ISRCTN68072469 https://doi.org/10.1186/ISRCTN68072469

Using minocycline to help to identify carotid artery disease that may cause future strokes

Submission date	**Recruitment status**	[X] Prospectively registered
19/10/2023	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
30/10/2023	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
04/04/2025	Circulatory System	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

The carotid arteries are the main blood vessels supplying blood to the brain and are found on both sides of the neck. The narrowing of these arteries is an important cause of stroke. Narrowing is commonly caused by fatty deposits in the lining of the blood vessels, called 'atheroma' or 'plaques,' otherwise described as 'furring up' of the arteries. Typically these deposits build up over a person's lifetime and when they reach a significant size can limit the blood supply to the brain. An 'ischaemic stroke,' the most common type of stroke, occurs when insufficient blood supply reaches the brain, causing a part of it to die. This usually occurs when the plaque ruptures, causing a blood clot to form over the area that may break off and block the blood supply to the brain.

Work done by our group has found that the shell overlying the plaque can become damaged by small deposits of calcium ('microcalcification'), which makes the plaque more likely to rupture. To date, there is no drug treatment for reversing this microcalcification. However, recent research has shown a drug called minocycline reduced microcalcification developing in rats. Minocycline is an antibiotic used in routine clinical practice, typically to treat acne.

This study aims to test whether minocycline reduces microcalcification in humans. We can measure the amount of microcalcification in your arteries using a specialist scan called Positron Emission Tomography (PET), which uses radioactive 'tags' that show areas of microcalcification. This tag, called NaF (sodium fluoride), shows areas of microcalcification.

Who can participate?

Patients aged 50 years or above who have had an ischaemic stroke or transient ischaemic attack (TIA) in the last 7 days that has been confirmed to be due to atheroma in the carotid artery.

What does the study involve?

If you decide to take part, we will ask you to come on two occasions (the first of which may be during your admission) to Addenbrooke's Hospital. You will be reimbursed for any travel expenses incurred in attending the scan sessions.

At the PET scan, a cannula (a thin plastic tube similar to the one you will have had during your hospital admission) will be inserted into a vein in your arm through which the tracer would be injected. A blood sample will be taken through this cannula to test for markers linked with microcalcification. We would then aim to do the scan 60 minutes after the injection of the NaF tracer. You will be asked to lie with your neck in a PET/CT machine (which is shaped like a large doughnut). The PET/CT scanner can detect the tracer, identifying where it is in the blood vessels of your neck, and how much is present. The technique is so sensitive that only a very tiny amount of the radioactive tracer is required. During the scan, you will be asked to lie flat on a bed on your back. Your neck will be supported by a stiff collar to limit movement, which can interfere with the images the scan produces. Once you are settled comfortably, we will ask you to stay in the same position for the time it takes to do the scan (approximately 20 minutes). During the PET /CT scan, a detailed CT scan of the arteries in your neck will also be performed with contrast dye injected through the cannula in your arm. You are strongly advised not to go to work on the day of your scan. We also recommend that you don't have close contact with pregnant women or young children for 8 hours after the scans, as the tracer takes a little while to leave your body (it comes out through the urine). You are encouraged to drink plenty of fluids of any type as this will help flush the tracer through your kidneys.

Overall, the visits will last approximately two hours. You will be accompanied by one of the research team. You are welcome to bring someone with you who can be present at all times except from the injection of the tracer to the completion of the scan.

All participants in the study will receive standard medical care following their stroke, with half of participants randomly assigned to receive the minocycline drug in addition to the standard medical care. Therefore, it is not guaranteed you will receive the drug, but we would still perform the scans and clinical review (as above).

The entire research project will be carried out over two years and it is expected that you will be involved for a maximum of 12 weeks (from signing the consent form to the second PET scan). At the end of this 12 week period, participants taking minocycline will then stop this medication.

There are no specific additional things you need to do before any of the scans.

What are the possible benefits and risks of participating?
Any results that may be useful in making decisions about your care will be passed on to the doctors looking after you. There may be no direct benefit for you in taking part, but the results of this study will help our understanding of the processes involved in stroke and may help to improve the treatment of the disease in the future.

The PET/CT scans use radioactive tracers which are safe and have been used in human studies without any serious side effects, but do involve some radiation. The tracers break down very quickly and disappear from the body within a few hours through the urine. There is also a small radiation dose from the CT part of the scan. The total radiation dose in the study is comparable to roughly 5 years of exposure to natural background radiation in the UK. This radiation dose carries a risk of cancer of 0.06% (equivalent to roughly 1 in 2000 people), but this should be compared to the natural lifetime risk of cancer of about 1 in 2 over an average person's lifetime.

Although it is extremely unlikely that an allergic reaction or other side effect will occur, there are facilities in place within the PET/CT Unit and at the hospital to deal with them. Placing a cannula (small plastic tube) into a vein can cause some discomfort and very occasionally can lead to infection but this is unlikely in the short time it will be in place. Some people can also get bruising at the site where the cannula is inserted. This procedure is performed regularly in the

hospital and is generally very safe. The cannula will be inserted 60-90 minutes before the scan and will be removed immediately afterwards.

Minocycline is an antibiotic used in routine clinical care. Like any drug it may cause side-effects, including nausea, vomiting, diarrhoea, skin reactions, or allergic reactions. If you experience any of these, or are concerned about other possible side-effects, then please contact the study team for review. Your other medications will be reviewed at the time of enrolment into the study to ensure that the minocycline does not interact with any medications you are currently taking.

There is a small chance that your scan may show something abnormal that you did not know about. This is because the field of view of the scan includes the tissues and bones in the neck, as well as the blood vessels we are interested in. Examples might include growths in the tissues of the neck, or abnormalities of the bones or blood vessels. There may be areas of PET tracer uptake (“hot spots”) that appear abnormal. Though the scans used in this trial may not be the ideal technique for defining exactly what the abnormality might be, you would be given advice about what is found. We would contact you in writing or by telephone if it should appear more urgent. You would be referred to the appropriate specialist for any further investigation required. This may include a further review in an out-patient clinic by one of the stroke team. We would also in this instance strongly recommend that you allow us to inform your General Practitioner (GP) so that he/she is aware of any on-going investigation or treatment you may require. Finding something early in this way has the advantage that treatment can be started early, but, in a small number of cases, it may have an effect on future employment and insurance.

If you have private medical insurance you should check with the company before agreeing to take part in the study to ensure that your participation will not affect your insurance.

Where is the study run from?
Cambridge University Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
February 2021 to December 2026

Who is funding the study?
Varsity Pharmaceuticals Limited (UK)

Who is the main contact?
Dr Nicholas Evans, ne214@cam.ac.uk
Dr Shiv Bhakta, sab201@medschl.cam.ac.uk

Contact information

Type(s)
Principal investigator

Contact name
Dr Nicholas Evans

Contact details
Department of Clinical Neurosciences
R3, Box 83
Cambridge Biomedical Campus

Cambridge
United Kingdom
CB2 0QQ
-
ne214@cam.ac.uk

Type(s)
Public, Scientific

Contact name
Dr Shiv Bhakta

Contact details
Department of Clinical Neurosciences
Desk 273
Victor Phillip Dahdaleh Heart and Lung Research Institute
Cambridge Biomedical Campus
Hills Road
Cambridge
United Kingdom
CB2 0BB
-
sab201@medschl.cam.ac.uk

Additional identifiers

Integrated Research Application System (IRAS)
269021

Central Portfolio Management System (CPMS)
48122

Study information

Scientific Title
MINOcycline in the Treatment of Atheroma that are Unstable or Ruptured Study

Acronym
MINOTAUR

Study objectives
To investigate whether treatment with minocycline reduces microcalcification activity in symptomatic carotid atherosclerotic plaques compared to 'standard care' (i.e. the primary hypothesis is that minocycline will reduce microcalcification in symptomatic carotid atherosclerotic plaques compared to standard care).

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 05/03/2021, Wales REC 6 (c/o Public Health Wales Building, 1 Jobswell Road, St David’s Park , Camarthen, SA31 3HB, United Kingdom; +44 1267 611164; Wales.REC6@wales.nhs.uk), ref: 21/WA/0011

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Atheroma

Interventions
Following recruitment, we will arrange for the participant to have two PET scans. The first will take place in the three weeks following their stroke and the second will take place approximately 90 days later. Participants will be expected to attend both scans. Participation will end after the second scan.

The PET scan involves the participant attending the PET/CT Department located in Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust. Here they will have a 'tracer' (a dye) injected through a cannula (a thin plastic tube similar to the one they will have had during their hospital admission) into the vein. The tracer will be given an hour to circulate around the body, during which time the participant will wait in an armchair in the department. During this time they can continue with usual activities and can eat and drink. After this hour, the participant will lie on their back in the PET/CT machine (shaped like a large doughnut) for approximately 20 minutes whilst the tracer is detected. During the scan, a detailed scan of the arteries in the neck will be performed using a contrast dye injected through the cannula. Once the scan is complete, the cannula will be removed and the participant can leave. Overall the visit will take approximately two hours. Typically they are done on Friday mornings.

If an individual is still admitted to hospital then they can attend the department, otherwise they will be reimbursed for any travel expenses to attend these scans. Participants will be accompanied throughout the visit by one of the research or radiography teams. Participants are welcome to bring someone with them who can be present at all times except the period between injection of the tracer and completion of the scan.

