blood samples will be taken, as described below, for the purposes both of measuring plasma drug levels and of determining safety and efficacy biomarkers. At weeks 4, 8, 12, 16, 20 and 24, spot urines will be obtained from women of child-bearing potential in order to exclude pregnancy; if positive at any point, they will be immediately withdrawn from the study. At the final visit, a repeat ammonia PET scan will be performed, again at rest and during pharmacological stress, to assess change from baseline in CFR; and at the time of the study endpoint, repeat coronary angiography together with IVUS and virtual histology will be performed, to assess change in plaque composition and degree of restenosis. Those patients that initially had ComboWire assessment, will be invited to have repeat ComboWire assessment at the time of their repeat coronary angiography.

At day 1, pre-dose samples for full blood biochemistry will be taken (renal, liver, glycaemic and lipid profiles, and creatine kinase), and additional biomarkers (hs-CRP, circulating MPA) to establish baseline before the study start. 10 mL blood will be banked at -80C to allow for the possibility of future analyses. At the week 1, 2, 4, 8, 12, 16, 20 and 24 visits, in all subjects, all of the pre-dose measurements from day 1 will be repeated; pre-dose (trough) and peak (2 h post-dose) AZD5069 plasma concentration will also be measured at the week 1, 12 and 24 time points in all subjects. Following the final dose at week 24, a 2-week post-dosing follow-up safety visit will be conducted.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
AZD5069

Primary outcome(s)
Coronary vascular function, measured by change in coronary flow reserve (a measure of the coronary arteries to dilate, assessed by PET scanning, and, in a subset, invasive coronary flow measurements) from baseline to 6 months.

Key secondary outcome(s))
1. Change in plaque composition, measured using intravascular ultrasound (IVUS) at baseline and at 24 weeks
2. Degree of in-stent restenosis, measured using intravascular ultrasound at baseline and at 24 weeks
3. Change in microvascular resistance, done by by CombiWire assessment (involving insertion of a specialised flow-measurement wire into the coronary arteries) at baseline and at 6 months (on a subgroup of patients)

Completion date

28/02/2022

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. Men and women ≥ 18 years of age
2. Angiographically proven coronary heart disease undergoing native-vessel PCI for non-ST-elevation myocardial infarction or unstable or stable coronary disease
3. Absolute blood neutrophil count at the time of PCI as well as 4 weeks after PCI of >4.0 x 109/L
4. Otherwise receiving standard of care for ischaemic heart disease (including appropriate anti-platelet therapy, statin, antihypertensive as clinically indicated)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
14

Key exclusion criteria
1. At any time after initial screening (ie at the time of PCI + IVUS), requirement or anticipated requirement, by clinical care guideline or in the opinion of the treating physician, for a new medication which may affect trial primary and / or secondary endpoints (ie specifically new lipid lowering therapy, anti-hypertensive therapy, or immunomodulatory therapy). Note that dose titration of chronic therapy initiated prior to PCI is permissible during the trial.
2. History of inability or, in the opinion of the investigator, anticipated inability to tolerate adenosine-based pharmacologic stress testing (e.g. active pulmonary broncho-constrictive disorder, second or third degree AV block without a cardiac pacemaker, resting systolic blood pressure <90mmHg, unstable coronary disease, use of medications which may interfere with the test)
3. Acute ST-elevation myocardial infarction
4. Prior cardiovascular surgery
5. Significant vascular anatomic abnormality which in the opinion of the investigator portends unacceptable risk to serial coronary IVUS examination
6. Scheduled inpatient surgery or planned hospitalisation during the study period
7. Any clinically significant disease or disorder (eg, cardiovascular, gastrointestinal, liver, renal,

neurological, musculoskeletal, endocrine, metabolic, psychiatric, major physical impairment) which, as judged by the investigator, might put the patient at risk because of participation in the study
8. Recurrent, latent, or chronic infections, as judged by the investigator, or with a history of osteomyelitis, or at risk of infection (surgery, trauma, or significant infection within 30 days before enrolment), or with a history of skin abscesses or a soft tissue infection within 60 days before enrolment
9. Evidence of active tuberculosis, either treated or untreated, or latent tuberculosis without completion of an appropriate course of treatment or appropriate ongoing prophylactic treatment
10. Positive test for serum hepatitis B surface antigen, hepatitis C antibody, or HIV
11. Patients vaccinated with a live or live-attenuated vaccine in the 2 weeks prior to enrolment
12. Use of any immunosuppressive treatment (eg, methotrexate, troleandomycin oral gold, cyclosporine, azathioprine, intramuscular long-acting corticosteroid [except for asthma exacerbations]) within 60 days prior to enrolment
13. Prior solid organ or bone marrow transplantation
14. History of any primary immunodeficiency disorder excluding asymptomatic selective IgA or IgG subclass deficiency
15. Active malignancy or neoplastic disease in the previous 5 years other than superficial basal cell carcinoma
16. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.5 times the upper limit of normal (ULN) 4 weeks after PCI
17. QTc of >450 ms for males and 470 ms for females 4-weeks after PCI
18. Current evidence of drug abuse or significant history of drug abuse, as judged by the investigator.;
19. Current evidence of alcohol abuse or a significant history of alcohol abuse, as judged by the investigator
20. Pregnancy or breast feeding during the study
21. Contraindication to any of the study treatments or known or suspected hypersensitivity to the investigational product, compounds of the same class, other study treatments or any excipients as specified in Section 5.7
22. Unwilling, or unable, to give informed consent

Date of first enrolment
01/06/2016

Date of final enrolment
30/06/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St Thomas' Hospital
Westminster Bridge Road

London
United Kingdom
SE1 7EH

Sponsor information

Organisation
King's College London

Organisation
Guy's & St Thomas' NHS Foundation Trust

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 5.0	05/07/2019	12/08/2022	No	No