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Randomized evaluation of the effects of anacetrapib through lipid-modification

Submission date
17/11/2010

Recruitment status
No longer recruiting

Registration date
18/11/2010

Overall study status
Ongoing

Last Edited
27/09/2023

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
Anacetrapib is a new cholesterol treatment which is being developed by MSD (known as Merck in the US and Canada). In previous studies anacetrapib reduced levels of bad LDL cholesterol in the blood in addition to the reductions achieved with statin drugs, and it more than doubled good HDL cholesterol levels. The aim of this study is to see whether fewer participants given anacetrapib have heart attacks, revascularisation procedures or die from coronary heart disease compared with participants treated with a placebo (dummy) drug.

Who can participate?
Men and women aged at least 50 with a history of heart attack, stroke or peripheral arterial disease.

What does the study involve?
All participants are given atorvastatin (a commonly used statin drug) to ensure good control of LDL (bad) cholesterol. In addition, they are randomly allocated to receive anacetrapib or matching placebo (dummy) tablets daily for at least 4 years. There is a further period of at least 2 years of off-treatment follow-up.

What are the possible benefits and risks of participating?
Statin treatment is known to reduce the risk of heart attacks and strokes and is generally well-tolerated. However, atorvastatin is associated with a small increase in the risk of liver enzyme abnormalities (although it is not thought to cause liver damage) and can also rarely (typically < 1 in 10,000 per year) cause muscle pain or weakness associated with blood test abnormalities showing muscle damage (known as myopathy). Blood tests are used to monitor liver function and, where indicated, muscle enzymes, throughout the study. Anacetrapib is not known to have any side effects and, in particular, has not been found to cause elevations in liver enzymes or muscle adverse effects. However, reliable assessment of the safety of anacetrapib in a large-scale study is essential before it can be used in routine practice. On the other hand, the lipid changes that are produced by anacetrapib might well reduce the risk of vascular events substantially and participants might potentially benefit from participating in the study.

Where is the study run from?
The Clinical Trial Service Unit (CTSU) at Oxford University (UK)

When is the study starting and how long is it expected to run for?
The study started in May 2011. All participants stopped study treatment prior to February 2017 and direct participant follow-up was completed in April 2019. However, in the UK the researchers will continue to collect information on health outcomes via registries and NHS sources for many years.

Who is funding the study?
Merck and Co, Inc. (USA)

Who is the main contact?
Dr Louise Bowman
reveal@ndph.ox.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Louise Bowman

Contact details
Clinical Trial Service Unit
Richard Doll Building
University of Oxford
Old Road Campus
Headington
Oxford
United Kingdom
OX3 7LF
+44 (0)1865 743875
reveal@ndph.ox.ac.uk

Additional identifiers

ClinicalTrials.gov (NCT)
NCT01252953

Clinical Trials Information System (CTIS)
2010-023467-18

Protocol serial number
CTSUREVEAL1

Study information

Scientific Title

REVEAL: Randomized EValuation of the Effects of Anacetrapib through Lipid-modification. A large-scale, randomized placebo-controlled trial of the clinical effects of anacetrapib among people with established vascular disease

Acronym
REVEAL

Study objectives
To determine whether lipid modification with anacetrapib 100mg daily reduces the risk of coronary death, myocardial infarction or coronary revascularization (collectively known as major coronary events) in patients with circulatory problems who have their LDL cholesterol level treated with a statin.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Oxfordshire REC B, 25/01/2011, ref: 10/H0605/83

Study design
Multicentre multinational double-blind randomised placebo-controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Atherosclerotic cardiovascular disease

Interventions
Current interventions as of 19/05/2017:
Anacetrapib 100 mg daily or matching placebo. All participants receive background LDL-lowering with
atorvastatin. Both treatments taken orally. The median duration of on-treatment follow-up will be 4 years, and will vary depending on the patient's date of entry into the study. The maximum duration will be 6 years. There will be a further period of at least 2 years of off-treatment follow-up.

Previous interventions:
Anacetrapib 100 mg daily or matching placebo. All participants receive background LDL-lowering with atorvastatin. Both treatments taken orally. The median duration of treatment and follow-up will be 4 years, and vary depending on the patient's date of entry into the study. The maximum duration will be 6 years.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Intention-to-treat comparison among all randomized participants of the effects of allocation to anacetrapib versus placebo on major coronary events (defined as the occurrence of coronary death, myocardial infarction or coronary revascularization procedure) during the scheduled treatment period.

Key secondary outcome(s))
Current secondary outcome measures as of 05/07/2016:
Intention-to-treat comparisons among all randomized participants of the effects of allocation to anacetrapib versus placebo during the scheduled treatment period on:
1. Major atherosclerotic events (defined as coronary death, myocardial infarction or presumed ischaemic stroke; the key secondary outcome)
2. Presumed ischaemic stroke (i.e. not known to be haemorrhagic)
3. Major vascular events (defined as coronary death, myocardial infarction, coronary revascularization or presumed ischaemic stroke)
In addition, each of the individual components of the primary outcome (i.e. coronary death; myocardial infarction; and coronary revascularization) will be tested separately.