The PET/CT scans use radioactive tracers which are safe and have been used in clinical care in humans without any serious side effects, but do involve some radiation. The tracers break down very quickly and disappear from the body within a few hours through the urine. There is also a small radiation dose from the CT part of the scan. The total radiation dose in the study is comparable to less than 5 years of exposure to natural background radiation in the UK. This radiation dose carries a risk of cancer of around 1 in 2000, but this should be compared to the overall risk of cancer of about 1 in 2 over an average person’s lifetime. We advise participants not to attend work after the scan and that they should avoid close contact with pregnant women or young children for eight hours after the scan whilst the tracer leaves the body (it comes out through the urine).

During the 90 days between scans, half of participants will be assigned to taking minocycline, an antibiotic used routinely to treat acne. Participants will be taking the dose used in routine clinical practice. They will be taking this drug in addition to any medication prescribed by the clinical team following their stroke. Minocycline is typically well tolerated, but like any drug it may cause side-effects (including nausea, vomiting, diarrhoea, skin reactions, or allergic reactions). The participant's other medications will be reviewed at the time of enrolment into the study to ensure that the minocycline does not interact with any medications they are currently taking. After the second PET scan, the individual will stop taking the minocycline.

Our study will measure the amount of the tracer found in the arteries and compare them between visits, as well as between those taking minocycline and those not.

Intervention Type
Other

Phase
Not Specified

Primary outcome(s)
1. Microcalcification activity in the asymptomatic/non-culprit carotid atheroma as measured by NaF MDS TBRmax on PET/CT at baseline and at 90 days
2. Macrocalcification in the aortic arch and carotid arteries as measured by calcium scoring using the Agatston method on non-contrast CT at baseline and at 90 days

Key secondary outcome(s)
There are no secondary outcome measures

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. Participant is willing and able to give informed consent for participation in the study.
2. Male or Female, aged 50 years or above.
3. Participants have had an ischaemic stroke or transient ischaemic attack (TIA) in the last 7 days that has been confirmed to be due to atheroma in the carotid artery.
4. Have evidence of carotid territory atheroma of at least 30% in the ipsilateral carotid artery to the infarct that is felt to be causative (using Doppler ultrasound or computed tomography angiography).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
50 Years

Sex
All

Key exclusion criteria
1. The participant has a medical history or clinically relevant abnormality identified on the screening medical examination, vital sign measurement, or clinical laboratory examination that is deemed by the principal investigator and/or designee to make the subject ineligible for inclusion,
2. The participant has had a haemorrhagic stroke.
3. The participant is a woman of childbearing potential.
4. The participant is in atrial fibrillation.
5. The participant has had a previous adverse reaction to minocycline.
6. The participant has a medical condition in which the use of minocycline is cautioned: systemic lupus erythematosus (SLE), liver dysfunction, myasthenia gravis, intracranial hypertension, or lactose intolerance.
7. The participant is taking medication where there is a significant risk of interaction with minocycline: anticoagulants, penicillins, isotretinoin.
8. Planned carotid revascularisation procedure prior to the 12-week re-imaging.
9. The participant has evidence of a complete occlusion of their internal carotid artery on the ipsilateral side to the infarct.
10. The participant has limited life expectancy due to another illness or chronic condition making follow-up difficult (e.g. widespread malignancy).
11. The participant has existing co-morbid medical conditions that would prevent them lying flat in the scanner (e.g. heart failure).
12. The participant has known chronic kidney disease that would preclude contrast use (i.e. excluded if eGFR < 30ml/min/1.73m2).
13. The participant is unable to give informed consent.
14. The participant is already participating in two other research studies.

Date of first enrolment
01/03/2024

Date of final enrolment
28/02/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge

United Kingdom
CB2 0QQ

Study participating centre
University of Cambridge
Department of Clinical Neurosciences
R3 Clinical Neurosciences (Box 83)
Addenbrooke's Hospital, Hills Road
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Industry

Funder Name
Varsity Pharmaceuticals Limited

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and analysed during the current study will be available upon reasonable request, from Dr Nicholas Evans (ne214@cam.ac.uk). Consent will be obtained from the participants via the study consent form, with participants asked for consent to the following statement: I understand that the information collected about me may be used to support other research in the future, and may be shared anonymously with other academic and commercial researchers external to the project within the UK and beyond. Fully anonymised data, including the results of the analysis of study imaging and relevant associated data, will be stored for up to 15 years following the conclusion of the study, as per the IRAS form and participant consent form.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.4	27/02/2021	27/10/2023	No	Yes
Participant information sheet	Summary participant information sheet version 1.1	13/07/2020	27/10/2023	No	Yes
Participant information sheet	version 2	12/01/2024	04/04/2025	No	Yes
Participant information sheet	version 2	12/01/2024	04/04/2025	No	Yes
Protocol file	version 1.7	27/02/2021	27/10/2023	No	No
Protocol file	version 2	12/01/2024	04/04/2025	No	No