ISRCTN14632228 https://doi.org/10.1186/ISRCTN14632228

Research study for people who have cerebral small vessel disease (cSVD, damaged small blood vessels in the brain) and a stroke, which may lead to impaired memory and thinking and then dementia

Submission date
02/07/2025

Recruitment status
Recruiting

Registration date
29/08/2025

Overall study status
Ongoing

Last Edited
01/09/2025

Condition category
Circulatory System

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
We intend to find new drug treatments for patients who have had a stroke and also have damaged small blood vessels in the brain, which are stiff and leaky. A stroke happens when a brain blood vessel blocks. Dementia can follow when stroke and small-vessel disease combine. We think that two drugs called cilostazol and isosorbide nitrate may be useful. Both are used in heart disease. We have already tested the drugs in lacunar (affecting the small vessels in the brain) stroke with promising results and are keen to see if we can perform a trial in other sorts of stroke.

Who can participate?
Patients aged over 50 years with a stroke and small-vessel disease

What does the study involve?
Patients will be randomly (like flipping a coin) given one or either drug, both drugs or neither, for a period of 6 months. We will then phone them to test their memory and thinking, and find out how much of the drugs they have taken and whether the drugs are safe and might reduce dementia.

What are the possible benefits and risks of participating?
This study will tell us whether it is possible to do a trial in people with a stroke and small-vessel disease and whether the drugs might work and are safe. This will help plan a larger trial to give a definite answer. If the drugs work then we will have new treatments to help prevent dementia after a stroke.
6 months of IMP is given to the participant on discharge from hospital. The dose will be escalated over the first few weeks. There is a slight risk that patients may not take the medication as prescribed, but this method of drug administration was used in the MHRA-

approved LACI-2 trial and is now being used in the LACI-3 trial. There were no issues highlighted in the LACI-3 trials. The hospital research staff will be trained by the coordinating centre to follow up patients and identify any issues with compliance.
Research staff at the hospital will provide a drug information sheet at randomisation with clear instructions on how much and when medication should be taken. The drug information sheet will contain information on who to contact if there is an issue with the medication if they have side effects or take an overdose of the medication.
Research staff at the hospital will ring the participant at 1-2 weeks, 3-4 weeks and 6 months after the participant starts to take the medication to check whether the dosage has been increased and whether there have been any side effects.
At 6 months when the medication stops, a trained follow-up coordinator from the coordinating centre will ring the participant to ask a few questions about how they are, complete some assessments and check that they have not had any side effects of the medication.

Where is the study run from?
University of Nottingham (UK)

When is the study starting and how long is it expected to run for?
October 2025 to May 2028

Who is funding the study?
Alzheimer's Society (UK)

Who is the main contact?
1. Dr Philip Bath, philip.bath@nottingham.ac.uk
2. Trial Manager, CVD-Cog@nottingham.ac.uk

Contact information

Type(s)
Scientific, Principal investigator

Contact name
Dr Philip Bath

Contact details
Stroke Trials Unit
D Floor South Block
QMC Derby Road
Nottingham
United Kingdom
NG7 2UH
+44 (0)115 823 1255
philip.bath@nottingham.ac.uk

Additional identifiers

Integrated Research Application System (IRAS)
1011543

Central Portfolio Management System (CPMS)
67586

Protocol serial number
25017

Study information

Scientific Title
CerebroVascular Disease-Cognition (CVD-Cog) Phase II trial in non-lacunar ischaemic stroke with cerebral small vessel disease

Acronym
CVD-Cog

Study objectives
Feasibility:
Recruitment of 400 patients from 25 UK sites at an average recruitment rate of 0.9/site/month

Retention:
>90% participants at end-of-trial/6 months

Adherence:
>75% of participants are taking >50% trial dose at end-of-trial

Completeness of primary clinical outcome:
>85% of participants have a DSM-5-7L ordinal cognition scale at end-of-trial

Safety:
All cause death; serious adverse events; targeted drug-related adverse events

Proof-of-concept:
Estimate of effect size and variance on DSM-5-7L ordinal cognition scale

Ethics approval required
Ethics approval required

Ethics approval(s)
Not yet submitted, ref: 25/WM/0144

Primary study design
Interventional

Study design
Open randomized controlled parallel-group trial

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied

Clinical syndrome of cortical or large subcortical stroke or TIA (TACS, PACS or cerebellar POCS)

Interventions
IMP is defined by the active substance only, so any brand of isosorbide mononitrate (ISMN) and cilostazol that are available in the hospital pharmacy may be used.

All patients: Participants will be randomised to ISMN 25 mg od po SR/MR for two weeks then 50 mg od po SR/MR for 5½ months, versus no ISMN. If a slow-release ISMN is not available, non-slow-release tablets may be used. The target dose of ISMN is 40-60 mg daily.

Patients on monoplatelet therapy (not an oral anticoagulant, OAC): Participants will also be randomised to cilostazol 50 mg bd po for 2 weeks then 100 mg bd po for 5½ months versus no cilostazol. Hence, participants on mono-antiplatelet therapy will be randomised to start one of four treatments:
1. ISMN only
2. Cilostazol only
3. Both ISMN and cilostazol
4. Neither ISMN nor cilostazol

Patients with contraindications to one drug may be randomised to the other drug versus control; patients who develop a contraindication to one of the drugs during the trial may continue taking the other drug.

Comparator: None (PROBE design).
Standard of care: UK guideline-based stroke prophylaxis with antithrombotic, blood pressure lowering, lipid-lowering, carotid endarterectomy, lifestyle etc and recorded.

The trial drug will be dispensed in the original manufacturer's packaging from participating hospital pharmacies. The drug will be supplied in a treatment pack marked with the participant ID and including instructions on how to take the tablets, including the dose initiation and escalation phase. Patients will be phoned by the local centre at one to two weeks and three to four weeks after starting medication to check and advise on dose escalation. A maximum of 6 months' supply will be dispensed.

Randomisation - Computerised randomisation to reduce bias with:

Stratification:
No oral anticoagulation - ISMN: cilostazol: both: neither 1:1:1:1.
On oral anticoagulation - ISMN: no ISMN 1:1.

Minimisation:
Age, sex, premorbid mRS, stroke impairment (NIHSS), age of leaving education, cognition (DSM-5 7L), time from stroke/TIA onset to randomisation, systolic blood pressure, smoking.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Cilostazol, isosorbide mononitrate

Primary outcome(s)
Feasibility: Recruitment of 400 patients from 25 UK sites at 6 months, information collected from the trial database.

Key secondary outcome(s)
1. Retention: >90% participants at end of trial/6 months, information collected from database following the Day 183 follow-up.
2. Adherence: >75% of participants are taking >50% trial dose, information collected from database following week 1-2, week 3-4 and Day 183 follow-ups.
3. Completeness of primary clinical outcome: >85% of participants have a DSM-5-7L ordinal cognition scale at end-of-trial, information collected from database following the Day 183 follow-up.
4. Safety: All cause death; serious adverse events targeted drug-related adverse events (headache, loose stools, palpitations, nausea, dizziness, falls), information collected from database following week 1-2, week 3-4 and Day 183 follow-ups.
5. Proof-of-concept: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) 7-level ordinal cognition scale at end-of-trial, information collected from database following week 1-2, week 3-4 and Day 183 follow-ups.

Completion date
01/05/2028

Eligibility

Key inclusion criteria
1. Adult, age >50 years, with no upper limit.
2. Clinical syndrome of cortical or large subcortical stroke or TIA (TACS, PACS or cerebellar POCS).
3. At least 7 days after the index event.
4. Stable medically according to the PI.
5. Has completed any phase of dual antiplatelet therapy.
6. Independent functionally or requires only limited help (mRS 0-3).
7. Able to swallow or has established enteral feeding route.
8. Brain imaging (CT or MRI scan) at the time of the index stroke/TIA shows moderate-severe white matter hyperintensities, Fazekas Score periventricular and deep ≥2.
9. The relevant radiology report will be uploaded as part of eligibility and assessed for these criteria.
10. Patient has capacity to give consent in the opinion of the PI or any delegated member of the research team; OR Patient lacks capacity and a legal representative is available to give proxy consent.
11. Likely to be available for follow-up at 6 months.
12. Women of childbearing potential and men with partners of childbearing potential must be willing to use contraception, provided they have the capacity.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
50 Years

Sex
All

Key exclusion criteria
1. Lacunar infarct (LACS; so is eligible for LACI-3 trial).
2. Brain stem-only posterior circulation stroke syndrome (POCS). Note: cerebellar POCS are eligible.
3. Known monogenic cerebral small vessel disease.
4. Index event was an intracranial haemorrhage. Note: a past history of ICH before the index event is eligible.
5. Other active brain disease, e.g. brain tumour, multiple sclerosis, Parkinson's disease, recurrent seizures, neurodevelopmental disorder. Note: well-controlled epilepsy present prior to the stroke, a single seizure at onset of the stroke, or provoked seizure, is not an exclusion.
6. Clinical diagnosis of dementia, e.g. letter from a memory clinic and/or taking acetylcholinesterase inhibitor or memantine.
7. Contraindication to both trial drugs
8. Indication for both trial drugs. Planned surgery during the trial period including carotid endarterectomy. Note: Patient becomes eligible after planned surgery. 'Prior and apparently successful carotid endarterectomy (or other surgery) is not an exclusion criterion and patients who would otherwise be eligible but require endarterectomy first may be randomised after recovery from successful endarterectomy
9. Diagnosis of hypotension, defined as sitting systolic blood pressure less than 100 mmHg.
10. History of drug overdose or attempted suicide.
11. Person is a visitor to the hospital's region so cannot be followed, e.g. on holiday/from overseas.
12. Unlikely to comply with study procedures and follow-up procedures for whatever reason (e.g. history of poor medication compliance) in the opinion of the randomising physician.
13. Pregnancy, breastfeeding, or of child-bearing potential (a negative pregnancy test is needed prior to enrolment) and not using highly effective contraception.
14. Known renal impairment (most recent creatinine clearance <25 ml/min).
15. Known hepatic impairment (most recent transaminase >3 times upper limit normal).
16. Previously enrolled in CVD-Cog.
17. Enrolled in a study that does not have an agreement with CVD-Cog allowing co-enrolment (see up-to-date list of trials allowing co-enrolment on CVD-Cog website).
18. Women of childbearing potential and men with partners of childbearing potential who lack capacity
19. Cilostazol exclusion criteria - still allows randomisation to ISMN:
20. Definite indication for cilostazol: i.e. already prescribed.
21. Definite contraindication to cilostazol: see SmPC.
22. Prohibited medications to cilostazol: see SmPC.
23. Active cardiac disease, e.g. atrial fibrillation, myocardial infarction in past 6 months, active angina, symptomatic cardiac failure.
24. Bleeding tendency, e.g. known platelets<100, active peptic ulcer, history of intracranial haemorrhage such as subdural haematoma, subarachnoid haemorrhage, intracerebral

haemorrhage (but not asymptomatic haemorrhagic transformation of infarction or a few microbleeds), taking anticoagulant medication).
25. Uncontrolled high blood pressure: systolic BP >200 mmHg

ISMN exclusion criteria:
7. Definite indication for ISMN: i.e. already prescribed.
8. Definite contraindication to ISMN: see SmPC.
9. Prohibited medications to ISMN: see SmPC – phosphodiesterase-5-inhibitor, e.g. sildenafil, tadalafil and verdenafil.

Date of first enrolment
01/12/2025

Date of final enrolment
01/12/2027

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Royal United Hospital Bath
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
Royal Victoria Hospital
274 Grosvenor Road
Belfast

United Kingdom
BT12 6BA

Study participating centre
Good Hope Hospital
Rectory Road
Sutton Coldfield
United Kingdom
B75 7RR

Study participating centre
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
Fairfield General Hospital
Fairfield General Hospital
Rochdale Old Road
Bury
United Kingdom
BL9 7TD

Study participating centre
Craigavon Area Hospital
Lurgan Rd
Craigavon
United Kingdom
BT63 5QQ

Study participating centre
Royal Derby Hospital
Uttoxeter Road
Derby
United Kingdom
DE22 3NE

Study participating centre
Dorset County Hospital
Dorset County Hospital
Princes Street
Dorchester
United Kingdom
DT1 1TS

Study participating centre
Royal Infirmary of Edinburgh at Little France
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian
United Kingdom
EH16 4SA

Study participating centre
Northwick Park Hospital
Watford Road
Harrow
United Kingdom
HA1 3UJ

Study participating centre
Victoria Hospital
Hayfield Road
Kirkcaldy
United Kingdom
KY2 5AH

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre

Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre
University College London Hospital
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Luton and Dunstable University Hospital
Lewsey Road
Luton
United Kingdom
LU4 0DZ

Study participating centre
The James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Northampton
Northampton General Hospital
Cliftonville
Northampton
United Kingdom
NN1 5BD

Study participating centre
Queens Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre
Royal Cornwall Hospital (treliske)
Treliske
Truro
United Kingdom
TR1 3LJ

Study participating centre
Ulster Hospital
Upper Newtownards Rd

Dundonald
Belfast
United Kingdom
BT16 1RH

Sponsor information

Organisation
University of Nottingham

ROR
https://ror.org/01ee9ar58

Funder(s)

Funder type
Charity

Funder Name
Alzheimer's Society

Alternative Name(s)
alzheimerssoc

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Results and Publications

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

IPD sharing plan summary
Data sharing statement to be made available at a later date