Previous secondary outcome measures:
Intention-to-treat comparisons among all randomized participants of the effects of allocation to anacetrapib versus placebo during the scheduled treatment period on:
1. Coronary death or myocardial infarction (key secondary outcome)
2. Coronary revascularization procedure
3. Presumed ischaemic stroke (i.e. not known to be haemorrhagic)
4. Death from all cardiovascular causes

Completion date
31/01/2037

Eligibility

Key inclusion criteria
1. Patients must be aged at least 50 at the time of initial invitation
2. At least one of the following inclusion criteria must be satisfied:
2.1. History of Myocardial Infarction (MI)
2.2. Cerebrovascular atherosclerotic disease (i.e. history of presumed ischaemic stroke or carotid revascularization)
2.3. Peripheral arterial disease (i.e. history of non-coronary revascularization, including aortic aneurysm repair or graft)
2.4. Diabetes mellitus with other evidence of symptomatic coronary heart disease (i.e. treatment or hospitalization for angina, or a history of coronary revascularization or acute coronary syndrome)

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Senior

Sex
All

Total final enrolment
30449

Key exclusion criteria
1. Acute MI, acute coronary syndrome or stroke within 4 weeks prior to Screening Visit or during Run-in (but such individuals may be entered later, if appropriate)
2. Planned coronary revascularization procedure within the next 6 months (such individuals may be entered later, if appropriate)
3. Definite history of chronic liver disease, or abnormal liver function (i.e. ALT >2x ULN). Note: Individuals with a history of acute hepatitis are eligible provided this ALT limit is not exceeded
4. Severe renal insufficiency (i.e. creatinine >200 µmol/L [2.3 mg/dL], dialysis or functioning renal transplant)
5. Evidence of active inflammatory muscle disease (e.g. dermatomyositis, polymyositis), or CK >3x ULN
6. Previous significant adverse reaction to a statin or anacetrapib
7. Current treatment with any of the following lipid-lowering treatments:
7.1. A regimen considered to produce substantially greater LDL cholesterol reduction than atorvastatin 80 mg daily for individuals in non-Asian countries or 20 mg daily for those in North East Asia
7.2. Fibric acid derivative ('fibrate', including gemfibrozil)
7.3. Niacin (nicotinic acid) at doses above 100 mg daily
8. Concurrent treatment with a medication that is contraindicated with anacetrapib or atorvastatin:
8.1. Any potent CYP3A4 inhibitor, such as:
8.1.1. Macrolide antibiotics (erythromycin, clarithromycin, telithromycin)
8.1.2. Daptomycin
8.1.3. Systemic imidazole or triazole antifungals (e.g. itraconazole, posaconazole)
8.1.4. Protease inhibitors (e.g. atazanavir)
8.1.5. Nefazodone
8.2. Ciclosporin
8.3. Systemic use of fusidic acid
9. Known to be poorly compliant with clinic visits or prescribed medication
10. Medical history that might limit the individuals ability to take trial treatments for the duration of the study (e.g. severe respiratory disease; history of cancer or evidence of spread within last 5 years, other than non-melanoma skin cancer; or recent history of alcohol or substance misuse)
11. Women of child-bearing potential (unless using adequate contraception)
12. Current participation in a clinical trial with an unlicensed drug or device
13. Individuals will also be excluded at the Screening visit if it is considered unlikely that they will achieve total cholesterol <3.5 mmol/L (135 mg/dL) on the highest atorvastatin dose available in their region (atorvastatin 80 mg daily in non-Asian countries or 20 mg daily in North East Asia).
14. In addition, individuals will be excluded at the Randomization visit if any of the following are true:

14.1. Total cholesterol above 4 mmol/L [155 mg/dL]
14.2. Non-compliant with run-in treatment (<90% scheduled run-in medication taken)
14.3. Individual is no longer willing to be randomized into the 4-5 year trial
14.4. The individuals doctor is of the view that their patient should not be randomized

Date of first enrolment
22/08/2011

Date of final enrolment
18/10/2013

Locations

Countries of recruitment
United Kingdom

England

Canada

China

Denmark

Finland

Germany

Italy

Norway

Sweden

United States of America

Study participating centre
University of Oxford
Oxford
United Kingdom
OX3 7LF

Sponsor information

Organisation
University of Oxford (UK)

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Industry

Funder Name
Merck

Alternative Name(s)
Merck & Co., Inc., Merck & Co.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The current 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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	28/09/2017		Yes	No
Results article	results	23/07/2019	25/07/2019	Yes	No
Results article	longer-term follow-up results	15/12/2021	01/02/2022	Yes	No
Results article	Immediate- and longer-term impacts of new vascular and nonvascular events on QoL and hospital costs	26/09/2023	27/09/2023	Yes	No
HRA research summary			28/06/2023	No	No

Other publications	design, recruitment, and baseline characteristics	01/05/2017		Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes